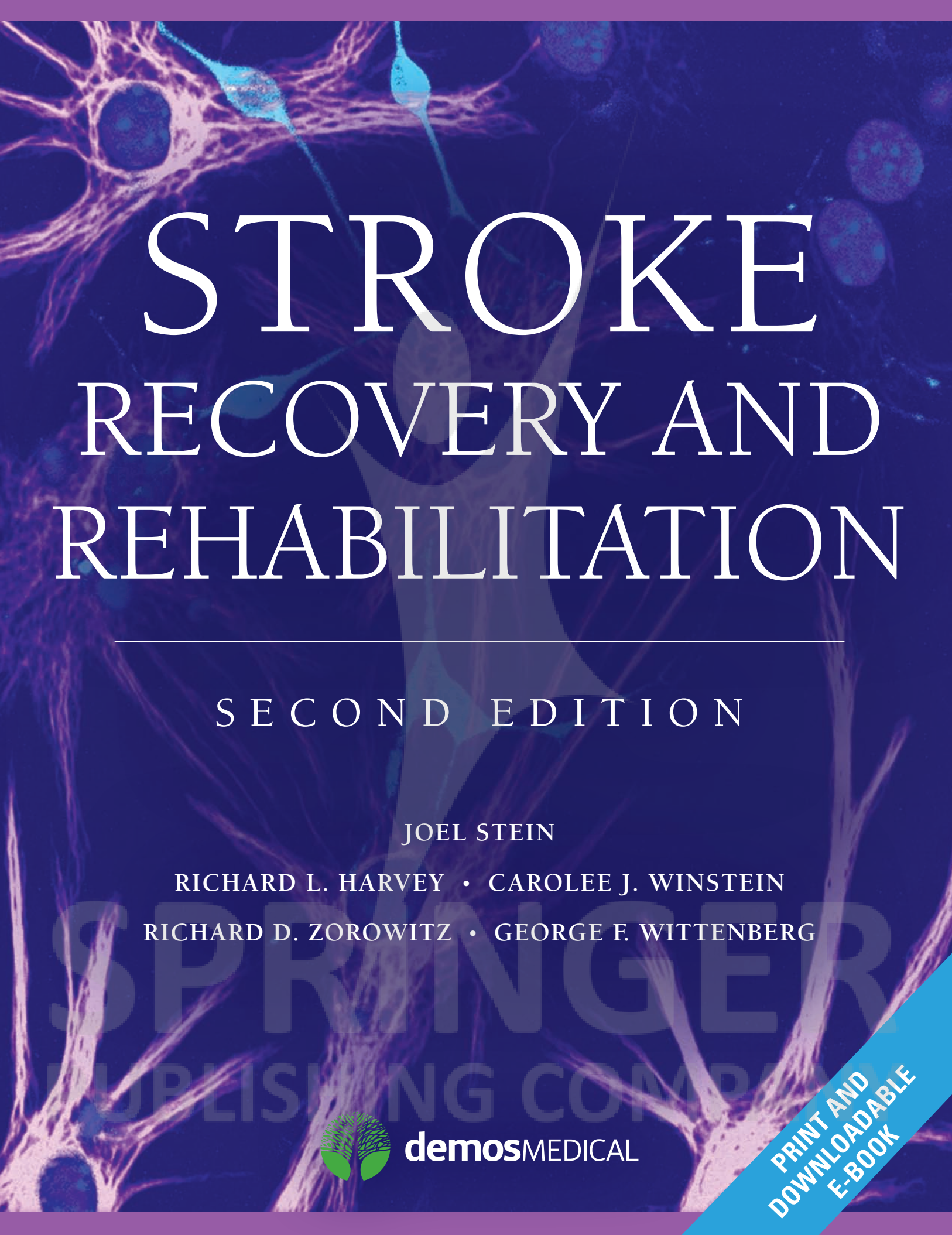

STROKE RECOVERY AND REHABILITATION

SECOND EDITION

JOEL STEIN

RICHARD L. HARVEY • CAROLEE J. WINSTEIN

RICHARD D. ZOROWITZ • GEORGE F. WITTENBERG

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Stroke Recovery and Rehabilitation

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Second Edition

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Preface to the Second Edition

Advances in our understanding of stroke recovery and rehabilitation have continued to accelerate since the first edition of this text was published, and this trend shows no signs of abating. These advances include new tools to understand the neurophysiological and anatomical underpinnings of stroke recovery, as well as a growing evidence base on an array of clinical therapies. Two broad principles continue to guide this field, however. First, optimizing functional recovery from stroke is contingent on intense and challenging activities that target functional motor and cognitive skills. The new learning and relearning that results produces measurable cortical neuroplastic changes. Second, despite the first principle and the demonstrated effectiveness of many rehabilitation techniques, many stroke survivors continue to exhibit substantial activity limitations and participation restrictions. Accordingly, we continue to rely on compensatory approaches for restoring mobility and activities of daily living. The tension between these restorative and compensatory approaches arguably drives the field forward, prompting advocates of each strategy to design studies to find the most effective treatment for each stroke-related impairment.

Our goal for the second edition of this book is to provide updated information on all aspects of stroke recovery and rehabilitation, and to expand areas that were not fully addressed in the first edition. Examples include the inclusion of a chapter written by a stroke survivor to provide the most important perspective of this field—that of the person affected by stroke. New chapters have been added on transcranial magnetic stimulation and biomarkers of stroke recovery, on the genetics of stroke recovery, and the use of medications to facilitate recovery after stroke. Topics that have grown too large for a single chapter, such as robotics and virtual reality, have been divided into more manageable and focused chapters.

Some aspects of this text have not changed. As in the prior edition, the chapters are written by basic scientists and clinicians from a variety of fields including biomedical engineering, neurology, physical medicine and rehabilitation, psychology, neuroscience, physical therapy, occupational therapy, speech and language pathology, neuroradiology, optometry, orthotics, and rehabilitation nursing. The intent is to provide an up-to-date practical clinical guide to evidence-based stroke recovery and rehabilitation built on a foundation of basic neurophysiology, neuroscience, and psychological science.

We would like to thank the authors for taking the time away from busy clinical activities, mentoring students, proposing, performing, and publishing research, and other academic responsibilities to write these chapters. We also thank the editorial staff at Demos Medical Publishing for their patience, encouragement, and support. We hope that this updated second edition of *Stroke Recovery and Rehabilitation* continues to serve as a valuable reference for academicians and clinicians alike, and for all disciplines that have the responsibility and pleasure of helping stroke survivors achieve their maximum potential.

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Preface to the First Edition

The 1990s were declared the decade of the brain by the National Institutes of Health. It was during this decade that neuroscience and clinical rehabilitation research began to converge into a new science of neurorehabilitation. The knowledge gleaned from the past 20 years has led to the clear understanding that optimizing functional recovery from stroke is contingent on relatively intense and challenging targeted motor and cognitive relearning of functional skills. This relearning results in measurable cortical neuroplastic changes. This consensus represents a paradigm shift for rehabilitation clinicians who had for the most part previously focused on the neurodevelopmental process of carefully normalizing trunk and limb movement, teaching one-handed techniques, and educating patients on the use of adaptive equipment.

If there had been a standard comprehensive text on stroke rehabilitation, these changes in our conception of rehabilitation and recovery would most certainly require that it be updated. In fact, no such text has been previously assembled that included the basic neuroscience and anatomy of stroke, the physiology of neural recovery after focal injury, or clinical rehabilitation interventions for stroke based on randomized clinical trials. This text was written to fulfill that need: providing the reader with a multidisciplinary and international perspective. The chapters are written by basic scientists and clinicians from a variety of fields including biomedical engineering, neurology, physical medicine and rehabilitation, psychology, neuroscience, physical therapy, occupational therapy, speech and language pathology, neuroradiology, optometry, orthotics, and rehabilitation nursing. The intent was to provide a practical clinical guide to evidence-based stroke rehabilitation built on a foundation of basic neurophysiology and neuroscience.

We would like to thank the authors of this text for taking the time away from their busy clinical schedules, grant writing, and other academic responsibilities to write these chapters. We also would like to thank the editorial staff at Demos Medical Publishing for their patience, encouragement, and support. We hope that this text on stroke recovery and rehabilitation becomes a valuable reference for academicians and clinicians alike, and for all disciplines that have the pleasure of helping survivors of stroke achieve their maximum potential.

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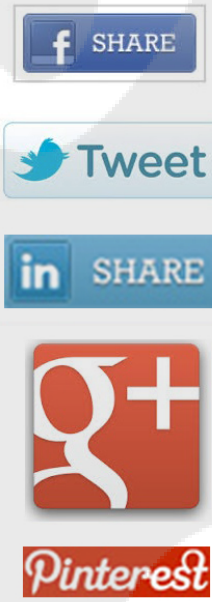
Stroke Recovery and Rehabilitation: Second Edition



I

INTRODUCTION

1

The Historical Origins of Stroke Rehabilitation

Douglas J. Lanska

Physical medicine and rehabilitation (PM&R) is a relatively young specialty that developed during the 20th century, with significant growth and development stimulated by two World Wars and by increasingly severe epidemics of paralytic poliomyelitis during the first half of the 20th century (1–4). During and after each of the World Wars, many soldiers returned with serious injuries and severe disabilities, and physicians and therapists were needed to treat and manage their chronic disabling conditions. This was particularly true after World War II, when the availability of antibiotics and improved surgical techniques allowed more injured soldiers to survive, albeit with significant disabilities. Similarly, over the same time period, increasingly severe epidemics of polio, frequent industrial accidents, and escalating motor vehicle accidents as a result of the increased availability of automobiles and higher-speed roadways added greatly to the burden of impairment and disability among the civilian population. Thus, events in the first half of the 20th century necessitated the development of new restorative treatment programs incorporating new physical and rehabilitative techniques, and the establishment of training programs for physicians and therapists to administer the treatments.

Nevertheless, with the exception of a relatively few scattered physical medicine physicians, it was not until the second half of the 20th century that specialists in rehabilitation medicine could profitably direct their energies exclusively, or even preferentially, to rehabilitation outside of the unprecedented and unsustainable circumstances of wartime military programs. Also largely missing until the second half of the 20th century were separate departments in academic and nonacademic medical centers devoted to the specialty, established training programs in PM&R, a sufficient number of PM&R practitioners, separate dedicated facilities for provision of rehabilitation services (e.g., dedicated wards in hospitals or separate rehabilitation centers), forums for the interchange of ideas (e.g., texts, journals, and professional societies), recognition by professional colleagues and the public that rehabilitation medicine specialists provided a needed service, and supportive legislation that would provide financial mechanisms to develop and provide such resources (5).

WORLD WAR I AND ITS AFTERMATH: BEGINNINGS OF PHYSICAL MEDICINE AND VOCATIONAL REHABILITATION

During much of the 19th century, physicians who employed physical modalities or advocated treatment with fresh air, water, exercise, and dietary modification were at risk of being labeled quacks by other members of the medical profession. However, near the turn of the century, orthopedic surgeons, in particular, began using selected physical treatments—massage, exercise, hydrotherapy—as part of special programs to augment medical care and convalescence within hospitals under physician supervision.

During World War I (1914–1918), physical and occupational therapy became increasingly important adjuncts to surgical practice, particularly in the treatment of orthopedic casualties, because surgeons realized that surgery alone was insufficient to achieve maximum return of function, and because empirical experience indicated that physical methods were useful adjuncts in the medical care and convalescence of wounded and disabled soldiers (1,4). In particular, with active U.S. involvement in the war beginning in 1917, Colonel Joel Ernst Goldthwait, MD (1866–1961), chief surgeon in the Orthopedic Medical Corp of the American Expeditionary Forces, and Colonel Elliott G. Brackett, MD, in the Home Service, also an orthopedic surgeon, enthusiastically supported a role for physical therapists in the rehabilitation of orthopedic casualties (6,7). Late in 1917, a program of Women's Auxiliary Medical Aides was established in the Surgeon General's Office, but by April 1918, this was transferred to the Division of Physical Reconstruction and renamed "Reconstruction Aides" (Figure 1.1) (6). Major (later Lieutenant Colonel) Frank B. Granger, MD (1875–1928), was named director of the Physiotherapy Service of the Reconstruction Division for the Army, and under his command the reconstruction aid program was directed by Chief Aide Marquerite Sanderson (formerly from Dr. Goldthwait's office in Boston) (6,8). Training programs for the reconstruction aides were established at Walter Reed General Hospital, headed by therapist Mary McMillan; later at Reed College in Portland, Oregon (where McMillan also initially taught during a leave of absence from Walter Reed); and eventually at 13 other programs across the country (6,9,10).

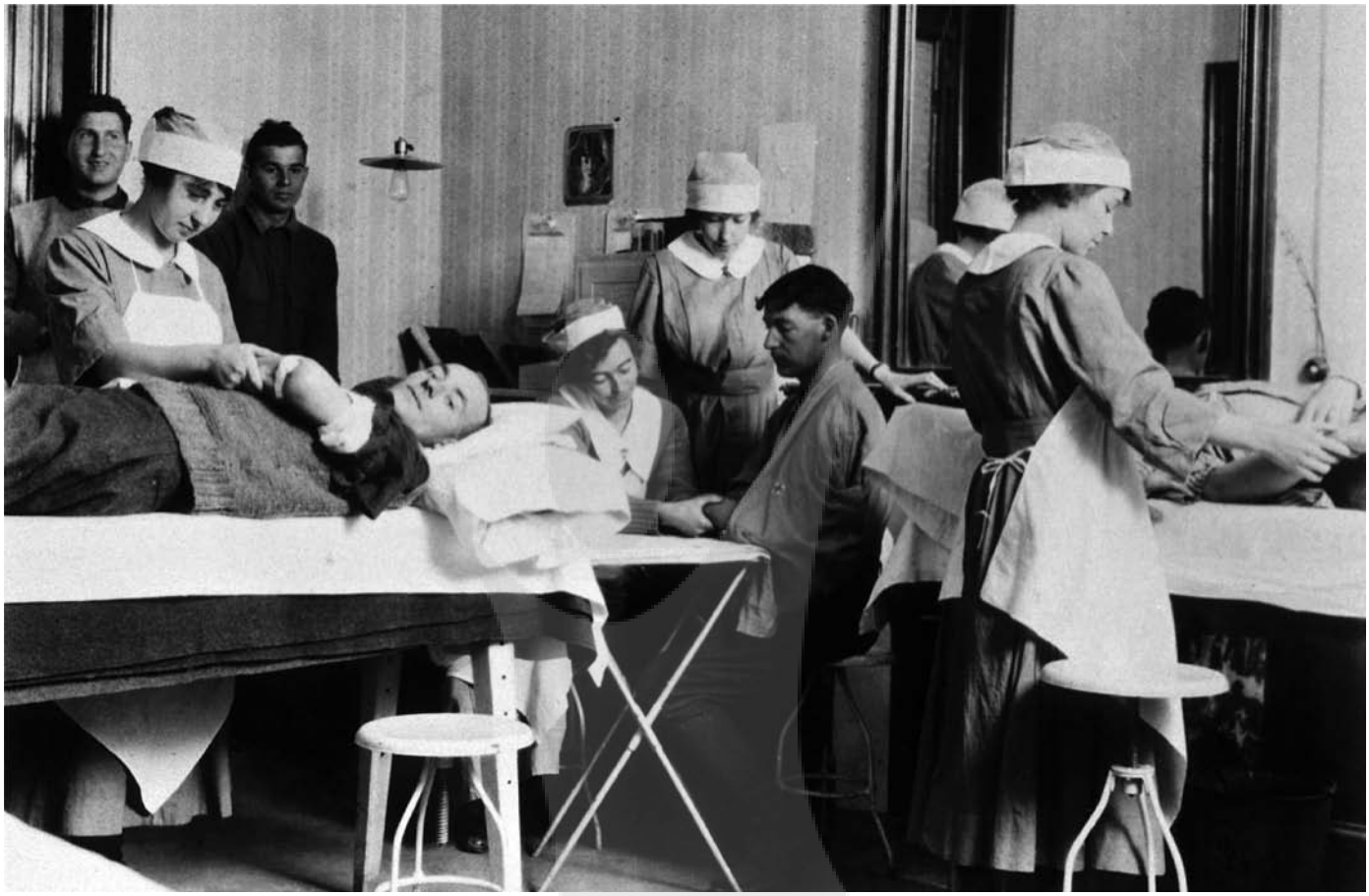


FIGURE 1.1 Reconstruction aides at work, U.S. Army Base Hospital No. 20, Chatel Guyon, France, during World War I.
Courtesy of the U.S. National Library of Medicine.

Colonel Frank C. Billings, MD (1854–1932), chief of the Division of Physical Reconstruction in the Medical Department of the U.S. Army, established separate sections for education, therapy, and clinical work (Figure 1.2). Military physicians in "reconstruction hospitals" then began treating wounded and disabled soldiers with occupational therapy (then called bedside occupations and curative workshops) and "physiotherapy" (a term indicating use of various physical methods in treatment, including heat, exercise, hydrotherapy, electrotherapy, and massage) (7). By the end of the war, therapy was provided by nearly 800 women volunteers (physical educators or nurses) trained as "reconstruction aides" under the Reconstruction Aide Program (4,6,7,10,11).

Some individuals criticized the prolonged bedside therapeutic activities provided by female reconstruction aides because they were felt to promote dependence and invalidism (12,13). However, in 1918, Billings described the work of the reconstruction aides and clearly distinguished it as superior to the types of "diversional" tasks previously employed:

> [Ward work] has consisted frequently of work not so purposeful in its character, but rather as diversional in character, in the form of knitting, in the form of basket weaving, etc. But the work which the Surgeon-General utilizes as curative in character in the general hospital for these soldiers is more purposeful than knitting, basket weaving and the like. In other words, it is of the kind and character of curative work that will look toward the training of the soldier for employment after his discharge from the Army. (14)

By the end of the war, physical reconstruction services were available in 35 general hospitals and 18 base hospitals across the country (4,15), and nearly 50,000 veterans (or about 40% of the 125,000 disabled during the war) had been treated at these facilities (16).

In 1923, Dr. F.B. Granger, who had been instrumental in developing the program for reconstruction aides in the United States and who was the first physician specializing in physical medicine to become a member of the American Medical Association (AMA) Council on Physical Therapy (9), summarized how physical therapy originated:

> With the onset of the World War the urgent need of hastening the return of the wounded to the front lines, or rehabilitating them sufficiently so that they could be

FIGURE 1.2 Colonel Frank C. Billings (1854–1932), chief of the Division of Physical Reconstruction in the Medical Department of the U.S. Army during World War I. Knopf Collection.

Courtesy of the U.S. National Library of Medicine.

> given noncombatant duty, thus presumably relieving an able-bodied man, forced the unification of [the separate treatment modalities]. The Surgeon General of the U.S. Army, at one stroke, completed their amalgamation when he defined physiotherapy as "Physical measures such as are employed under physiotherapy, including hydro, electro, mechano therapy, active exercises, indoor and outdoor games, and passive exercises in the form of massage." Thus was born modern physiotherapy. (17)

Following the war, Dr. Elliott Brackett, a Harvard-trained orthopedic surgeon, promoted the establishment of hospitals "devoted to the medical care of all men who should be returned, also planned and equipped to reinstate the disabled soldier in the industrial world and allow him to become an independent wage earner" (16). Unfortunately, interest in rehabilitative services in the military waned after the war (1).

THE 1920s: BEGINNINGS OF PROFESSIONAL ORGANIZATIONS AND FORMAL TRAINING PROGRAMS

Physical Medicine

The 1920s and 1930s saw the beginnings of professional organizational development in the nascent field of PM&R. The so-called "physical therapy physicians" (i.e., physicians practicing early forms of physical medicine) began efforts to organize themselves and vied for a voice in the AMA. Specifically, in 1923, the American College of Radiology and Physiotherapy was founded as a professional organization of physicians who used physical methods to diagnose and treat illness and disability. Samuel B. Childs, MD, a radiologist from Denver, was elected as the first president. Very soon, however, radiologists separated and developed their own organizations so that, by 1925, the organization became the American Congress of Physical Therapy. Subsequent developments included the assimilation in 1933 of the American Physical Therapy Association (whose membership comprised only physicians) and various changes in the name of the organization initially intended to clarify the distinction between physicians and nonphysician therapists using physical methods in treatment (until the present name of the American Congress of Rehabilitation Medicine was selected in 1966).

Specialty physical medicine journals also developed during this period, corresponding to the increasing professional orientation of a small group of physicians to this new area of specialization. The journal *Radiology* began publication in 1920 under the editorship of Albert Franklin Tyler, MD (1881–?), and in 1926, it was renamed the *Archives of Physical Therapy, X-ray, Radium* to reflect its expanded focus. Subsequent name changes in the journal reflected an early shift away from radiology; a later distinction between physician and nonphysician therapists utilizing physical methods in treatment; and, ultimately, a broadening emphasis on rehabilitation (until the present name of the *Archives of Physical Medicine and Rehabilitation* was selected in 1952).

Most physicians who practiced physical medicine in this era used it as an adjunct to their regular general medical practices, but starting in the mid-1920s, some physicians began devoting their careers to this area and were recognized with academic faculty appointments. The first of these was John Stanley Coulter, MD, who joined the faculty of Northwestern University Medical School in Chicago in 1926 as the first full-time academic physician specializing in physical medicine. He initiated the first continuing teaching program in physical medicine in the form of 3- to 6-month, and later, 12-month courses. He became chairman of the AMA Council on Physical Therapy (18). For the next two decades, he was a key leader in the development of educational programs for the practice of physical medicine as well as in the development of professional organizations for physical medicine.

Physical Therapy

Formal training for allied health professionals in civilian practice was not available until 1918, when the Mayo Clinic initiated a training program in physiotherapy (19). In 1920, Lieutenant Colonel Hard D. Corbusier wrote to former reconstruction aide Mary McMillan, proposing the formation of a professional society of physical therapists to "advertise to all the physicians and surgeons of the country the importance of treatment by physical means and to elevate and standardize the work and place it on a more substantial basis" (6). In 1921, McMillan organized a group of nearly 300 former reconstruction aides to form the American Women's Physical Therapeutic Association, which elected McMillan as the first president. The first issue of the association's official publication, *The P.T. Review*, was published in March 1921, and the same year McMillan published *Massage and Therapeutic Exercise*, the first textbook written by a physical therapist (10,20). The organization was renamed the American Physiotherapy Association in 1922, and in 1930 the organization was incorporated to establish educational standards for physical therapists to support regulation of physical therapy practice and to cooperate with the medical profession to establish a central registry of physical therapists (10,21).

Occupational Therapy

In 1914, George Edward Barton—a disabled architect who had benefited from care he received at a convalescent hospital—introduced the term *occupational therapy* at a meeting of the Massachusetts State Board of Insanity in Boston (22) and subsequently founded Consolation House in Clifton Springs, New York, where he provided vocational assistance and workshop activities to other disabled people (13,22–24). In 1917, Barton organized the first meeting of the National Society for the Promotion of Occupational Therapy at Clifton Springs for "the advancement of occupation as a therapeutic measure, the study of the effects of occupation upon the human being, and the dissemination of scientific knowledge on this subject" (25). In addition to Barton, the founding members included Dr. William Rush Dunton, Jr., a Maryland psychiatrist, who was responsible for the occupations program at the Sheppard and Pratt Institute and had written monographs and articles on using occupational activities as therapy, including one of the first textbooks on occupational therapy, *Occupational Therapy—A Manual for Nurses* (1915) (26,27); Eleanor Clarke Slagle, who worked with Dunton at Johns Hopkins in Baltimore and who developed a regimented treatment program ("habit training") for chronic schizophrenic patients; Susan Cox Johnson, director of occupations for the New York State Department of Public Charities; Thomas Kidner, an architect who was the vocational secretary of the Canadian Military Hospitals Commission; Isabel Newton, who was Barton's secretary; and Susan Tracy, a nurse who was a training school superintendent and instructor of occupational therapy courses for nursing students, including the first such course (in 1911) at the Massachusetts General Hospital Training School for Nurses (13,22–24,28,29). Barton became the first president (22). The organization was renamed the American Occupational Therapy Association in 1923 (22). The *Maryland Psychiatric Quarterly*, edited by Dunton, became the official organ of the National Society for the Promotion of Occupational Therapy until 1922, when the *Archives of Occupational Therapy* was first published as the official publication of the organization (13,22).

In 1929, Colonel James A. Mattison described the purposes of occupational therapy as employed at the National Home for Disabled Volunteer Soldiers:

> One of the principal aims of occupational therapy is to create morale, and to provide every opportunity for the coordination of all hospital efforts toward returning the patient to community life and economic usefulness. (30)

The first textbook in the United States concerning occupational therapy, written primarily by occupational therapists, was *Principles of Occupational Therapy*, edited by Helen S. Willard and Clare S. Spackman and first published in 1947 (31).

Speech Therapy

Speech therapy had 18th- and 19th-century antecedents—particularly in the practical treatment approaches of the elocutionists (i.e., focused on improving speaking, orating, or singing); the beginnings of aphasiology with French neurologist Paul Broca (1824–1880), German neuropsychiatrist Carl Wernicke (1848–1905), and others; and the various "methods" for treating speech impediments, mispronunciation, and articulatory disturbances among the deaf (32,33). Development of professional organizations for speech therapy in the United States began with the founding of the American Speech and Hearing Association in 1925 as the American Academy of Speech Correction (33–35). In 1927, a nomenclature committee of the American Speech Correction Association outlined and described the conditions treated by "speech correctionists" under seven major categories: dysarthria, dyslalia, dyslogia, dysphasia, dysphemia, dysphonia, and dysrhythmia (33,36).

PROFILE OF FRANK KRUSEN (1898–1973): "THE FATHER OF PHYSICAL MEDICINE"

Frank Hammond Krusen (1898–1973) is widely regarded as "the father of physical medicine," and during the 1930s and 1940s, was influential in the development of this field both in the United States and internationally (Figure 1.3) (37). Krusen graduated from Jefferson Medical College in Philadelphia in 1921, but his planned surgical career was interrupted when he developed pulmonary tuberculosis in 1924. During his convalescence at a sanitarium, he became interested in physical medicine. In particular, his own experiences and observations at this time helped Krusen

FIGURE 1.3 American physician Frank Krusen (1898–1973), "the Father of Physical Medicine."

Courtesy of the U.S. National Library of Medicine with permission of the Mayo Clinic Archives.

realize that physical deconditioning increased dependence on institutional living and eroded self-esteem. He believed that self-assurance and independence could be restored in disabled patients with appropriate physical reconditioning, vocational rehabilitation, and reintegration into noninstitutional society (38). From this point forward, Krusen worked to develop physical medicine into a scientifically based and accepted medical specialty.

On his return to Philadelphia in 1926, Krusen was appointed as associate dean at Temple Medical School, where in 1929, he started the first academic department of physical medicine in the United States (38–40). In 1930, Krusen published an undergraduate curriculum in physical medicine (41). In 1935, at the invitation of one of the founders of the Mayo Clinic, surgeon William James Mayo, MD (1861–1939), Krusen moved to the Mayo Clinic in Rochester, Minnesota, where he founded the department of physical medicine (1935), initiated the first 3-year residency program in physical medicine (1936), and developed a school of physical therapy (1938) (18,19,39). In 1941, he was promoted to professor. In 1942, during World War II, he helped train a large cadre of medical officers from the U.S. Armed Forces through 90-day intensive courses in physical medicine at the Mayo Graduate School of Medicine, with the trainees being labeled "90-day wonders" (3,15). Krusen's influence was tremendous as judged by his own contributions as well as by the number and quality of his trainees, and their roles in, and subsequent contributions to, the further development of the specialty (42).

In addition to his role in the development of clinical practice and training programs in physical medicine, Krusen was an organizational leader for the specialty during the late 1930s and through the 1940s. In 1937, with William Bierman and John S. Coulter, Krusen established the American Registry of Physical Therapy Technicians to credential physical therapists (who were conferred the title of "registered physical therapist" on passing the certifying examination) (3,38). In 1938, with a small group of other pioneering physical medicine physicians, Krusen and Coulter founded the Society of Physical Therapy Physicians (later named the American Academy of Physical Medicine and Rehabilitation) "to develop physical therapy as a formally recognized specialty," and Krusen was elected its first president (38). In 1941, Krusen wrote the first widely used textbook of physical medicine, *Physical Medicine: The Employment of Physical Agents for Diagnosis and Therapy* (43). Subsequently, Krusen played critical organizational roles in the founding and initial leadership of the Baruch Committee on Physical Medicine (1943), the American Board of Physical Medicine and Rehabilitation (1947), and the International Federation of Physical Medicine (1952).

In 1938, Krusen proposed the term "physiatrist" to designate the physician specializing in physical medicine, and further proposed that "physiatrist" should be pronounced with the accent on the third syllable (fiz ē at´ rist) to minimize confusion with "psychiatrist." The name "physiatrist" was derived from the Greek words "physics" (physical phenomena) and "iatreia" (healer or physician) (15). Later, in 1946, the AMA Council on Physical Medicine voted to support the terms "physiatrist" and "physiatry" (11). In 1961, Arthur Watkins proposed "physiatrics" as a new name for the specialty of PM&R based on Krusen's 1938 proposal, and Watkins further proposed changing the name of the American Academy of Physical Medicine and Rehabilitation to the American Academy of Physiatrics (44). However, Krusen supported maintaining the existing name of the organization because otherwise "the rest of the world wouldn't recognize us" (44).

Beginning in the late 1930s, Krusen, in conjunction with more than a dozen other "physical therapy physicians," repeatedly petitioned the American Medical Association for specialty status and an examining board for physical medicine, but controversies over certification, financing, and whether PM&R should be an independent specialty or a subspecialty delayed its successful resolution for more than a decade. Ultimately, under Krusen's leadership, the American Board of Physical Medicine and Rehabilitation was founded in 1947 and Krusen served as its first chairman (from 1947 to 1951) (39,40).

From 1943 to 1951, Krusen served as a critical leader of the Baruch Committee on Physical Medicine (later the Baruch Committee on PM&R), an activity that greatly fostered the development of physical medicine in the United States (3,18,39,45). The Baruch Committee was established by financier and philanthropist Bernard Mannes Baruch (1870–1965) in honor of his father, Simon Baruch, MD (1840–1921), to advance physical medicine through education, clinical care, and research (Figure 1.4). Dr. Ray Lyman Wilbur (1875–1949), who had been the third President of Stanford University, was the initial chairman of the Committee and Krusen served with him on the Administrative Board; Krusen was also selected as the chairman of both the Scientific Advisory Committee and the Committee on Physical Rehabilitation (3). The Baruch Committee soon recommended the establishment of teaching and research centers for physical medicine, fellowships and residencies in PM&R, the promotion of teaching and research in PM&R in medical schools, and the development of the American Board of Physical Medicine and Rehabilitation (3,46). Through the remainder of the 1940s until its disbanding in 1951, the Committee provided grant funds for fellowships, and for teaching and research programs in physical medicine at universities and medical schools. The legacy of the Baruch Committee included a marked increase in the number of medical schools teaching PM&R, a distinct increase in the number of residencies in PM&R, and more than 30 Baruch Fellows who went on to become department heads in medical schools, the military, or Veterans Administration hospitals (3).

FIGURE 1.4 American financier and philanthropist Bernard Mannes Baruch (1870–1965) shown in 1913, as chairman of the War Industries Board. Photograph by Harris & Ewing.

Courtesy of the Library of Congress Prints and Photographs Division, Washington, DC.

POLIO EPIDEMICS EXPANDED THE NEED AND ROLE FOR PM&R AMONG CIVILIANS

Although unrecognized at the time, the growing epidemics of paralytic poliomyelitis beginning in the 1890s and occurring throughout the first half of the 20th century were partly an unanticipated consequence of improved sanitation. Hygienic advances delayed exposure to polioviruses from early infancy (when protection against paralytic disease was afforded by maternal antibodies) to later in childhood or adulthood, at which time paralytic manifestations were much more likely, a phenomenon expressed memorably by pediatrician John F. Modlin, MD: "Polio . . . was the unanticipated consequence of the invention of the flush toilet and the adoption of the use of toilet paper" (47).

The first major epidemic of poliomyelitis in the United States, and the one that brought polio into national consciousness, occurred in 1916: Nationwide, there were 27,000 cases, with 6,000 deaths, almost all under 5 years of age; and a large number of the survivors were left with lifelong disabilities and, often, deformities. Although there was considerable variability from year to year, subsequent annual summer epidemics were less severe, until they began progressively increasing during the 1940s and early 1950s, with the worst epidemic in 1952 causing nearly 58,000 cases of paralytic poliomyelitis. As increasing numbers of older children and adults became affected during the 1930s and afterward, the original label of "infantile paralysis" was replaced by either the medical term "poliomyelitis" or the shorter term "polio." Because mortality was high, and because survivors were often left with severe paralysis and resulting disability, these epidemics caused widespread anxiety and fear, particularly during the summer months (48). These polio epidemics also led to major advances in respiratory management and physical therapy (49–51), and further established the role of physiatrists in the management of neuromuscular diseases, especially limb and respiratory muscle weakness, contractures, and gait disorders.

The "Iron Lung"

In 1928, following the early epidemics of poliomyelitis in the United States, industrial hygienist Philip A. Drinker (1894–1972) and physiologist Louis Agassiz Shaw, Jr. (1886–1940) at Harvard University designed an electrically

FIGURE 1.5 A U.S. Army nurse and two corpsmen attending a poliomyelitis patient in an iron lung, 1949.

Courtesy of the U.S. National Library of Medicine.

powered tank respirator to facilitate the breathing of patients paralyzed by poliomyelitis (Figure 1.5) (52). This "iron lung" was the first practical means of respiratory support, and in 1929, Drinker and pediatrician Charles F. McKhann soon demonstrated the potential of artificial respiration, using the iron lung for an 8-year-old girl with poliomyelitis who had developed respiratory failure and coma (53,54). Manufacture of these "iron lungs" began in the early 1930s and expanded in the 1940s and early 1950s, until the respirators were replaced in the late 1950s and early 1960s by more sophisticated ventilation devices. The iron lung required intensive nursing care and respiratory therapy, and a supporting hospital infrastructure. Although the iron lung saved thousands of lives, many patients, who would otherwise have died, survived with severe disabilities requiring considerable physical therapy, orthotics, and adaptive equipment.

"Sister" Kenny: An Outspoken Nurse Challenges the Orthodox Treatment of Polio

From the 1920s through at least the early 1940s, the orthodox treatment for polio consisted largely in absolute immobilization of affected limbs through splinting or the use of plaster casts (often for many months) and, subsequently, orthopedic braces (often permanent), leading to disuse atrophy, joint contractures, and lifelong disability (10,55–57). However, since 1911, an unregistered independent nurse practitioner named Elizabeth Kenny (1880–1952) had been treating patients with poliomyelitis using an alternative approach she had developed empirically in a sparsely populated backcountry area of Australia in ignorance of the prevailing orthodox treatments (58–60). Later, when she came into prominence, Kenny employed the title of "Sister," an honorific designation for a head nurse in the British system that she earned during her military service in the Australian Army Nurse Corps during World War I (60–62). "Sister" Kenny's approach to the treatment of poliomyelitis used physical methods (e.g., the labor-intensive application of moist warm wraps of heavy woollen cloth for muscle spasms, aggressive use of passive range of motion, and massage), avoidance of immobilization and bracing, and strong encouragement of functional independence, as well as early mobilization and prompt return to normal activities, coupled with confident optimism for improvement (58,59,61,63–65). Kenny later criticized the immobilization approach then in vogue, claiming that it prolonged muscle spasms, promoted joint stiffness, and prevented restoration of normal muscle action:

> My reasons for the condemnation of the principles of immobilization as generally accepted are as follows: 1. Immobilization prevents the treatment of the disease, that is, the symptoms of the disease, in the acute stage. 2. It prolongs the condition of muscle spasm and prevents its treatment. 3. It prevents the treatment for the restoration of coordination of muscle action, a serious error. 4. It promotes the condition of stiffness which according to all reports prevents satisfactory treatment for the symptoms that brought about the condition (muscle spasm) or the development of muscle power by reeducation, or re-awakening of impulse. (64)

During the 1930s, 10 Sister Kenny Clinics were established in eastern Australia, initially as "Muscle Re-Education Centres" (58). However, Kenny was not accepted by orthodox medicine in Australia, was denounced by an Australian Royal Commission in the late 1930s, and was widely criticized by orthopedic surgeons and other physicians, who charged that she understood neither the pathophysiology of the disease nor the physiology of muscle (58,59). Nevertheless, her approach was empirically successful and she developed a large popular following. In 1939, the Queensland government—in spite of the unpopular conclusions of its own Royal Commission—ordered that the Kenny treatment be made available in the Queensland public hospital system (58,59).

Kenny came to the United States in 1940, where her ideas were initially ignored or resisted until tested by Dr. Wallace Cole, chief of orthopedic surgery at the University of Minnesota Medical School and Dr. Miland Knapp, a surgeon who chaired the school's department of physical therapy (66). The Kenny methods were eventually found to reduce length of hospital stay, greatly diminish contracture formation, and improve functional recovery (66–69). As a result, with encouragement from the American Medical Association and initial funding from the National Foundation for Infantile Paralysis and other donors, a well-regarded and very successful Sister Kenny Institute (later known as the Sister Kenny Rehabilitation Institute) was established in Minneapolis in early 1942 and developed a strong affiliation with the University of Minnesota Medical School, with rotating residents and various specialist staff including physiatrists, orthopedic surgeons, neurologists,

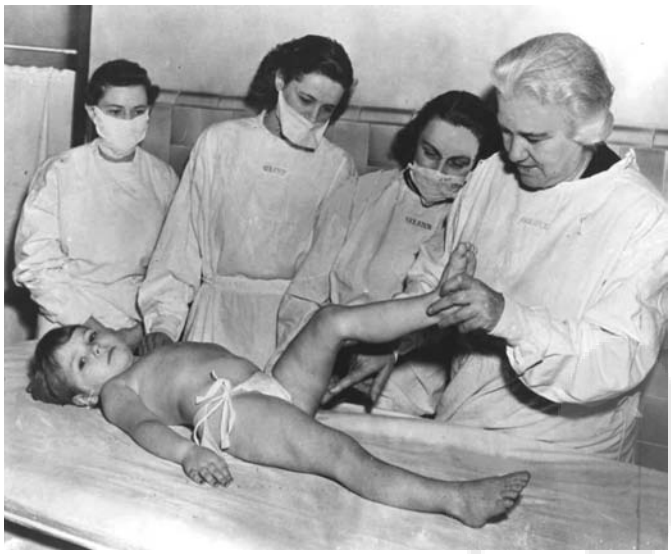


FIGURE 1.6 "Sister" Elizabeth Kenny (1880–1952), shown here demonstrating therapy techniques at the Sister Kenny Institute in Minneapolis, Minnesota, c. 1942.

Courtesy of the Minnesota Historical Society, St. Paul, Minnesota.

and others (Figure 1.6) (10,50,58,60,62). The Kenny methods were widely adopted in the United States and elsewhere in the 1940s (though not in Australia), and were taught to physical therapists and physicians at training satellites around the country. Although the controversial Kenny had her detractors, she also had numerous supporters, including Krusen of the Mayo Clinic. Kenny's approach represented a significant advance in the care of paralyzed patients and helped foster the growth of physical therapy and physical medicine (6,50,70).

> In retrospect there is no denying that Sister Kenny's ideas and techniques marked a turning point, even an about-face, in the aftercare of paralytic poliomyelitis. By determination and sheer willpower she helped to raise the treatment of paralyzed patients out of the slough into which it had sunk in the 1930s. The system which prevailed before her advent, that is, prolonged immobilization of affected limbs which in some instances led to a certain amount of calculated neglect, militated against involving the patient in early efforts to aid return of muscle function. It also eliminated the element of continued encouragement, which [is] so important as a psychological asset to rehabilitation. There was little use in exhorting a patient to exert himself physically if he was in a plaster cast. (71)

FDR, the National Foundation for Infantile Paralysis, and the March of Dimes

Franklin Delano Roosevelt (1882–1945), the most famous victim of polio, contracted the disease in the summer of 1921 and was permanently paralyzed from the waist down (57). Despite his disability, Roosevelt was later elected to the first of four terms as President of the United States in 1932 (57). From the time he became disabled, Roosevelt played an important role in the development of rehabilitation medicine, helped remove some of the social stigma from physical disability, provided inspiration and hope, promoted the idea that polio victims could become "normal" again (even if this was partly because of careful media management limiting the public's knowledge of the extent of his disability), and provided a mechanism for widespread supportive social action and philanthropy. In 1926, Roosevelt purchased a spa in Warm Springs, Georgia, to help facilitate his personal rehabilitation. By 1927, Roosevelt had founded the Georgia Warm Springs Foundation, which helped develop physical therapy and rehabilitation approaches for polio victims (50). In 1937, the Foundation was reorganized as the National Foundation for Infantile Paralysis (and officially incorporated in 1938), under the direction of Roosevelt's former law partner, D. Basil O'Connor (1892–1972). Under O'Connor's effective organizational leadership, the National Foundation began an unprecedented, innovative, and highly successful fundraising campaign utilizing an annual "President's Birthday Ball" with President Roosevelt and a variety of celebrities promoting the event and print advertisements with images of happy children ("poster children") in wheelchairs or braces and crutches asking for financial support, as well as public appeals requesting people to send dimes directly to the White House to help find a cure for polio; this latter campaign was labeled the "The March of Dimes" by entertainer Eddie Cantor (1892–1964) as a play on the words of "The March of Time" newsreel series (72–76). The first March of Dimes appeal in 1938—during the severe 1937 to 1938 recession following closely on the heels of the Great Depression of 1929 to 1934—generated extraordinary interest and raised an unprecedented $268,000 (the equivalent of over $3.4 million in year 2007 currency) (Figure 1.7) (76–78). A stunned President Roosevelt commented on the eve of his birthday:

> During the past few days bags of mail have been coming, literally by the truck load, to the White House. Yesterday between forty and fifty thousand letters came to the mail room of the White House. Today an even greater number—how many I cannot tell you, for we can only estimate the actual count by counting the mail bags. In all the envelopes are dimes and quarters and even dollar bills—gifts from grownups and children—mostly from children who want to help other children to get well. Literally, by the countless thousands, they are pouring in, and I have figured that if the White House Staff and I were to work on nothing else for two or three months to come we could not possibly thank the donors. Therefore . . . I must take this opportunity . . . to thank all who have aided and cooperated in the splendid work we are doing. (76)

The public's fear of contracting the disease, appeals to altruism with heartbreaking stories of afflicted children, requests

FIGURE 1.7 President Franklin Delano Roosevelt (1882–1945) and his former law partner Basil O'Connor (1892–1972) shown counting dimes at the White House, c. 1938.

Courtesy of the March of Dimes.

FIGURE 1.8 American virologist Jonas Salk (1914–1995). Salk developed a killed-virus polio vaccine.

Photograph taken by Yousuf Karsh (1908–2002) for *Wisdom Magazine* (Cover photograph August 1956, Vol. 1, No. 8). (Public domain photograph courtesy of Wikimedia Commons).

from admired role models (movie stars and politicians), and hope that the disease would soon be conquered were all used so effectively in the campaigns that the nonprofit National Foundation became the largest private charity in history. The National Foundation led the "first large-scale, nationwide biomedical initiative" by a charitable organization (75) and, as a result, was instrumental in subsidizing the hospital and rehabilitation costs of polio patients, funding basic and applied research concerning the causes and prevention of polio in the 1940s and early 1950s, training nurses and physical therapists in rehabilitation, sponsoring pilot programs to improve the teaching of rehabilitation medicine in medical schools in the early 1950s, and, ultimately, underwriting the Salk Vaccine Field Trial in 1954 (6,72,73,75). The National Foundation officially changed its name to the March of Dimes in 1979 (after the threat of polio in the United States had passed) (75).

The Salk Vaccine Field Trial of 1954 and Aftermath

Austrian biologist and physician Karl Landsteiner (1868–1943) and his assistant Erwin Popper demonstrated as early as 1908 that poliomyelitis was transmitted by a virus, work for which Landsteiner won the 1930 Nobel Prize in Physiology or Medicine (70,79,80). By 1948, neuroscientist David Bodian, MD, PhD (1910–1992) and colleagues at Johns Hopkins University, and virologist John Rodman Paul, MD (1893–1971) and epidemiologist James Dowling Trask, MD, PhD (1890–1942) at Yale University independently showed that there were three strains of poliovirus (rather than one) as defined by cross-protection within the same group—a finding confirmed by the more extensive work of the Committee on Typing of the National Foundation for Infantile Paralysis in 1951 (in which Jonas Salk was a participant) (70,80–85). In 1949, microbiologist John Franklin Enders, PhD (1897–1985), along with virologist Thomas Huckle Weller, MD (1915–2008) and microbiologist and pediatrician Frederick Chapman Robbins, MD (1916–2003), working at Harvard Medical School and Children's Medical Center in Boston, first cultivated the poliovirus in (nonnervous) tissue culture, for which they were later awarded the 1954 Nobel Prize in Physiology or Medicine (86–90). Also by 1954, several researchers, including epidemiologist, virologist, and pediatrician Dorothy Millicent Horstman, MD (1911–2001) at Yale, had demonstrated that there was a period of viremia preceding neurologic involvement (91,92). These important advances made possible the development, by virologist Jonas Edward Salk, MD (1914–1995), of an inactivated trivalent poliovirus vaccine, which was tested in 1954 in a huge clinical trial funded by the National Foundation for Infantile Paralysis (Figure 1.8) (74,93–96). The 1954 Field Trial of the Salk vaccine was the largest public health experiment ever, involving 1.8 million children who were labeled "Polio Pioneers" and were inoculated with either vaccine or placebo, or were simply observed (70,72,93,97,98). On April 12, 1955, at a press conference in Ann Arbor, Michigan, epidemiologist and virologist Thomas Francis Jr., MD (1900–1969), who had conducted the field trial, declared that the Salk inactivated polio vaccine was both safe and effective (93,98,99). That same afternoon, an advisory committee to the Laboratory of Biologics Control, the federal agency that was responsible for licensing biologic products, recommended that vaccine licenses be granted to five pharmaceutical companies: Eli Lilly, Parke-Davis, Wyeth, Pitman-Moore, and Cutter Laboratories.

FIGURE 1.9 Russian-American virologist Albert Sabin (1908–1993). Sabin developed a live attenuated-virus polio vaccine. From Theodore Woodward's *The Armed Forces Epidemiological Board: Its First Fifty Years* (1990).

This image is a work of a U.S. Army soldier or employee, taken or made as part of that person's official duties. As a work of the U.S. federal government, the image is in the public domain.

However, shortly thereafter, unforeseen manufacturing difficulties with clumping of material and inadequate formaldehyde inactivation of the virus during large-scale processing resulted in a huge outbreak of iatrogenic paralytic poliomyelitis (the so-called "Cutter Incident") with muscle weakness developing in 70,000 people, of whom 164 developed severe paralysis and 10 died (100–104). The litigation that followed (particularly *Gottsdanker v. Cutter Laboratories*, 1957) led to new legal interpretations (i.e., the doctrine of liability without fault) and, ultimately, the development of the National Vaccine Injury Compensation Program in 1986 (103,104). Although these legal issues dragged on for decades, the manufacturing problems were soon corrected, and with wide-scale immunization using the Salk vaccine, the rates of paralytic poliomyelitis plummeted.

In 1957, Russian-American virologist Albert Sabin, MD (1908–1993), utilizing the time-consuming process of infecting monkeys with poliovirus, developed a trivalent live attenuated polio vaccine that was then tested in Russia, endorsed by the American Medical Association in 1961 even before American field trials were begun, and, ultimately, licensed in the United States in 1963 (Figure 1.9). The Sabin vaccine soon became the polio vaccine of choice, because it (a) was less costly, (b) required minimal training to administer, (c) prevented the disease carrier state, and (d) helped prevent the spread of wild poliovirus. However, by this time, the rates of polio in the United States had dropped to 50 to 100 cases per year—down from tens of thousands per year—so the Sabin vaccine had a relatively limited impact on overall polio incidence in the United States, but it did have an important role around the world. By the early 1970s, the remaining incident cases of paralytic poliomyelitis in the United States were almost exclusively either imported cases or those caused by the vaccine itself. The Sabin oral polio vaccine was discontinued in the United States in 2000, because the continued risk of vaccine-related polio outweighed the potential benefits of a live-virus vaccine.

PROFILE OF HOWARD RUSK (1901–1989): THE FATHER OF COMPREHENSIVE REHABILITATION MEDICINE

Origins of Comprehensive Rehabilitation During World War II

In 1942, internist Howard Rusk, MD (1901–1989) (Figure 1.10) left his well-established medical practice in St. Louis to join the Army Air Corps. As Chief of Medical Services at the 1,000-bed hospital at Jefferson Barracks in St. Louis, Rusk observed both a high degree of boredom among the patients and a high rate of readmission because patients were not physically fit enough to return to active duty in their units after hospital discharge, even though they were no longer in need of acute hospitalization (1,48,105–107). Rusk, therefore, sought to engage the patients in mental and physical restorative and training activities that would utilize their time efficiently, increase their fitness, and decrease the rate of recidivism. Rusk's approach to rehabilitation emphasized treating the entire person, including his or her emotional, psychological, and social needs, and not just the illness or a specific disability. By 1943, seven special "convalescent hospitals" had been established in the Army Air Corps, with multidisciplinary staff comprising

> medical and surgical specialists, but also physical therapists, educators, athletic trainers [later called "corrective therapists" and still later called "kinesiotherapists"], occupational therapists, social service workers, personal counselors, and vocational guidance advisors—all of whom worked as a team to meet on an individual basis, the needs of the "whole man." . . . [A] broad program of rehabilitation was put into operation at each convalescent hospital, with the result that each hospital became part school, gymnasium, machine shop, psychiatric clinic, vocational guidance center, and town hall. (45)

FIGURE 1.10 Dr. Howard A. Rusk (1901–1989), the father of comprehensive rehabilitation medicine.

Courtesy of the National Library of Medicine.

Rusk's efforts were soon recognized by generals (Dr.) David N.W. Grant (1891–1964) and Henry Harley (Hap) Arnold (1886–1950), whereupon Rusk was sent to Washington, DC, in 1943 to set up similar programs for all 253 Army Air Corps hospitals (1,105,108). Rusk's novel Convalescent Training Program was highly effective in decreasing hospital readmissions, saving man-hours, and giving injured and disabled soldiers hope and purpose (Figure 1.11).

> Despite such success, many of us felt our program was grossly inadequate. The feeling became intensified when wounded boys from the battlefields began being packed into our hospitals by the planeload. Suddenly we were faced by men with broken bodies and, all too often, broken spirits. We concluded that our program was a schoolboy project in the context of what needed to be done for the severely wounded—the amputees (the double, triple, and quadruple amputees), the paraplegics and quadriplegics, the blind, the deaf, the disfigured, the emotionally disturbed. These men would need complete rehabilitation, whatever that might be—I wasn't sure. Just exactly what could be done for them? . . . It was horrible to realize that there was no precedent for rehabilitation programs on a large scale in the military. And as far as I knew, there was no extensive civilian programs either. (105)

Later, similar programs, loosely modeled after Rusk's Convalescent Training Program, were adopted by all branches of the service at the instigation of Bernard Baruch and the subsequent request of President Franklin Delano Roosevelt (1882–1945) to Secretary of War Henry Lewis Stimson (1867–1950) (1). Rusk had sought Baruch's assistance, and the letter drafted by Baruch for the President's signature became *de facto* military policy giving official standing to rehabilitation medicine:

> My dear Mr. Secretary, I'm deeply concerned about our casualties returning from overseas, as I know you are. I would like you to see that no one is discharged from service until he has had the full benefit of hospitalization, which will include not only medical care but resocialization, psychological adjustment and rehabilitation. I would like you to see that this is put in operation as soon as possible. (105)

Because of the limited rehabilitation programs available prior to World War II, and the widely held expectation at the time that disabled people could not be productive, people with strokes or other brain and spinal cord injuries received, at best, custodial care and often died within a short time (1).

> I recall someone asking me how paraplegics had lived up to that time. The answer was, except in extremely rare cases, they usually died—their life expectancy in those days was often less than a year. They got terrible bedsores, developed kidney and bladder problems, and simply lay in bed, waiting for death. It was almost the same with strokes. The old wives' tale was that you had one stroke, and then you sat around waiting for a second one, or a third one, or however many it took to kill you. If you had any kind of brain injury affecting your locomotive functions, everyone assumed your life was finished. (105)

Rusk's experience in the rehabilitation of wounded soldiers during World War II helped usher in the concept of comprehensive rehabilitation, with both utilitarian and humanitarian aims (1).

> The modern concept of "the treatment of the whole man" [developed by Rusk, himself] did not develop . . . until World War II, when rehabilitation got its biggest impetus because so many wounded survived—but survived with severe disabilities. (46)

> One of our most immediate frustrations in early 1943 was that if we discharged these wounded and disabled veterans from the service—which we had to do since they could no longer function as soldiers—we were turning them over to the Veterans Administration, which at that time was like sending them into limbo. The V.A. had no program for them. They would simply lie around getting custodial care, with nothing to do, bored to distraction, helpless, hopeless, waiting for some kind of infection or disease

FIGURE 1.11 Vocational rehabilitation posters of the U.S. Army Air Forces during World War II. Photomechanical print created by Jack Wittrup (1912–1987). Published by the Training Aids Division, 1944.

Courtesy of the U.S. National Library of Medicine.

> to carry them off. Gradually the concept of rehabilitation came to me as I found out how much really could be done for these men. In the beginning, I knew only that everything possible should be done to return them to physical and mental health. This meant finding ways for them to function despite their disabilities. First, I had to remember that this was the Air Force, that we were fighting a desperate war, and that we needed all the manpower we could find. It was immediately important, then, to make these men in some way able again. Our initial aim had to be to send them back to duty in the best possible condition and in the shortest time. If they could no longer do their previous jobs, we should help them choose jobs they could do, and then retrain them. This approach would be beneficial to the Air Force and it seemed the best for the boys themselves, too. (105)

The development of comprehensive rehabilitation in the military during World War II was truly novel and the outcomes were unprecedented (1):

> We discovered we had saved at least forty million man-hours of duty time, and that we had gotten more sick or injured men back on duty than any branch of service had done during any war in history. More important, we had prepared thousands of boys for useful roles in civilian life after the war who might otherwise have wasted away for years in veterans hospitals. And by proving the value of rehabilitation, we had made certain that the Veterans Administration, after this war, would actually rehabilitate its disabled men rather than letting them languish in bed, or die for lack of understanding and a program. It is worth noting that of the four hundred men who became paraplegics in World War I, a third died in France, another third died within six weeks thereafter, and of the remaining third, 90 percent were dead within a year. In World War II there were 2,500 American service-connected combat paraplegics, and three-fourths of them were alive 20 years later. I might add parenthetically that of these survivors, 1,400 were holding down jobs. (105)

Rusk earned a Distinguished Service Medal for his work in the U.S. military, and retired as a Brigadier General in the U.S. Air Force Reserve.

Later, in retrospect, he was struck by the irony of such progress having been made in the field of rehabilitation medicine as a result of a brutal war:

> It is paradoxical that through war, a concerted effort to annihilate man, we have learned more and better ways to preserve him. (45)

Change in Management of Disability After Stroke

As an internist prior to World War II, Rusk had been frustrated with the options available for treating patients disabled by stroke, and had felt that his own knowledge was woefully inadequate. Rethinking his prior management and discussing his career options with several former patients who had suffered from stroke reinforced Rusk's belief in the concept of comprehensive rehabilitation and gave him the determination to abandon his previous internal medicine practice and seek opportunities to develop this concept for civilian patients.

> There was so little you could do to help a stroke victim in those days that, like many other doctors, I had developed a technique in dealing with them that did no more than pacify them. I had scores of them in my practice, people who were partially paralyzed, and who, therefore, sat home all day, no longer considered fit to work, and with nothing to do but think about their condition. They would want to see me periodically for checkups, but I wanted to see them as seldom as possible. I didn't realize it at the time, but in front of such patients I was overcome by a feeling of insecurity. Deep down inside I felt guilty because I didn't know how to help them. Whenever they came into the office they wanted to talk. They would talk for an hour if you let them, while thirty other people sat in the waiting room. So I would go through the routine of taking their blood pressure . . . and prescribe a little meaningless change in their medication that would make them feel that at least something was being done. Then I'd hurry out of the room while the nurse came in to dismiss them. I didn't want to talk to them because I really didn't know what to say, and I'm sure that's always been true of most doctors everyplace . . . . If [a patient] was paralyzed . . . or disabled in some other way, there was virtually no one to whom you could send him. You could get him maybe a "nickel's worth" of physical therapy, and that was about all. Such reminiscences reinforced my determination to throw my energies into rehabilitation. (105)

Moreover, by this time Rusk had an entirely different view of the potential for rehabilitation of patients following a stroke, emphasizing what could be done, focusing on remaining abilities, and utilizing simple techniques and equipment to minimize contractures and other secondary impairments and to maximize function:

> There are a number of simple progressive procedures in the rehabilitation of the hemiplegic who suffers from one of the commonest disabilities seen in general practice. In the early stages of treatment, the following procedures should be instituted to prevent deformities: (1) footboard or posterior leg splint to prevent foot drop; (2) sandbags to prevent outward rotation of the affected leg; (3) a pillow in the axilla to prevent adduction of the shoulder, and (4) quadriceps setting to maintain muscle strength. All of these procedures are relatively simple and require no special equipment. Their use, however, will prevent crippling anatomic deformities and hasten the rehabilitation of the patient.
>
> The next procedure indicated is the institution of pulley therapy. This can be done simply with a small pulley attached to a goose neck pipe over the head of the bed, the ordinary clothes line rope being used with a 1 inch (2.5 cm) webbing for the hand loop. With the stretching and passive exercise provided by pulley therapy, the range of motion can be increased and adhesions prevented. Pulley therapy has the advantage over the usual stretching exercises that are done passively, for the patient, knowing his own pain threshold, will proceed to fully tolerated motion much more quickly. . . .
>
> [Ambulation] should be started by (1) the practice of balance in the standing position, progressing to parallel bars; (2) the teaching of a heel and toe gait to minimize clonus and to reestablish normal walking habits stressing reciprocal motion, and (3) a short leg brace, which will be needed in approximately half of all cases to correct foot drop. All of the equipment for training in ambulation is simple and readily obtained by the general practitioner. If parallel bars are not available, two kitchen chairs may be substituted. In the advanced stages of retraining, ambulation is continued with (1) instruction in crutch walking, starting usually with the alternate four point gait, and (2) teaching elevation, stressing climbing steps, curbs, stairs and ramps. Concurrently with the training in ambulation, attention should be given to retraining in the activities of self care and daily living . . . With such a program, many of the complications usually following apoplexy can be avoided and a great deal of time and ability salvaged. (109)

Not only did Rusk feel that such approaches were extremely helpful, but he also felt strongly that *failure* to provide rehabilitation to patients was a form of medical negligence:

> The physician who fails to see that those patients under his care receive the full benefits of modern methods of medical rehabilitation and retraining is in the same category as the physician who still persists in using dietary restriction alone in the management of diabetes, when insulin is available, for medical care is not complete until the patient has been trained to live and work with what he has left. (109)

Rusk later explained the potential for rehabilitation of stroke patients to colleagues at a meeting of the American College of Physicians in Boston:

> I'm talking about the two million people in this country who have suffered strokes and are now sitting around,

> waiting to die because no one is helping them to live. I'd like to tell you today about a few simple things you can do for many of these people, right in your offices, or in the home or bedside. I told them how to prevent painful hips by sandbagging the patient's leg. I told them how to sandbag a shoulder so it wouldn't become what we call "frozen" and require several weeks of painful therapy and stretching to get it back to normal. I took out some props and showed them how they could make an exercise device for arms and shoulders for stroke victims simply by using a window pulley and six or eight feet of clothesline. I pointed out that a patient could help himself more with this device than a therapist could help him because, by doing it himself, he could sense the pain threshold and therefore stretch farther than a therapist would dare to try. I talked about aphasia, the speech difficulty stroke victims suffer, which seems to me one of the most frustrating problems of all. It's like not being able to say an old friend's name, multiplied to infinity. As I talked, this time I noticed there was absolute silence in the hall, and instead of seeing people leave, I noticed that more people kept arriving until, by the end of my presentation, they were standing in the aisles. (105)

Although such information generated considerable interest, referral options were extremely limited because of the lack of comprehensive rehabilitation programs across the country.

FIGURE 1.12 American physician and rehabilitation medicine pioneer George Gilbert Deaver (1890–?).

Courtesy of the U.S. National Library of Medicine with permission of the New York University Archives.

Program for Civilian Rehabilitation

After World War II, Rusk began efforts to establish a program for civilian rehabilitation, based in large part upon what he had learned in the military (1). He initially intended to open a rehabilitation institute in St. Louis, where he had practiced internal medicine for 16 years prior to his military service, but colleagues there were not supportive.

> I can't say the idea was well received. The orthopedists, in particular, said, "We're doing all that anyway," and it was true that they had adopted some good methods of therapy. But they failed to see my point: the whole person needed rehabilitation, not just the part of him that had been damaged. They had no concept of the emotional problems which follow disability, or the problems of job placement, or the other fundamentals behind our philosophy. (105)

In 1945, Rusk joined the staff at New York University Medical School, and several wards in Bellevue and Goldwater Hospitals were designated for rehabilitation, although initially the beds were also simultaneously utilized by other services. The previously separate programs for physical and occupational therapy were combined into a new Department of Rehabilitation Medicine (3), and Rusk hired George Gilbert Deaver, MD (1890–?), from New York's Institute of Crippled and Disabled as the medical director (Figure 1.12) (3,46). Deaver had been a pioneer in rehabilitating the severely handicapped, including those with spinal cord injury, cerebral palsy, muscular dystrophy, multiple sclerosis, and rheumatoid arthritis. "At a time when these patients were being rejected and discarded as permanently disabled, Deaver was accepting of them and patiently working with them to achieve the best possible outcomes through rehabilitation" (3). Deaver made unprecedented progress in rehabilitating those with spinal cord injury to independence in self-care, crutch or brace-assisted ambulation, or wheelchair living (3,46): According to Rusk, "It was he who first taught paraplegics how to walk" (46). Deaver had also developed tools and techniques for assessing activities of daily

living (as a guide for independent living capability), crutch walking, and prevocational evaluation (3,46). By 1947, Rusk and Deaver had established the "first comprehensive, total medical rehabilitation program in any community hospital" in the United States at Bellevue Hospital in New York (109).

Despite Rusk's enthusiasm and his previous successes, his initial civilian efforts were regarded skeptically by colleagues:

> Many people, even in the medical profession, considered it foolish to spend money or effort on such a "frilly boondoggle." It wasn't that they disapproved of getting disabled people onto their feet and back into the mainstream of life; it was just that they didn't think it was possible. (105)

Nevertheless, Rusk persevered and gained the support of prominent philanthropists, including Bernard Baruch, Polish-American builder and developer Louis J. Horowitz (1875–1956) and his wife Mary Decker Horowitz (c. 1877–c. 1966), and retail innovator Bernard Feustman Gimbel (1885–1966) and his wife Alva Bernheimer Gimbel (1893–1983). In 1950, Rusk founded the Institute of Physical Medicine and Rehabilitation at New York University Medical Center. The institute opened its doors in 1951, but was initially derided as "Rusk's Folly" by former colleagues in St. Louis (108). Renamed the Howard A. Rusk Institute of Rehabilitation Medicine in 1984, 2 years after Rusk's retirement in 1982, the institute is now the largest university-affiliated center for treatment of civilians with disabilities and for research and training in rehabilitation medicine (110).

Promoting Rehabilitation Medicine

Rusk worked tirelessly, promoting the nascent field of rehabilitation and increasing public awareness of the need for rehabilitation in the spectrum of medical practice in numerous speeches and consultations across the country and around the world, in a weekly column on health issues for *The New York Times* (which Rusk continued until 1971), through influential private sector and government contacts, and through the establishment of rehabilitation training programs, which helped expand the message through various disciples (1). In 1955, Rusk founded the World Rehabilitation Fund to provide technical assistance for the development of rehabilitation programs in underdeveloped countries, as well as funding for education and training programs on prosthetics around the world, and grants for foreign physicians to study rehabilitation in the United States: "Its basic aim was to sponsor international projects which would help the handicapped and create a better understanding of them and their problems" (105). Rusk also authored several books, including *New Hope for the Handicapped* (1949) and *Living with a Disability* (1953), both with his colleague Eugene (Jack) Taylor (1913–1978); served as the senior author of *Rehabilitation Medicine* (1958); and wrote his acclaimed autobiography, *A World to Care For* (1972), which summarized the development of his concepts of comprehensive rehabilitation.

In his autobiography, Rusk explained why he got such satisfaction from working with disabled people:

> You don't get fine china by putting clay in the sun. You have to put the clay through the white heat of the kiln if you want to make porcelain. Heat breaks some pieces. Life breaks some people. Disability breaks some people. But once the clay goes through the white-hot fire and comes out whole, it can never be clay again; once a person overcomes a disability through his own courage, determination and hard work, he has a depth of spirit you and I know little about . . . . Rehabilitation is one branch of medicine in which the patient has more power than the doctor in setting the limits and possibilities. The doctor can tell the patient what to do, but only the patient himself can decide how much he's going to do. In making these decisions, patients are constantly teaching us doctors new things about rehabilitation by proving that they can do more than we had presumed possible. (105)

Rusk promoted these ideas among medical students as well:

> When I lecture to medical students, it's the brightest day of the year for me. They're so delighted to leave the basic sciences behind for an hour, so eager to heal. I always tell them: "If you can get the same satisfaction out of taking an old hemiplegic out of a wet bed, teaching him to walk, to speak so he can be understood, to take care of himself, getting him to the point where he can live a non-institutional life, perhaps getting him a job, and get the same satisfaction as from making some fancy diagnosis of an arcane disease that you may see once in a lifetime, then you'll make a good doctor. Like it or not, if you go into general medicine, 80% of your patients will have either a chronic or a psychosomatic sickness. (108)

Rusk emphasized that physical disability could be accommodated and that through vocational rehabilitation, many disabled people could live productive lives and be valuable members of the workforce:

> When you work with a handicapped person, you've got to think of his abilities more than his disabilities. You've got to remember that our society doesn't pay for physical strength. We now have machines to do the heavy labor. Our society really pays for just two things, the skill of your hands and what you have in your head. (105)
>
> The disabled, if properly placed and trained, are good workers with a better production rate, lower accident and absentee rates, and a labor turnover 10 times less than that of normal workers. (110)

In 1955, Rusk received a Christmas card from Adlai Stevenson containing what has been attributed to be the personal prayer of an unknown Confederate soldier in the Civil War (46):

> I asked God for strength, that I might achieve
> I was made weak that I might learn humbly to obey . . .
> I asked for health, that I might do greater things
> I was given infirmity, that I might do better things.
> I asked for riches, that I might be happy
> I was given poverty, that I might be wise . . .
> I asked for power, that I might have the praise of men
> I was given weakness, that I might feel the need of God . . .
> I asked for all things, that I might enjoy life
> I was given life, that I might enjoy all things . . .
> I got nothing that I asked for
> —but everything I had hoped for
> Almost despite myself,
> my unspoken prayers were answered.
> I am among all men, most richly blessed!

Rusk's disabled patients found personal meaning in this prayer, as did their families, so much so that the father of one young patient had the prayer cast in bronze. The prayer that the boy's father cast in bronze now hangs on the wall in the lobby of the institute Rusk founded (46). The prayer continues to be widely reproduced, and is sometimes referred to as the "Prayer of the Disabled."

Rusk closed his autobiography with a quote from French chemist and microbiologist Louis Pasteur (1822–1895), emphasizing the patient's role in rehabilitation, and in Pasteur's particular case, his successful rehabilitation following a serious stroke:

> Ultimately, the success of all rehabilitation depends on the patient himself . . . I can never forget a philosophical quotation that serves as a constant reminder of this truth: "I hold the unconquerable belief that science and peace will triumph over ignorance and war, that nations will come together not to destroy but to construct, and that the future belongs to those who accomplish most for suffering humanity." Those words were spoken by the great 19th-century scientist Louis Pasteur. Few people know that he suffered a serious stroke when he was in his forties . . . He rehabilitated himself—working to the age of seventy three—and many of his greatest scientific achievements came after his stroke. Pasteur's words express what anyone working in this field must feel. To believe in rehabilitation is to believe in humanity. (105)

Rusk never stopped promoting the concept of rehabilitation. As he noted in 1969:

> We who have dedicated our lives to rehabilitation medicine must be not only practitioners but teachers, crusaders, and zealots. The stakes are high, not only for the welfare of the disabled, but also for the future of world understanding . . . . If we have the courage and strength and the spirit, this program of rehabilitation medicine will never die but will continue to grow and flourish for the benefit of all mankind. (45)

Rusk received many awards and honors, including three Lasker Awards, the first an Albert Lasker Public Service Award in 1952 "for his pioneering work in the service of the physically disabled and as distinguished rehabilitation mentor to the world," the second an Albert Lasker Award given by the International Society for the Rehabilitation of the Disabled in 1957, and the third an Albert Lasker Medical Journalism Special Award in 1959 "for his editorial leadership in advancing medical research and public health programs in his weekly columns in the *New York Times*" (111,112). In 1966, Rusk was recognized by the American Congress of Physical Medicine and Rehabilitation with a gold medal bearing the inscription: "Physician, teacher, author, inspiration to patients and disciples and a prime mover in the development and spread of medical rehabilitation throughout the world" (111).

In 1981, in the "Year of the Disabled," Rusk—then 80—was nominated for the Nobel Peace Prize. At that time, a reporter for the American Medical Association interviewed Rusk, who was still actively promoting comprehensive rehabilitation.

> Although some people, Ronald Reagan among them, call Howard Rusk "The Father of Rehabilitation Medicine," he declines that honor. "Minnesota's Dr. Frank Krusen deserves that title," he says. "He was far ahead of me. He succeeded in getting the AMA to recognize physical medicine as a specialty when most doctors made no bones about brushing it off as a 'social service boondoggle.'" Rusk will admit, however, to being "father, midwife, and pediatrician" to the modern concept of rehabilitation, the radical who argues that physicians should treat the "whole person. Not just the ring finger or toe." . . . Before World War II, physiatrists were concerned almost exclusively with physical and electrical modalities of treating neuromusculoskeletal disease. Under Howard Rusk, rehabilitation medicine has blossomed into a multidisciplinary, in-hospital training program. (108)

Despite Rusk's statement to the contrary, many of his colleagues continued to apply that label to him (3), and to this day the Association of Academic Physiatrists continues to label Rusk the "Father of Rehabilitation Medicine" (and Krusen the "Father of Physical Medicine") (11).

The fully formulated definition of rehabilitation by Rusk, the acknowledged father of comprehensive rehabilitation medicine, is worthwhile recounting:

> Rehabilitation is the restoration of the handicapped to the fullest physical, mental, social, and economic usefulness of which they are capable. Frequently, it has

> been called "the third phase of medicine"—following preventive medicine, and curative medicine (and surgery). In contrast to "convalescence, wherein the patient is left alone to rest while time and nature do their cures," medical rehabilitation is a dynamic concept—an active program. The first objective of medical rehabilitation is to eliminate the disability, if that is possible; the second is to reduce or alleviate the disability to the greatest possible degree; and the third, to retrain the person with a residual physical disability "to live and to work within the limits of his disability, but to the hilt of his capabilities." (46)

At the time of renaming of the Institute of Rehabilitation Medicine as the Rusk Institute in 1984, Rusk noted that he used "the phenomenon of hope" to train people "not just within the limits of their ability, but up to the heights of their latent ability—to help them live the very best lives possible with what is left" (110). Rusk's framework and focus on treating the "whole person" has been the basis of subsequent programs and developments in the field, and has been incorporated into definitions of the field used by major rehabilitation organizations (11).

EVOLVING CONCEPTS OF DISABILITY AND REHABILITATION SINCE THE 1960s

There have been three fundamentally different approaches to modeling disability: the medical model, the social model, and, more recently, various bio-psycho-social models that incorporate features of both the medical and social frameworks (113–116). The medical model of disability

> views disability as a feature of the person, directly caused by disease, trauma or other health condition, which requires medical care provided in the form of individual treatment by professionals. Disability, on this model, calls for medical or other treatment or intervention, to "correct" the problem with the individual. (116)

This medical framework was the foundation of many of the disability-related programs in the United States until the Americans with Disabilities Act (ADA) was passed in 1990:

> The [medical] model defines disabling conditions as principally the product of physical and mental impairments that constrain performance. Influenced by this view, health and social agencies provide a mix of services that, for the most part, categorize affected individuals as permanently ill and incapable of meeting their own needs. Therefore, the problems that disability-related programs seek to address are often viewed as inherent to the individual and as independent of society. (115)

People with disabilities, however, have championed the "demedicalization" of disability, and have argued for recognition that disability is, in large measure, the result of a social environment that does not address the needs of those with physical or mental limitations.

> The independent-living and disability-rights movements blame adherence to the medical model for the creation of disability-related programs that foster dependence rather than personal autonomy. Members of these movements correctly argue that disability is the result of a dynamic process involving complex interactions among biological, behavioral, psychological, social, and environmental factors. (115)

The social model of disability, in contrast, "sees disability as a socially-created problem and not at all an attribute of an individual" (113,116). Within this framework, "disability demands a political response, since the problem is created by an unaccommodating physical environment brought about by attitudes and other features of the social environment" (116). Particularly since the 1970s, there has been greater awareness of the social and environmental contributors to disability, facilitated in part by the advocacy of disability rights groups and by court cases and protest actions initiated by disabled individuals seeking basic civil and human rights (117). These actions helped bring about greater societal acceptance of disability, a shift in the federal government's official objectives to include equal opportunity, independent living, integration, and full participation for all citizens (i.e., a shift "from charity to rights") as well as the most comprehensive disability rights legislation in history, the ADA of 1990 (117). The ADA included provisions prohibiting employers from discriminating against a disabled person in hiring or promotion if the individual is otherwise qualified for the job, and mandating that businesses make "reasonable accommodations" for disabled workers including job restructuring and modification if required; that federal, state, and local governments and programs be accessible; that public transportation be accessible to handicapped people; and that privately operated public accommodations (e.g., restaurants, hotels, and retail stores) make "reasonable modifications" to ensure accessibility.

Both the medical and social models have value, and both can encourage communication among professionals across different disciplines, facilitate understanding of patients' problems, and help guide efforts to improve functioning of people with disability. Since the 1960s and 1970s, models of disability and rehabilitation have been developed and refined integrating aspects of both the medical and social frameworks into more balanced bio-psycho-social models (113–116,118–124). These models specifically acknowledge that "whether a person performs a socially expected activity depends not simply on the characteristics of the person but also on the larger context of social and physical environments" (115). As a result, such models help to "set the rehabilitation agenda clearly in a social context while still recognizing that disease has an important influence on patients' levels of physical activity and social participation and on the process of rehabilitation" (125). Such models also

extend "the boundaries of rehabilitation—from the few conditions where recovery is expected to any condition in which someone experiences disability or handicap secondary to (or as part of) illness" (125).

Unfortunately, the terminology employed in these models has changed over the years, making comparisons difficult and hampering understanding. The term "disability" has variably referred to dysfunction at the level of the person, dysfunction owing to an inadequate social and physical environment, or an entire spectrum of dysfunction affecting organs and organ systems, the person, and the person's interaction with his or her social and physical environment. In the United States and other countries, there has been a movement away from the use of the word "handicap" (115,126).

The World Health Organization's Impairments-Disabilities-Handicaps Framework (1980)

In 1980, the World Health Organization (WHO) introduced the *International Classification of Impairments, Disabilities, and Handicaps (ICIDH)*—a tool for the classification of the *consequences* of disease as a complementary framework for the *International Classification of Diseases (ICD)* (122,127). ICIDH defined the terms "impairment," "disability," and "handicap," and provided a preliminary classification and grading scale for each based on a conceptual framework developed initially in the 1970s by epidemiologist Dr. Philip H.N. Wood (1928–2008) of the University of Manchester Medical School in Manchester, England (122,127). Impairment was considered to represent "exteriorization" of a pathological state (disease), that is, an organ-level disturbance evident through symptoms or signs. Disability was considered "objectification" of impairment, a person-level restriction or lack of ability to perform a normal activity such as personal care or walking. Handicap was considered to represent "socialization" of a disability or impairment: a social disadvantage for an individual that limits or prevents fulfillment of a normal social role such as self-sufficiency. Under this framework, **disease → impairment → disability → handicap**.

ICIDH listed the goals for intervention as they pertain to disability:

1. *Prevention*
2. *Enhancement* (e.g., when activities can be performed unaided but only with difficulty)
3. *Supplementation* (e.g., when activities can be performed only with aid, including the assistance of others)
4. *Substitution* (i.e., when certain activities cannot be performed even with aid) (122).

Under this framework, rehabilitation focuses on the latter three categories (i.e., enhancement, supplementation, and substitution) to minimize handicap.

In many ways, the initial WHO formulation relied heavily on a medical model of disability (115,116), even though it recognized that social factors were inherent in what it called "handicap" (122). This approach resulted in charges that ICIDH promoted the "medicalization" of disability and failed to adequately address the major impact of social and environmental factors (115,121).

The Institute of Medicine's "Disabling Process" Framework (1991)

In a 1991 report of the Institute of Medicine (IOM) titled *Disability in America*, the components of the "disabling process" were refined from those initially described by sociologist Saad Z. Nagi of Ohio State University in the 1960s (115,119–121). Under this framework, the disabling process has four major components: pathology, impairment, functional limitation, and disability, with the usual (although not universal) progression being **pathology → impairment → functional limitation → disability**.

There are exceptions to this typical progression:

> Although [the model] seems to indicate a unidirectional progression from pathology to impairment to functional limitation to disability, and although a stepwise progression often occurs, progression from one stage to another is not always the case. An individual with a disabling condition might skip over components of the model, for example, when the public's attitude toward a disfiguring impairment causes no functional limitation but imposes a disability by affecting social interaction. Also, the effects of specific stages in the model can be moderated by such interventions as assistive devices. Similarly, environmental modification (e.g., elimination of physical obstacles and barriers) is an important form of disability prevention . . . . (115)

There are clearly overlaps and differences between the IOM model and the earlier WHO model (122). In the IOM model, *pathology* concerns the abnormal interruption or interference of normal bodily structures or processes because of factors (e.g., disease, infection, trauma, and genetic defect) operating at the molecular, cellular, or tissue level. *Impairment* concerns the loss or abnormality of a mental, physiological, or biochemical function at the organ or organ systems level. A *functional limitation* is the impaired ability or inability to perform a specific task at the level of the whole organism, such as walking or climbing a flight of stairs. A *disability* is a limitation in performing roles and tasks expected of an individual within a social and physical environment—an abnormal gap between the individual's capabilities and the environmental and societal demands.

In the IOM model, the amount of disability a person experiences is directly linked to the "quality of the surrounding environment—for example, whether appropriate and adequate care is accessible and whether a social support network is in place" (118). Thus, a major focus of rehabilitation is minimizing disability by physical and social environmental modifications so that an individual can participate fully in society.

Although to some degree a mixed bio-psycho-social model, the IOM framework is based heavily on a social model of disability:

> Disability is the expression of a physical or mental limitation in a social context—the gap between a person's capabilities and the demands of the environment. People with such functional limitations are not inherently disabled, that is, incapable of carrying out their personal, familial, and social responsibilities. It is the interaction of their physical and mental limitations with social and environmental factors that determines whether they have a disability. Most disability is thus preventable. (115)

Further, the IOM report correctly emphasized that disability prevention can be directed at any of the stages of the disabling process. Even at the disability stage, "efforts can focus on reversal of disability, restoration of function, or prevention of complications (secondary conditions) that can greatly exacerbate existing limitations or lead to new ones" (115). However, the focus of disability prevention was placed heavily on social and environmental modification:

> [A]lthough disability can be prevented by improving the functional capacity of the individual—the traditional aim of rehabilitation—this is not the only or perhaps even the most effective method. Disability can be prevented by changing societal attitudes that now restrict employment opportunities for persons with functional limitations, by modifying the buildings in which the people work, or by providing accessible modes of transportation (all of which are components of the ADA). (115)

The IOM's "Enabling–Disabling Process" Framework (1997)

In 1997, the IOM published a report titled *Enabling America* as a follow-up to and revision of its previous *Disability in America* report from 1991 (115,118). The 1997 report revised the earlier "Disabling Process" model to formally recognize that the focus of rehabilitative efforts is to assist the individual in reversing the disabling process through an "enabling process":

> *[R]ehabilitation* is the process by which physical, sensory, and mental capacities are restored or developed in (and for) people with disabling conditions—reversing what has been called the disabling process, and may therefore be called the *enabling process*. This is achieved not only through functional changes in the person (e.g., development of compensatory muscular strength, use of prosthetic limbs, and treatment of posttraumatic behavioral disturbances) but also through changes in the physical and social environments that surround them (e.g., reductions in architectural and attitudinal barriers). (118)

A person without disability is considered to be "fully integrated into society" and has access to social opportunities (e.g., education, employment, and parenthood) and physical space, whereas a person with a potentially disabling condition has increased needs that can manifest as a true disability if the social and physical environment are inadequate for these needs. The enabling (or rehabilitative) process attempts to counteract the disabling process by functional restoration and environmental modification.

The WHO's Functioning-Disability-Health Framework (2001)

The initial version of ICIDH promulgated by the WHO in 1980 was widely adopted around the world and was very influential in stimulating research as well as discussion of the best framework for considering disability. Beginning in 1995, ICIDH underwent an exhaustive revision process, with comments from more than 80 countries, field tests in 42 countries, and input from scientists, disability groups, and other nongovernmental organizations. The culmination of this revision process was the publication of the *International Classification of Functioning, Disability and Health* (ICF) in 2001 (123,124).

In a shift from the previous WHO formulation, ICF emphasized health and functioning, rather than disability:

> Previously, disability began where health ended; once you were disabled, you were in a separate category. We want to get away from this kind of thinking . . . . This is a radical shift. From emphasizing people's disabilities, we now focus on their level of health. ICF puts the notions of "health" and "disability" in a new light. It acknowledges that every human being can experience a decrement in health and thereby experience some disability. ICF thus "mainstreams" the experience of disability and recognizes it as a universal human experience. By shifting the focus from cause to impact it places all health conditions on an equal footing allowing them to be compared using a common metric—the ruler of health and disability. (116)

"Functioning" in the ICF framework is specifically structured around two broad components: (a) body functions and structure; and (b) activities and participation (i.e., involvement in a life situation). Further, participation can be viewed from either a performance perspective (i.e., what an individual does in the current environment) or a capacity perspective (i.e., what an individual can do in an optimized environment). The discrepancy between capacity and performance, the capacity–performance gap, suggests what could be changed in the current environment to improve performance (128).

ICF is based on a bio-psycho-social model that integrates medical and social frameworks of disability from earlier models:

> Disability is always an interaction between features of the person and features of the overall context in which

> the person lives, but some aspects of disability are almost entirely internal to the person, while another aspect is almost entirely external. In other words, both medical and social responses are appropriate to the problems associated with disability; we cannot wholly reject either kind of intervention . . . . [In] ICF disability and functioning are viewed as outcomes of interactions between health conditions (diseases, disorders and injuries) and contextual factors. Among the contextual factors are external environmental factors (e.g., social attitudes, architectural characteristics, legal and social structures, as well as climate, terrain, and so forth); and internal personal factors . . . . (116)

Health conditions (i.e., diseases, disorders, and injuries) lead to impairments (i.e., problems in body functions and structure) that may be associated with activity limitations (i.e., difficulties in executing activities), and/or participation restrictions (i.e., problems with involvement in life situations). Thus, a stroke (a health condition) can cause hemiparesis (an impairment), which is associated with impaired mobility (an activity limitation), and which may cause inability to use mass transit, find a job, and so on (participation restrictions). Under this framework, the impairments, activity limitations, and participation restrictions are different categories subsumed under the broad umbrella of "disability." This spectrum of disability is dependent on further interactions with the underlying health condition, and also with contextual factors, including environmental and personal factors. The ICF framework can also be linked to different treatment, rehabilitation, and social/environmental interventions and prevention approaches (116).

EVOLUTION OF STROKE REHABILITATION

In the late 19th and early 20th centuries, most medical investigations concerning stroke dealt with clinical phenomenology, pathology, clinical–pathologic correlation, and pathophysiology. At this time, very little was attempted as far as retraining or rehabilitation of stroke victims was concerned. Although a few scattered prophets of rehabilitation concepts can retrospectively be identified during this period, they made relatively little impact and their proposed treatments were, at best, haphazardly employed (129,130).

Some of the antecedents of rehabilitation available in the early 20th century included, for example, the tedious repetition of reading, spelling, and repeating words for aphasia; passive movement of severely paralyzed limbs or programs of exercises for less severe paralysis; various orthotic and assistive devices such as splints to prevent contractures, light braces for support, canes (Figure 1.13) (131–135), crutches (Figure 1.14) (131–135), and wheelchairs; attempts to use electrical stimulation to facilitate recovery or prevent muscle wasting; and various surgical procedures to try to limit contractures or spasticity (129,130). Even in the 1950s, as noted by Barrow and Metts (1986), the prevailing attitude was one of therapeutic nihilism born of hopelessness, compounded by a lack of resources and trained staff:

> As late as the mid '50s, the attitude of both doctors and families of patients with a completed stroke was one of hopelessness. The patients were placed in a nursing home or in a back room, usually at complete bed rest, and they were waited on and pampered as invalids. Under these conditions, the patients usually deteriorated rapidly and complications of decubitus ulcers, muscle spasms, atrophy, and infections were frequent. Other factors of importance at this time were the lack of physical therapy departments in the hospitals . . . and the unavailability of outpatient physical therapy resources. Even the rehabilitation facilities such as Warm Springs, Georgia, had little activity in the field of stroke rehabilitation. (130)

Rehabilitation of stroke victims was not systemically developed until the second half of the 20th century (129,130). In the 1970s and 1980s, the stroke rehabilitation team approach began to develop and spread; stroke units, sometimes employing a seamless transition between acute care and rehabilitation, were developed in larger hospitals in urban areas; and outpatient rehabilitation resources were developed including services provided by health departments, visiting nurse associations, free-standing day care centers, and hospital-associated and independent physical therapy practices (130). The 1970s and 1980s also saw the beginning of an explosion in stroke rehabilitation research, with an exponential escalation in the use of randomized trials of stroke rehabilitation therapies, particularly since the 1990s (136). Both the total number of journal articles and the number of journal articles reporting the results of randomized clinical trials have grown exponentially, although the rate of growth for randomized trials of stroke rehabilitation has been greater since the 1970s (DJ Lanska, unpublished analyses, 2007). Although spontaneous recovery accounts for most of the improvement in functional ability following stroke (137), a growing body of evidence since the 1990s supports a modest and marginal, but clinically important, benefit of stroke rehabilitation, generally for patients with, at most, moderate disability (138–143).

Organized Inpatient Multidisciplinary Stroke Rehabilitation

Since the 1970s, and particularly since the 1990s, it has become clear that organized inpatient multidisciplinary rehabilitation in the postacute period provides clinically important benefits (138–143). Most data supporting the clinical benefits of inpatient stroke rehabilitation are based on studies of comprehensive stroke units (that provide acute stroke care and rehabilitation) or rehabilitation stroke units (dedicated to rehabilitative care of postacute patients with stroke), rather than the more common mixed rehabilitation

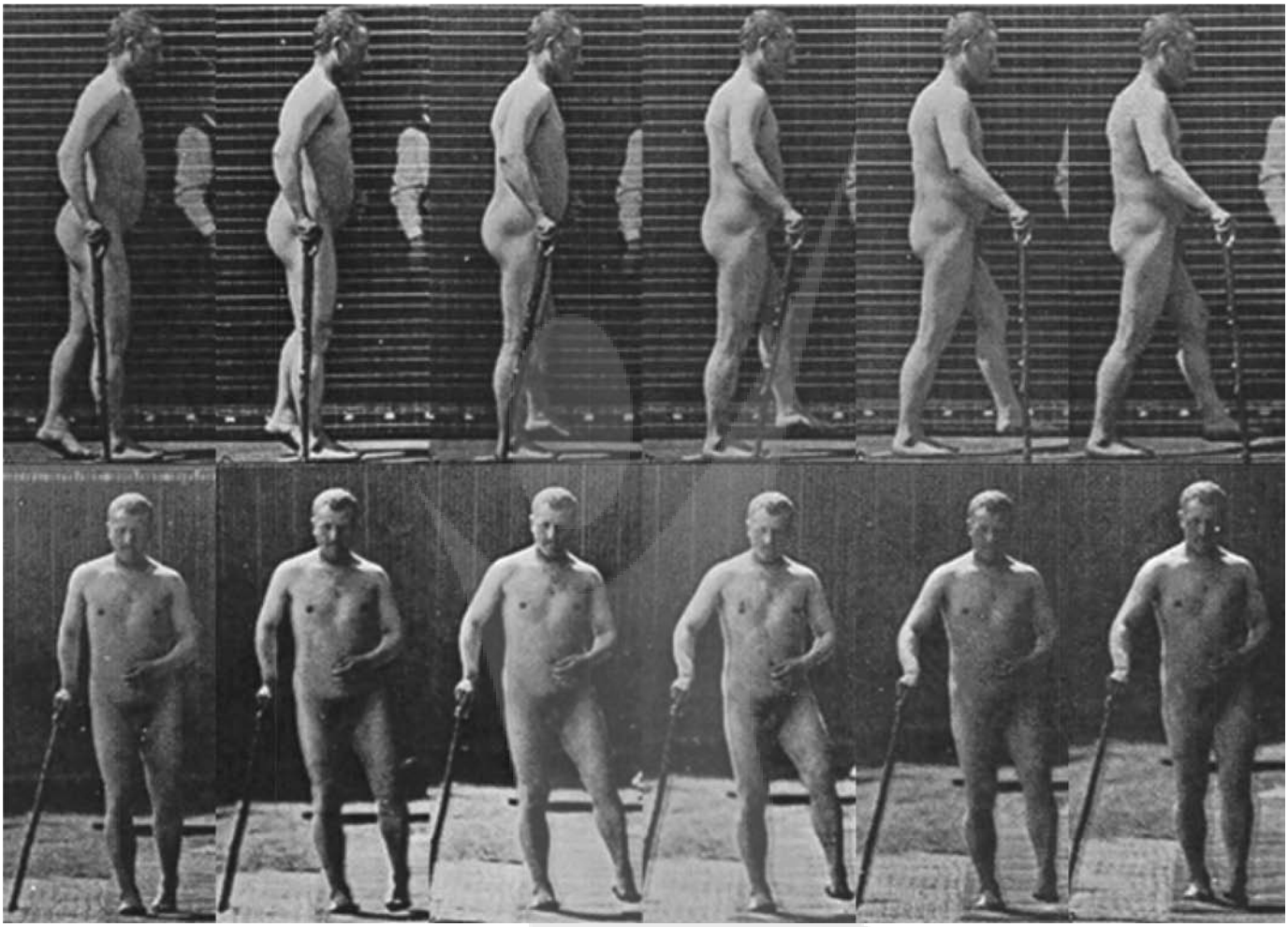


FIGURE 1.13 In the late 1870s and 1880s, prior to the development of movie cameras or projectors, American photographer Eadweard Muybridge (1830–1904) photographed sequential images of people and animals in motion, using arrays of sequentially triggered single-image cameras. In 1885, Philadelphia neurologist Francis Dercum (1856–1931) collaborated with Muybridge at the University of Pennsylvania. This figure shows sequential images of lateral and frontal views from a portion of Muybridge's "Plate 552. Spastic, walking with cane" (*Source*: From Ref. 133). This sequence shows a man with a dense spastic left hemiparesis with the arm held in a flexed posture. As noted by Dercum, "the paralyzed leg is quite stiff, little or no flexion taking place at the knee . . . ." Circumduction of the left leg (seen especially on the frontal views) is quite prominent, with the leg first swinging outward during forward motion and then returning toward the midline in an arc. Notice as well, the equinovarus deformity, or as Dercum commented, "the exaggeration of the normal tendency of bringing the outer edge of the foot to the ground in advance of the sole" (*Source*: From Refs. 131, 132, and 133).

units (that provide stroke rehabilitation in a mixed rehabilitation setting) (142). Stroke patients who receive inpatient rehabilitation provided by a coordinated multidisciplinary team are more likely to recover the ability to perform activities of daily living, more likely to return to the community, and less likely to die—results that are fairly robust in different meta-analyses and across recent controlled trials (140,144–151). A Danish population-based study comparing two communities—one where care was provided in a dedicated comprehensive stroke unit with both acute care and rehabilitation care, and the other in which care was provided on general medical and neurologic wards—found that stroke unit care reduced the length of hospital stay by 30%, reduced the risk of discharge to nursing home by 40%, and reduced the relative risk of death by 50% (140). In a systematic review of 9 trials recruiting 1,437 patients, Langhorne and Duncan found that for every 100 patients who received organized inpatient multidisciplinary rehabilitation, 5 more returned home in an independent state compared to those who do not receive such care (141). Functional, independence, and survival benefits to those who underwent early multidisciplinary stroke rehabilitation after stroke are sustained even 5 to 10 years after stroke (152–156). Patients with moderate or severe strokes appear to benefit the most (150).

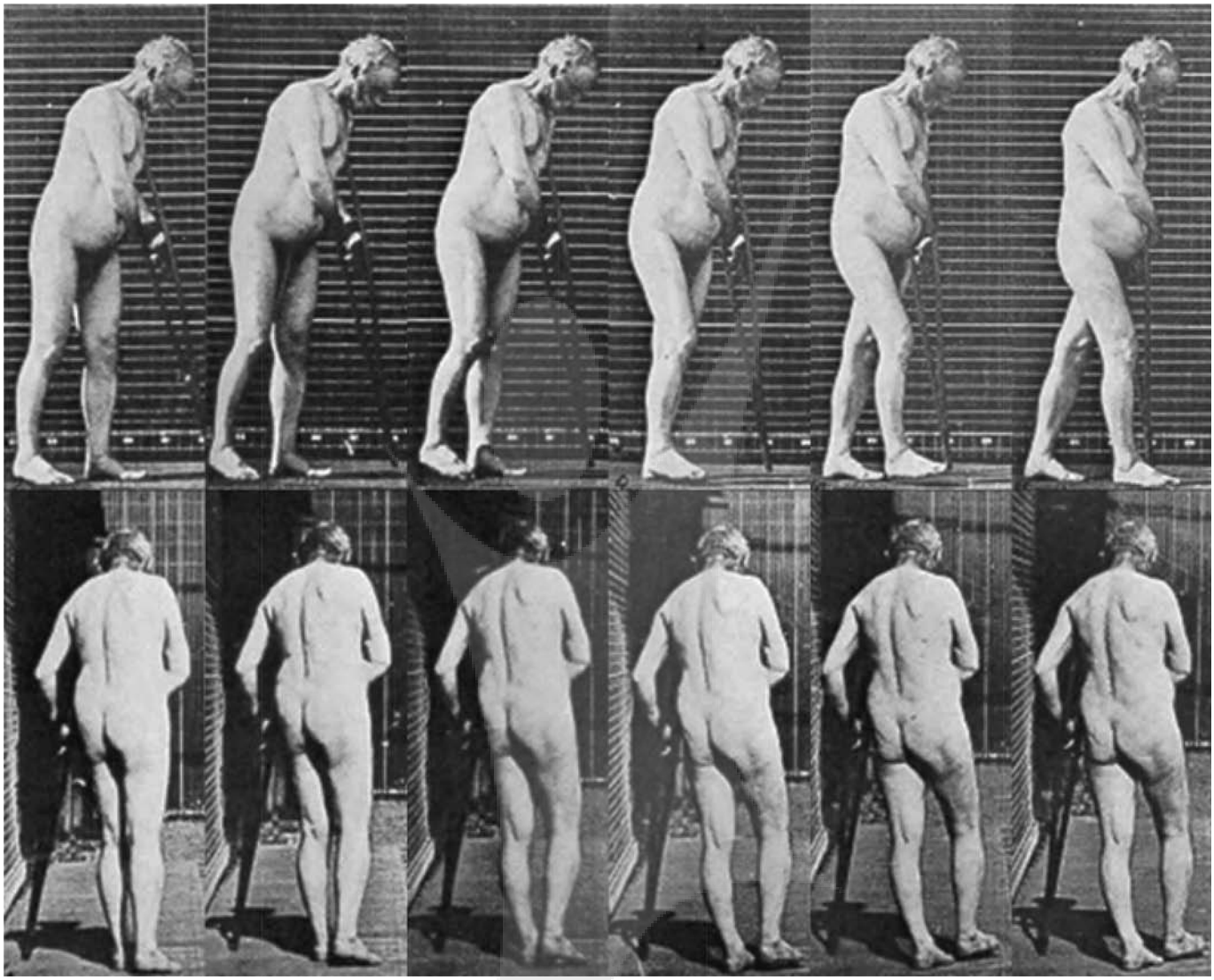


FIGURE 1.14 Sequential images of lateral and posterior views from a portion of Muybridge's "Plate 547. Spastic, walking with crutch" taken in 1885 (*Source*: From Ref. 134). This shows an elderly man with a dense spastic right hemiparesis with the arm held in a flexed posture while using a crutch to walk. As noted by Dercum, "the paralyzed leg is quite stiff, little or no flexion taking place at the knee . . . [The foot is] raised from the ground by the enormous swaying of the trunk toward the sound side, to which additional support is given to receive the sway by means of the crutch." See the legend for Figure 1.4 for further details (*Source*: From Refs. 131, 132, and 133).

Even where evidence supports a clinical benefit of stroke rehabilitation, it has generally been unclear which specific factors, including which therapies or combinations of therapies, among the entire package of individualized treatments for a given patient are most important for providing benefit (142,157–159). Although data supporting the value of individual team members in the multidisciplinary team are limited, most authorities and clinical care guidelines have advocated a broad team composition, including physicians, nurses, physical therapists, occupational therapists, speech therapists, and social workers (140). Although available studies are limited, the intensity of rehabilitation services is a modest predictor of recovery among stroke patients (151,160–164), as is, particularly, an early start to intensive treatment (158,159). It has also been unclear to what extent findings of randomized clinical trials could be generalized to the routine clinical setting: the limited available data suggest that the routine clinical rehabilitation setting can reproduce the benefits of stroke rehabilitation units in controlled trials and meta-analyses, but the magnitude of benefit is smaller outside of the formalized experimental setting (165). Inpatient rehabilitation is also expensive, and the limited available cost–benefit analyses have not strongly supported the cost-effectiveness of inpatient stroke rehabilitation overall (166–168), making it imperative to carefully select patients who will benefit most from such intensive care (169), and also to identify the least expensive care settings that will provide maximum clinical benefit to individual patients (170).

Clinical Pathways

Integrated care pathways have not been shown to improve the outcome of inpatient stroke rehabilitation (171–178). In fact, care pathways for rehabilitation programs have most often resulted simply in decreased patient satisfaction (171–174,178), and some studies have actually reported slower recovery and lower quality of life among patients receiving rehabilitation as part of an integrated care pathway as opposed to conventional multidisciplinary rehabilitative care (171,175). As noted by Teasell, "This apparent paradox may signify the importance of using evidence or guidelines to assist rehabilitation clinicians in individualizing the rehab of stroke patients as opposed to a 'one size fits all' approach" (178). Furthermore, despite potential benefits, many clinical pathway programs for acute or rehabilitation care of stroke fail because of inadequate planning and implementation (173,174). Effective implementation of such programs requires strong administrative and medical staff leadership, active participation of all clinical disciplines involved in the rehabilitative care of patients on the pathway, provision of regular feedback to clinicians, sufficient resources, improved (and often more detailed) documentation, incorporation of the entire rehabilitation period of care into the pathways, integration with ongoing quality and utilization management programs, and periodic evaluation and modification (173,174).

Specific Therapies

Based on expert opinion and limited controlled trial data, physical therapy is modestly beneficial for stroke patients (159,164,179,180). However, there continues to be considerable variation in the beliefs (181) and treatment approaches (182,183) of physical therapists concerning the treatment of stroke patients, in part a function of the treatment approach in vogue when the physical therapists were trained (184). Particularly since the 1950s, several different physical therapy approaches have been developed and applied in the treatment of stroke patients (139,180–194). Some physical therapists advocate and apply Bobath's "neuro-developmental" approach developed by physiotherapist Berta Bobath (c. 1908–c. 1991) and her husband, psychiatrist and neurophysiologist Karel Bobath, MD (c. 1906–c. 1991) (187), both Jewish refugees from Nazi Germany to England; the "motor re-learning programme" of Janet H. Carr, MA, EdD, and Roberta B. Sheperd, MA, EdD (188); Swedish physiotherapist Signe Brunnström's approach utilizing abnormal synergies (186); and various others. Controlled trial data are as yet inconsistent, and no clearly better approach has been identified from among the available approaches for the physical therapy of stroke patients (180,183). Progressive resistance exercises several times a week can help improve strength and functional abilities in patients with adequate motor control (138,195). The intensity of therapy initiated early seems to be important in maximizing the degree of functional improvement (161–164).

Based on the results of systematic reviews, comprehensive occupational therapy is modestly beneficial in improving activities of daily living and social participation among stroke patients (196,197), although there is limited or insufficient evidence supporting many specific occupational therapy interventions, including provision of splints for decreasing muscle tone (196,198). Even when provided in the community, occupational therapy can improve basic activities of daily living, as well as domestic and leisure skills, as indicated by systematic reviews (196,197). Different task-oriented practice strategies can be helpful, especially if intensive training in specific skills is provided (138,161–163,196). Constraint-induced-movement therapy—based on the idea that "learned nonuse" of a weak arm develops because of the greater effort required to use it—seeks to encourage the use of the weak arm and promote helpful cerebral plasticity (138,199); this approach can be helpful in increasing the amount and efficiency of the use of the weak arm in the relatively small subset of patients with fairly good motor control to begin with (138,200–202).

Available data from randomized controlled trials concerning the efficacy of speech therapy in stroke rehabilitation are limited and not entirely consistent (203), with some trials supporting a modest benefit within the first 3 to 6 months after stroke (160,204,205), and others finding lesser or no significant benefit for most patients (206–208). A greater intensity of therapy in the first several months poststroke seems to be an important factor in the degree of improvement (160,203,209).

Early Supported Discharge

In most countries, into the 1990s, stroke patients were treated initially in the hospital, followed by a variable period of inpatient rehabilitation, but rehabilitation often stopped after discharge (210). In some countries, early supported discharge (ESD) approaches have been developed since the 1990s that shorten the period of acute hospital stay and provide rehabilitation services beginning in the hospital and continuing for the first few weeks at home. Proponents have claimed that this approach is not only less costly, but can also improve care by providing "seamless service" spanning inpatient and home care environments; however, until recently there were limited data to evaluate such claims (210). Single-blind randomized controlled trials have been reported from the United Kingdom, Scandinavia, Australia, and Canada (211–224). Although some studies of ESD have not identified any significant benefits of this approach (213), others have reported similar efficacy compared with traditional inpatient rehabilitation along with significant cost savings (212,224); reductions in total hospitalization (of approximately 50%) (217,218,220); reduction in use of inpatient rehabilitation beds (211); improved patient satisfaction (214,217,220); less caregiver stress (221); and, in some cases, improved performance of activities of daily living (215,218,219,222), and longer sustained noninstitutional care (215). In one well-designed study

from Norway, stroke patients who received ESD rehabilitation services spent less time in hospital and were also more likely to be independent and to be living at home after one year (215). As suggested by Langhorne, presumably "the ESD service has improved the patient's ability to regain normal activities despite residual impairment. In particular, the patient's own home is probably the best place for him or her to relearn the skills needed to function in that environment" (210). A home environment for rehabilitation may also facilitate patients with moderate neurologic impairments taking greater responsibility and exercising a greater influence over their own rehabilitation (223). A systematic review of the economic costs of different settings of rehabilitation care found "'moderate' evidence that ESD services provide care at modestly lower total costs than usual care for stroke patients with mild or moderate disability" (166).

Outpatient Rehabilitation

The role of outpatient rehabilitation services (i.e., therapy-based rehabilitation services targeted at stroke patients living at home) has only recently been studied in any detail, and the results remain less certain than in the case of traditional inpatient multidisciplinary stroke rehabilitation (225–229). This is complicated by differences in the types of community-based rehabilitation provided, the setting in which such care is provided (day hospital versus the home), and the clinical circumstances for which this approach is used instead of traditional inpatient rehabilitation (228,229). Several studies have evaluated the use of day hospital rehabilitation care with inconsistent results compared with either inpatient multidisciplinary care or home care (230–232). Costs are generally higher for day hospital rehabilitation than for home care (230,232), but not universally so (231). Functional outcomes for day hospital rehabilitation are generally similar to rehabilitation provided in other settings (230,231), although one study reported better functional outcomes with day hospital rehabilitation than with home care (232). Nevertheless, preliminary results suggest that some therapy-based rehabilitation services provided in the home can result in a greater ability to perform activities of daily living and reduce the risk of deterioration in ability compared with conventional care (i.e., normal practice or no routine intervention) (225–229). Other studies have indicated no benefit for some outpatient services that were not primarily therapy-based, including the use of an outreach nursing support program (233,234). Further studies are needed to define the most appropriate level of service delivery, the most effective services and interventions, and their cost-effectiveness compared with other approaches (225). At present, there is "insufficient" evidence concerning the economic costs of community-based rehabilitation (166).

Caregiver Training

Family involvement in support of the poststroke patient has long been recognized as a strong independent predictor of discharge to home as opposed to an institution (169). Because the degree of family involvement can sometimes be influenced by the rehabilitation team, family and caregiver training has been a major target of therapeutic intervention, and is being increasingly recognized as a predictor of functional outcome as well (169). Caregiver training during the rehabilitation of stroke patients can reduce the cost of care and improve the overall quality of life among caregivers, even as long as a year poststroke (235,236). Problem-solving training, including an in-home visit and subsequent telephone contacts by a trained nurse, may also be useful for family caregivers of stroke survivors even after the latter's discharge from rehabilitation (237). Caregiver training and education may help caregivers be better prepared to deal with issues, facilitate development of caregiver problem-solving skills, lessen caregiver stress and depression, minimize secondary complications among the patients, and facilitate patient motor tasks that promote functional improvements and lessen the risk of further functional declines (e.g., safe swallowing and walking for exercise) (138,237).

Gaps in Theoretical Foundations and Practical Implementation Remain

The development of stroke rehabilitation concepts is still limited, with the recognition in the field that many of the therapeutic approaches currently employed have, at best, limited benefit in a select subgroup of patients; that much of the theoretical justification for different rehabilitation models and approaches remains speculative; and that there is no overall foundation for an accepted "theory of rehabilitation" that could help to prevent fragmentation and division, provide coherence, focus research and development in this area, and facilitate competition for limited research funding (138,142,238,239). Moreover, because rehabilitation interventions are typically multidisciplinary, multifaceted, and customized to the individual patient's needs and goals, they are, in practice, difficult to standardize, and therefore difficult to measure and compare (138,142,238). Available treatment studies are further complicated by the heterogeneity of impairments and disabilities of the patients studied, poor descriptions of the specific treatments administered, inadequate controls, lack of blinding, small sample sizes, and insensitive outcome measures (138).

Current expert consensus has strongly supported the importance of integrating rehabilitation into systems of care to ensure that all patients who could potentially benefit from appropriate stroke care and rehabilitation are provided with the appropriate treatment in a time frame that will maximize recovery and minimize disability (151). According to the American Stroke Association's Task Force on the Development of Stroke Systems:

> Stroke rehabilitation involves a combined and coordinated use of medical, social, educational, and vocational measures for retraining individuals to reach their maximal physical, psychological, social, vocational, and a

> vocational potential. Specifically, stroke rehabilitation programs are provided to optimize neurologic recovery, teach compensatory strategies for residual deficits, teach activities of daily living (ADLs) and skills required for community living, and provide psychosocial and medical interventions to manage depression. The team provides patient and family education about the medical management of post-stroke complications and secondary stroke prevention . . . . Practice guidelines for rehabilitation are well established in this area, although patients often do not receive a level of care that is consistent with these guidelines . . . . The intensity of rehabilitation services often is a critical determinant in the recovery of stroke patients. The use of coordinated, multidisciplinary stroke rehabilitation teams has been shown to diminish mortality rates for stroke patients. In addition, stroke patients who receive care in an inpatient rehabilitation facility are more likely to return to the community and to recover their ability to perform ADLs . . . . Building stroke systems throughout the United States is the critical next step in improving patient outcomes in the prevention, treatment, and rehabilitation of stroke. The current fragmented approach to stroke care in most regions of the United States provides inadequate linkages and coordination among the fundamental components of stroke care. (151)

Practice guidelines are now available for stroke rehabilitation (240–242), but in many cases patients do not receive care consistent with the guidelines (142,151,243,244). Further, there are sociodemographic inequalities in the use of rehabilitation services, suggesting inappropriate underuse among certain populations (245).

Even when patients receive inpatient stroke rehabilitation, they spend only a small amount of their inpatient stay participating in potentially rehabilitative activities, and this low intensity of therapy is less likely to produce beneficial outcomes (138,142,227,246). In an observational behavioral mapping study of five stroke units, patients had therapist contact during only 5% of the day, participated in minimal or moderate therapeutic activity for less than 13% of the therapeutic day (8 a.m. to 5 p.m.), and were resting in bed 53% of the time and alone 60% of the time (247). Poor participation in therapeutic activities is common during inpatient rehabilitation, and is associated with longer lengths of inpatient stay and lower degrees of improvement in functional performance (248). In addition, for financial or policy reasons, formal therapy is typically stopped when there are no evident qualitative gains in function after several weeks of treatment, even though, as Dobkin notes: "A plateau in recovery . . . does not necessarily imply a diminished capacity for further gains in physical speed or precision or in learning a new task" (138).

Furthermore, despite modern treatment and multidisciplinary rehabilitation, perhaps half of the patients with stroke are ultimately discharged home with serious, persistent neurologic impairments, functional limitations, and, often, disability resulting from inadequate environmental supports (249). Stroke survivors (whether residing at home or in institutional care environments) are prone to multiple secondary conditions that further erode health, including social isolation, depression, physical inactivity, painful joint contractures, deep venous thromboses and pulmonary emboli, decubitus ulcers, incontinence, aspiration pneumonia, inadequate nutrition, falls, hip fractures, and seizures. Such patients are often frail and susceptible to aggravation of existing disease or development of new illness, with resulting functional decline, high resource utilization, high rates of rehospitalization, significant added morbidity, and a high risk of death within the first year after stroke onset. Indeed, in the United States, approximately one-fifth of stroke patients die in the first month after stroke, a quarter within 2 months, and a third within 6 months (250). Patients and caregivers can benefit from a close liaison between inpatient and community care programs, and also from continuing professional support and counseling after discharge following a stroke (249).

Further studies are needed to define the most appropriate level of service delivery for stroke rehabilitation, the most effective services and interventions among the "complex packages of care" that comprise current rehabilitation programs, and the most cost-effective stroke rehabilitation service among the different types available (142,225).

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2

Stroke Epidemiology: Global Burden of First-Ever Strokes

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Stroke is the second most common cause of death worldwide and a frequent cause of adult disability in developed countries (1,2). Stroke burden on families and society is projected to rise from approximately 38 million disability-adjusted life years (DALYs) lost globally in 1990 to 61 million DALYs in 2020 (3) because of population aging. Stroke also has a large physical, psychological, and financial impact on patients/families, the health care system, and society (4,5). Lifetime costs per stroke patient range from US$59,800 to US$230,000 (5). The majority (about 75%) of cases of stroke occur in people over the age of 65 years (6,7), and about one-third of patients die of stroke within a year of onset (8,9). Over half of the survivors have long-term therapy needs and remain dependent on others for everyday activities, often with significant adverse effects on caregivers (10). Many factors increase the risk of stroke, and these are generally divided into two categories: modifiable and nonmodifiable risk factors. Age, gender, and ethnicity are nonmodifiable risk factors for stroke. Modifiable or potentially modifiable risk factors include a number of physiological and environmental factors, among them hypertension, elevated total cholesterol, smoking, physical inactivity, alcohol consumption, and atrial fibrillation (11).

Stroke mortality data are available from more than 24 countries (12,13) showing, in general, declining rates for several decades. In some countries, stroke mortality has declined since the early 1950s, but the rate of this decline has recently slowed (14,15). Although large national or international stroke mortality data may be used for determining overall burden of fatal strokes and trends in stroke mortality, stroke mortality data are often not accurate (diagnosis classification bias) and have limited value for health care planning and organization. The role of changes in incidence and improved survival to the downward trend in stroke mortality are not adequately quantified, chiefly because of the difficulties in measuring stroke incidence accurately (16,17). However, the results from the World Health Organization (WHO) Monitoring Trends and Determinants in Cardiovascular Disease (MONICA) project suggested that both declining and increasing stroke mortality were principally attributable to changes in case fatality rather than changes in incidence (18).

IMPORTANCE OF POPULATION-BASED STUDIES

Epidemiological studies form the basis of much of the medical research and current knowledge of stroke to inform health professionals about best strategies for stroke care organization, prevention, and management. The gaps in knowledge in stroke prevention and management are continually being filled by randomized controlled trials and case–control and cohort studies. Some of the most informative studies on stroke burden and optimal health care organization have arisen from population-based stroke incidence and outcome studies. It is important that stroke is seen and studied in a population context, as a large proportion of the burden of care for stroke is borne outside the hospital (11–13).

Further, changes in referral patterns can distort longitudinal trends derived from hospitalized cases. Assessing the need for prevention strategies and services is best achieved via population-based stroke registries to determine incidence and outcome (13).

Data on population trends in stroke incidence reflect the success/failure of prevention strategies, whereas trends in case fatality and outcome reflect changes in stroke management and mortality rates. Both are needed to plan stroke services, given high health care costs and limited resources. Accurate and representative population-based data are also crucial to: (a) determining the true incidence, causes, and outcome of stroke; (b) implementing evidence-based health care planning across the care spectrum; (c) evaluating the need for and impact of preventative/management strategies; (d) addressing persistent uncertainty about what key factors (socioeconomic and health service) impact stroke recovery; (e) examining the natural course of recovery, in particular for cognitive and behavioral outcomes; (f) providing information on access to and satisfaction with stroke services; and (g) identifying

service gaps/unmet needs for ensuring evidence-based policy, resource allocation, prevention planning, management services, and evaluation of service performance.

Assessing the need for prevention strategies and services is most sensitively achieved with the use of population-based registers to determine the incidence and outcome of stroke. However, studying stroke in a population-based fashion is particularly challenging (17), because such epidemiological studies are relatively rare compared with studies using mortality data, hospital-based stroke registers, or incidence studies in younger age groups only.

GLOBAL STROKE EPIDEMIOLOGY STUDIES

Investigation of stroke burden by its major pathological types, and study of their practical trends in different regions of the world, are important for targeted region-specific health care planning in stroke (e.g., estimation of resources needed to care for patients with stroke by type), and can provide information on priorities for type-specific prevention strategies. These data are also important for understanding the health consequences and patterns of epidemiological transitions reported worldwide. Findings from systematic reviews suggest that low-income and middle-income countries have a greater proportion of hemorrhagic stroke than do high-income countries (19), that geographical variation is high in the incidence of major pathological types of stroke (19), and that no substantial changes have taken place in the incidence of hemorrhagic stroke in the past three decades (20,21). However, no detailed, systematic, and comprehensive estimates have been made of the global and regional incidence, case-fatality, DALYs lost, and secular trends of incidence of ischemic or hemorrhagic stroke, especially for low-income and middle-income countries (22–24). This chapter provides a summary of the estimates from the Global Burden of Diseases, Injuries, and Risk Factors Study (GBD 2010) for incidence, mortality, mortality-to-incidence ratio, and DALYs lost in ischemic or hemorrhagic stroke in all 21 regions of the world (25) in 1990, 2005, and 2010.

METHODOLOGY OF DATA COMPILATION

Systematic literature review was conducted for data collection. The search included Medline, Embase, LILACS, Scopus, PubMed, Science Direct, Global Health Database, the WHO library, and WHO regional database between 1990 and 2010 to identify studies published between 1990 and 2010. The databases were searched with various key or title words: "stroke," "isch(a)emic stroke," "intracerebral," "intraparenchymal," "subarachnoid," "h(a)emorrhage," and title or key-words "population-based," "community-based," "community," "epidemiology," "epidemiological," "incidence," "attack rates," "survey," "surveillance," "mortality," "morbidity," "fatality," "case-fatality," or "trends." Pathological types of stroke were assessed only for studies that used head CT or MRI within the first two weeks of stroke onset, or for those in which brain autopsy findings for confirmation of type were available for at least 70% of stroke cases. Cases of stroke with no neuroimaging or autopsy verification of pathological types were classified as strokes of undetermined pathological type. Pathological types of stroke were categorized into two groups: ischemic strokes and hemorrhagic strokes (intracerebral hemorrhage and subarachnoid hemorrhage combined). Only first-ever stroke events were assessed.

CALCULATION OF INCIDENCE, MORTALITY, AND DALYS LOST

Statistical analysis strategies are described fully in *The Lancet* (26,27). Briefly, the GBD 2010 analytical technique (DisMod-MR) was applied to calculate regional and country-specific estimates of incidence and mortality per 100,000 person-years for ischemic and hemorrhagic stroke, and of DALYs lost per 100,000 people, by age group (<20 years, 20–64 years, 65–74 years, ≥75 years, total) and level of country income (high, low, and middle) for 1990, 2005, and 2010.

Disease Modeling

For modeling of mortality of ischemic and hemorrhagic stroke, a set of relevant covariates was selected and a plausible direction of effect (increase or decrease in incidence, mortality, and DALYs lost) was assumed based on existing literature. For a full description of methods, see the study by Bennet (26). The mortality-to-incidence ratio for each region and country serves as an indicator of the success or failure of stroke management strategies in a particular region (ratio numbers were based on the total number of incident cases and deaths). Full description of results can be found in *The Lancet* (26,27). The findings included 119 studies (58 from high-income countries and 61 from low-income and middle-income countries) in the analysis.

GLOBAL BURDEN OF ISCHEMIC AND HEMORRHAGIC STROKE

Overall, an estimated 11,569,538 incidents of ischemic stroke (63% in low-income and middle-income countries) and 5,324,997 incidents of hemorrhagic stroke (80% in low-income and middle-income countries) took place worldwide in 2010. A total of 2,835,419 individuals died from ischemic stroke (57% in low-income and middle-income countries) and 3,038,763 died from hemorrhagic stroke (84% in low-income and middle-income countries). A total of 39,389,408 DALYs were lost because of ischemic stroke (64% in low-income and middle-income countries) and 62,842,896 because of hemorrhagic stroke (86% in low-income and middle-income countries). The age-standardized incidence per 100,000 person-years of ischemic stroke ranged from 51.88 in Qatar to 433.97 in Lithuania, and that of hemorrhagic stroke ranged from 14.55 in Qatar to 159.81 in China. Age-standardized mortality rates per 100,000 person-years for ischemic stroke ranged from 9.17 in Qatar to 137.70 in

Russia, and that of hemorrhagic stroke ranged from 9.64 in the United States (USA) to 210.56 in Mongolia. DALYs lost per 100,000 people because of ischemic stroke ranged from 163.89 in Israel to 2032.11 in Afghanistan, and DALYs lost to hemorrhagic stroke ranged from 178.20 in Switzerland to 4118.90 in Mongolia. The mean age of people with incident and fatal stroke has increased worldwide, with the largest increase noted in high-income countries.

In high-income countries, the incidence of ischemic stroke has been significantly reduced by 13% (95% CI 6–18), mortality by 37% (19–39), DALYs by 34% (16–36), and mortality-to-incidence ratios by 21% over the past two decades. Reductions in hemorrhagic stroke were 19% (1%–15%) for incidence, 38% (32%–43%) for mortality, 39% (32%–44%) for DALYs, and 27% (19%–35%) for mortality-to-incidence ratio. Worldwide, in the younger age group, the incidence of ischemic stroke did not change, but there was a significant increase in the incidence of hemorrhagic stroke, from 54.07 (48.56–60.22) to 64.07 (56.45–73.33; $P = 0.028$). In the older age group (≥75 years), no significant change was noted in the incidence of ischemic stroke (from 2614.89/100,000 [2426.49–2809.55] to 2472.93/100,000 [2279.15–2687.39], $P = .176$), whereas a significant reduction was shown in the incidence of hemorrhagic stroke (from 558.61/100,000 [503.36–624.07] to 640.06/100,000 [569.10–724.72], $P = .046$).

In low-income and middle-income countries, the incidence of hemorrhagic stroke increased significantly, by 22% (95% CI 5–30) over the past two decades, with a 19% (5–30) increase in people younger than 75 years. A nonsignificant increase of 6% (18%, –7 to 32) was shown in the incidence of ischemic stroke, but the incidence of both ischemic and hemorrhagic stroke increased significantly in people aged 20 to 64 years. Additionally, nonsignificant reductions in mortality rates (14%, 95% CI –2% to 32%), DALYs lost (16%, 95% CI 1%–35%), and mortality-to-incidence ratio (16%, 95% CI –5% to 37%) were observed. Similarly for hemorrhagic stroke, nonsignificant reductions in mortality rates (23%, 95% CI –3% to 36%), DALYs lost (25%, 95% CI 7%–38%), and mortality-to-incidence ratio (36%, 95% CI 16%–49%) were also observed.

By GBD region, the largest increases in incidence of ischemic stroke were in Eastern Europe, Central and East Asia, North and Sub-Saharan Africa, and the Middle East (Figure 2.1), with the largest increase (22%) noted in the Democratic Republic of Congo. Notably, some of the largest decreases in incidence of ischemic stroke between 1990 and 2010 were also in these regions (South Korea 44%, Chile 41%, Brunei 41%; Figure 2.1). Up to 2010, the highest rates of ischemic stroke were in Eastern Europe (particularly Russia: 238–416/100,000) and Central and East Asia, North Africa, and the Middle East (178–238/100,000).

The largest increases in the incidence of hemorrhagic stroke by GBD region were in Eastern and Central Europe, North and Sub-Saharan Africa, and the Middle East. In contrast, the incidence of hemorrhage stroke decreased significantly in high-income regions of North America, Western Europe, and tropical and Southern Latin America (Figure 2.2). In 2010, the highest incidences of hemorrhagic stroke were in Central and East Asia (101–158/100,000) and East and Southern Sub-Saharan Africa (73–101/100,000), whereas the lowest rates were in high-income regions in North America, Central and Andean Latin America, Western Europe, and Oceania (Australasia; 25–40/100,000). Between 1990 and 2010, mortality-to-incidence ratios for ischemic stroke reduced noticeably in Western Europe, Australasia, and Central and Andean Latin America, but increased in North Africa, the Middle East, and Southeast Asia (Figure 2.3). For hemorrhagic stroke, decreases in mortality-to-incidence ratios occurred in Northern Africa, the Middle East, Central, East, and Southern Sub-Saharan Africa; and East and Southeast Asia, whereas moderate increases were evident in Central Latin America and high-income Asia-Pacific regions (Figure 2.4).

In 2010, the lowest mortality-to-incidence ratios for ischemic stroke were in high-income North America and East Asia (0.17–0.19), and for hemorrhagic stroke in high-income North America (0.25). The highest mortality-to-incidence ratios for ischemic stroke were in Central Europe and the Caribbean (0.34–0.38), and for hemorrhagic stroke in Oceania (0.94–1.27). Age-specific mortality rates, mortality-to-incidence ratios, and DALYs for both stroke types were greater overall in low-income to middle-income countries than in high-income countries, but significant differences between higher-income and lower-income countries were apparent only for hemorrhagic stroke incidence, mortality, DALYs in people older than 40 years, and mortality-to-incidence ratios across all age groups

IMPLICATIONS OF THE GLOBAL BURDEN OF ISCHEMIC AND HEMORRHAGIC STROKE

The burden of both ischemic and hemorrhagic stroke has increased significantly between 1990 and 2010 in terms of an increased absolute number of people with incident stroke, number of deaths, and number of DALYs lost. Although the absolute number of incident ischemic stroke is twice that of hemorrhagic stroke, the overall global burden of hemorrhagic stroke (deaths and DALYs) is higher. Despite the fact that ischemia is the more common etiology of stroke in high-income countries, most of the stroke burden worldwide is because of hemorrhage.

Second, the bulk of stroke burden in terms of incident events, deaths, and DALYs lost is borne by low-income to middle-income countries. These countries are disproportionately affected by the burden of hemorrhagic stroke compared with high-income countries. In contrast to high-income countries, where the overall incidence, mortality, DALYs, and mortality-to-incidence ratio of both ischemic and hemorrhagic stroke has declined in the past two decades in both younger (<75 years) and older (≥75 years) age groups, low-income and middle-income countries have experienced a significant increase in the incidence of both stroke types. The average age at which people had ischemic and hemorrhagic strokes is three to five years younger in low-income and middle-income countries than in high-income countries.

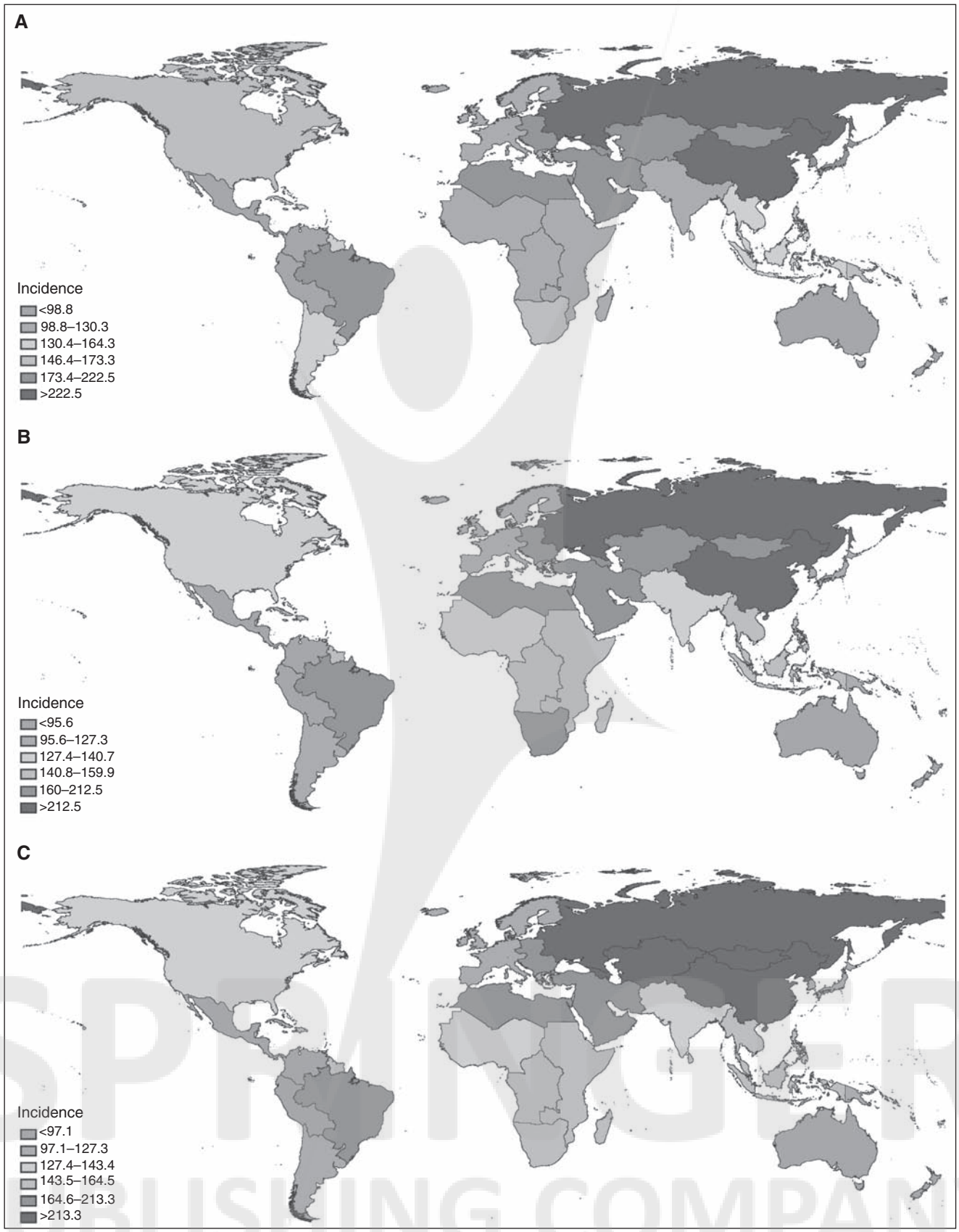

FIGURE 2.1 Age-standardized incidence of ischemic stroke per 100,000 person-years for 1990 (A), 2005 (B), and 2010 (C).

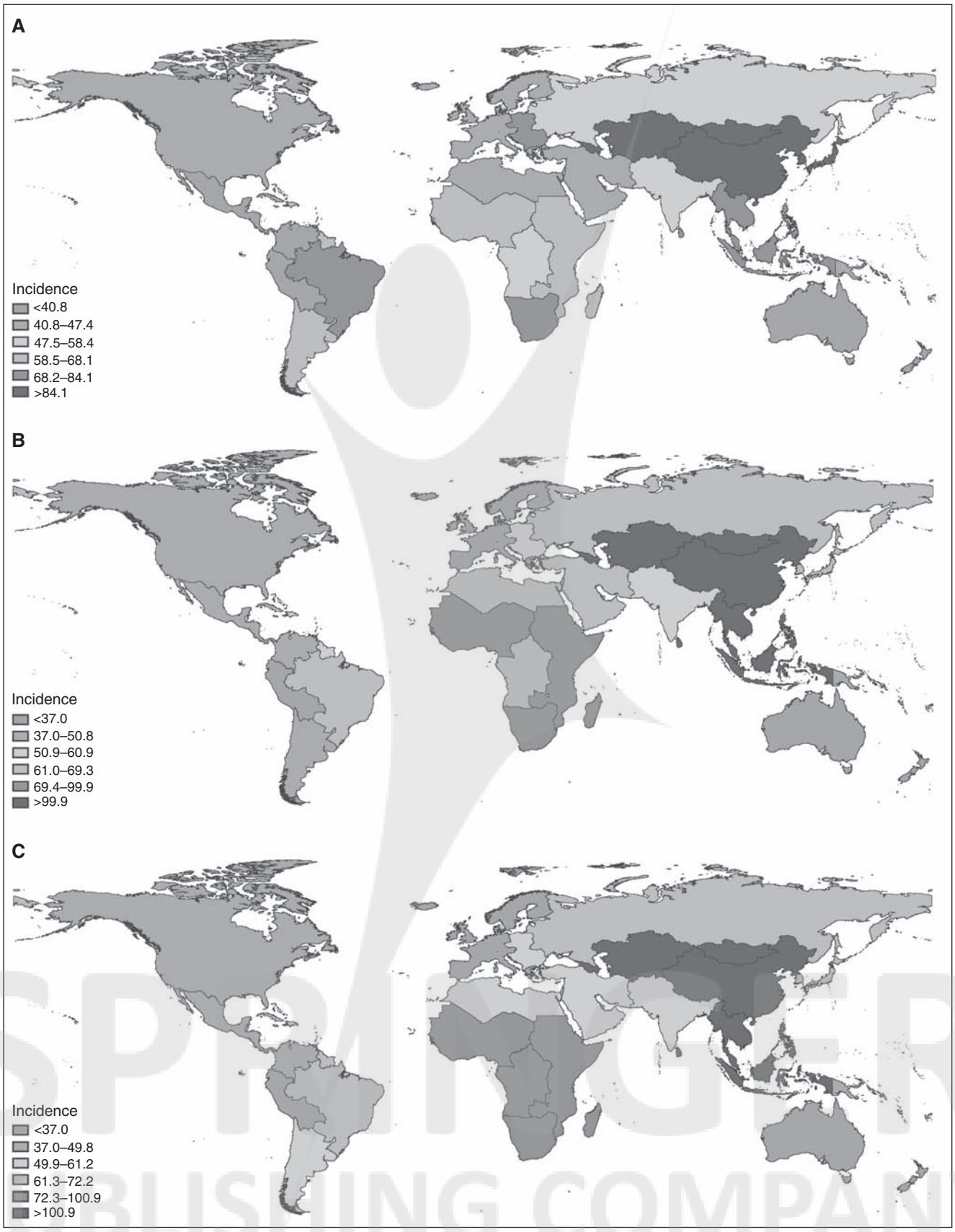

FIGURE 2.2 Age-standardized incidence of hemorrhagic stroke per 100,000 person-years for 1990 (A), 2005 (B), and 2010 (C).

FIGURE 2.3 Mortality-to-incidence ratio (MIR) for ischemic stroke for 1990 (A), 2005 (B), and 2010 (C).

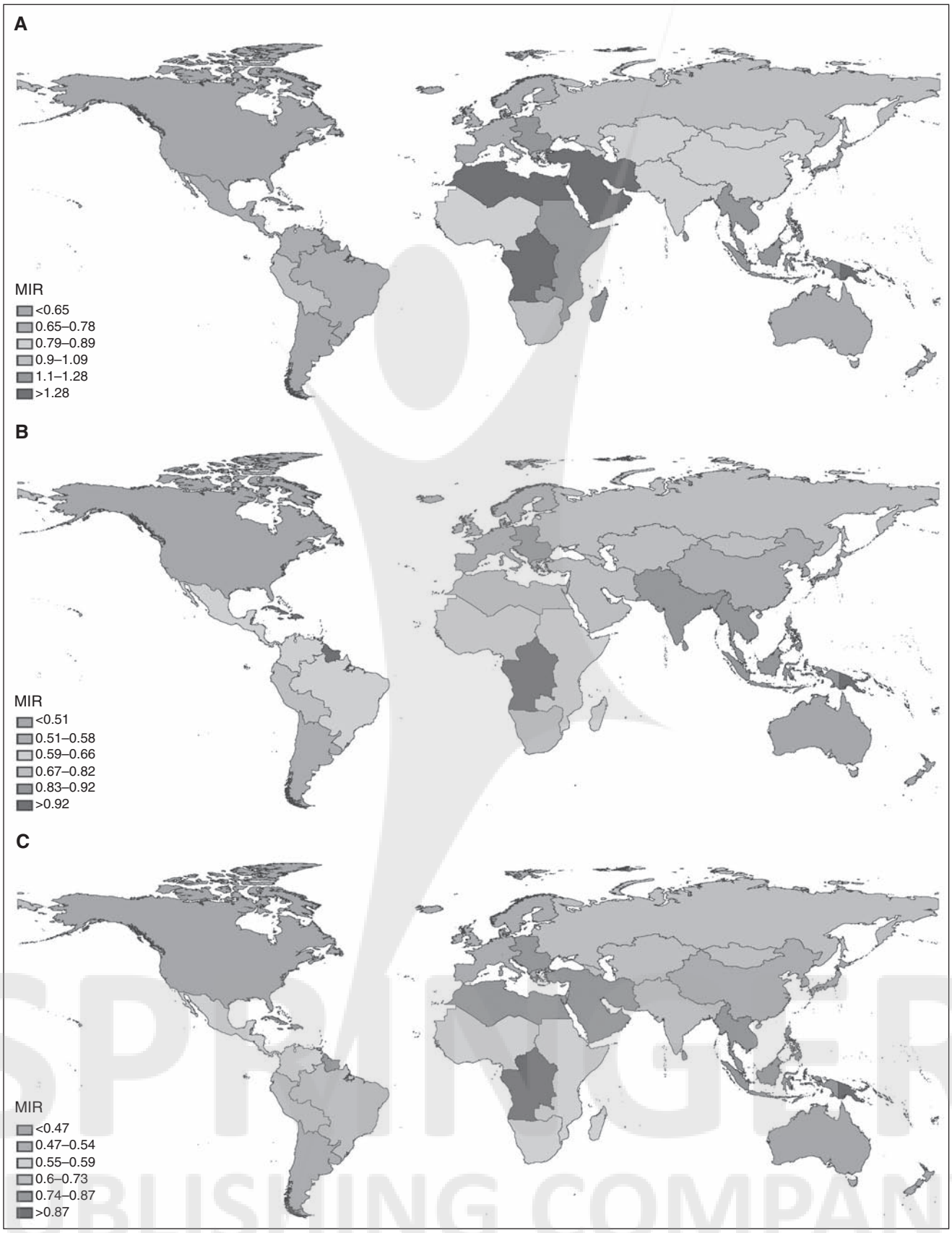

FIGURE 2.4 Mortality-to-incidence ratio (MIR) for hemorrhagic stroke for 1990 (A), 2005 (B), and 2010 (C).

Roughly a quarter of all ischemic strokes and about half of all hemorrhagic strokes occur in people younger than 65 years of age, with 73% and 83% of them, respectively, residing in low-income and middle-income countries. In 1990–2010, the incidence of both stroke types increased significantly in adults aged 20 to 64 years in low-income and middle-income countries. The findings of a greater proportion of hemorrhagic stroke in low-income and middle-income countries compared with high-income countries, noticeable geographical variation in the incidence of major pathological types of stroke, and diverging trends in stroke incidence between low-income countries (increase in rates) and high-income countries (decrease in rates) are in line with the results of a systematic review of population-based studies of stroke incidence (19). However, unlike findings from that review, there have been significant changes in the incidence of hemorrhagic stroke during the past two decades.

Encouragingly, although there is a trend toward an increase in the incidence of ischemic stroke, a trend toward reduction in mortality rates for both ischemic and hemorrhagic stroke, DALYs, and mortality-to-incidence ratios is also evident in low-income and middle-income countries. This finding might reflect advances in the diagnosis of stroke type, and more targeted health care in some developing regions in low-income and middle-income countries.

The discrepancies between countries of different income levels are probably driven by the occurrence of epidemiological transition (28). In the past few decades, life expectancy has increased, childhood mortality has reduced, and health status has improved overall in many regions of the world (29). Globally, aging populations are driving increases in the incidence of both ischemic and hemorrhagic stroke. In low-income and middle-income countries, diseases related to infection and undernutrition have been replaced with more chronic diseases such as stroke and heart disease as leading causes of disease burden. However, unlike many low-income and middle-income countries, most high-income countries have implemented improved prevention strategies and better health care for these chronic disorders (30). Moreover, industrialization and urbanization have led to changes in the nutritional quality of foods, with high-fiber carbohydrates and fresh produce being replaced with more processed carbohydrates and high-fat diets (31). The resultant increase in the prevalence of diabetes, together with increases in smoking rates and sedentary lifestyles, has contributed to increased atherosclerotic disease (30). During different phases of epidemiological transition, an increased incidence of hemorrhagic stroke is expected, particularly in low-income and middle-income countries, because hypertension is the dominant risk factor for this stroke type.

There are substantial differences between countries in incidence, mortality, DALYs, and mortality-to-incidence ratio for both stroke types. The alarmingly high stroke burden in China, particularly for hemorrhagic stroke, might be attributable to the increased prevalence of risk factors for this stroke type—namely high blood pressure and smoking—and an aging population (32,33). A review suggested that hemorrhagic stroke contributed to more stroke burden in China than in high-income countries, but wide regional differences were reported in the incidence and type of stroke (34). Hypertension, diabetes, dyslipidemia, and smoking are modifiable risk factors that have increased in China. In India, many deaths have been attributed to smoking, particularly in men, with vascular causes being among the main contributors to death (35). Eastern European countries have undergone many socioeconomic changes in the past two decades. In particular, in Russia, alcohol was strongly associated with adult mortality (36). More than half of the deaths among Russian men are attributable to cardiovascular disease, with hypertension, hypercholesterolemia, tobacco use, inadequate diet, obesity, insufficient physical activity, and alcohol being among the prevalent risk factors for death (37).

The decline in incidence, mortality, DALYs, and mortality-to-incidence ratios in high-income countries is likely a result of improved prevention, and better acute and chronic treatment of stroke. High-income regions such as Western Europe, North America, Australia, and New Zealand have increased efforts to prevent and diagnose stroke, which is shown by the delay of stroke incidence to older age groups (30). Mortality-to-incidence ratios for ischemic stroke in people younger than 40 years of age were significantly higher in low-income and middle-income countries when compared to that of high-income countries. This finding might reflect an increased prevalence of risk factors such as alcohol use, tobacco smoking (including second-hand exposure), and high blood pressure in this age group (38). By contrast, the increased overall global burden of stroke in low-income and middle-income countries could be attributable to reduced levels of awareness of risk factors, low levels of primary and follow-up health care, and a scarcity of basic drugs and equipment for the prevention and treatment of stroke (39).

Population-wide preventive strategies should be given priority because even modest changes in prevalence of risk factors (e.g., reduction of blood pressure, smoking cessation, and reduction of salt intake) could contribute substantially to the cumulative population risk reduction (24,40). Interventions to reduce the burden of chronic disease in low-income and middle-income countries should be cost effective and financially viable (41). Because of the overlap of risk factors related to ischemic stroke and ischemic heart disease, preventive efforts focused on these factors (e.g., raised blood pressure, cholesterol, diabetes, and smoking) would be a cost-effective way to target prevention in a wide population. Hypertension is the strongest risk factor for both ischemic and hemorrhagic stroke, and on the basis of the high burden of both types, prevention programs should focus on control of blood pressure, including both individual screening and treatment and population-wide lowering of blood pressure.

Tobacco control (via increased taxes, reduced advertising, and banning of smoking in public places), strategies for salt reduction, and evidence-based multidrug strategies to

treat those at high risk of cardiovascular disease, would be relevant for prevention of both hemorrhagic and ischemic stroke. Several successful and cost-effective campaigns have already been identified and need to be adopted on a wider scale worldwide (41). Government initiatives to encourage and support healthy diets and increased physical activity are imperative in countries of all income types. Similarly, engaging food manufacturers to achieve these goals by reduction of salt levels and fat content in processed foods would need to be implemented at government level (42,43). All of these strategies are applicable to secondary stroke prevention as well.

Hemorrhagic stroke was once a major cause of death in high-income nations, but its prevalence has decreased in those regions over the 20th century (44). However, hemorrhagic stroke remains an important cause of death and disability worldwide, particularly because of its disproportionate prevalence in low-income and middle-income countries. With the possible exception of hypertension, risk factors for hemorrhagic stroke have not been researched as well as those for ischemic stroke. Hence, studies to elucidate risk factors for hemorrhagic stroke are a high priority for future epidemiological research. A global perspective on stroke burden can be used as a vital source of information for future planning of prevention, treatment, and rehabilitation strategies for stroke worldwide.

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3

Pathophysiology and Management of Acute Stroke

Marco Gonzalez-Castellon and Tomoko Kitago

Stroke is the fourth leading cause of death in the United States, and the most common medical cause of disability. Each year 800,000 Americans have a new or recurrent stroke—a number that will double in the coming decades as our population advances in age. This condition is, therefore, the most significant neurologic condition managed in the hospital setting. With the advent of recombinant tissue plasminogen activator (rt-PA) for the acute treatment of stroke in 1996, the management of stroke changed dramatically. Acute stroke is a medical emergency in which the outcome is highly dependent on prompt recognition and treatment. Several states have adopted legislative Stroke Acts, which require emergency medical personnel to transport stroke victims to the nearest certified stroke center. The Joint Commission has developed certification criteria for Primary and Comprehensive Stroke Centers based on the evidence published in the medical literature. With the advent of specialized stroke centers, the inclusion of guideline-driven acute stroke care, including early rehabilitation, has become an important component in the total management of the stroke patient. Acute care issues address prevention of common poststroke complications such as deep venous thrombosis; emphasize early mobilization, assessment, and management of dysphagia and nutritional status, cognitive and communication deficits, incontinence, and preventative skin care; and initiate interactive rehabilitation education including the family and caregivers. Multiple rehabilitation modalities must be initiated during the acute care period, and continuity of care plans established to optimize long-term functional and health outcomes for the stroke survivor. The care of stroke patients is divided into phases of emergency management, acute inpatient care, rehabilitation, and long-term care. This chapter focuses primarily on the management of acute ischemic stroke and provides a brief introduction to major rehabilitation issues that are commonly encountered during early stroke care.

STROKE PATHOPHYSIOLOGY

The two main classifications of stroke are ischemic and hemorrhagic stroke. In ischemic stroke, which accounts for the majority, interruption or reduction of blood flow to an area of the central nervous system results in neuronal injury and clinical symptoms. Ischemic stroke can be caused by different mechanisms: thrombosis, embolism, or hypoperfusion. In thrombotic stroke, there is local occlusion of a blood vessel, most commonly because of atherosclerosis or a hypercoaguable state. In embolic stroke, thrombus or other material forms at a distant site and travels to the site of occlusion. Sources of emboli include the heart, proximal arteries (e.g., the aorta, carotid, and vertebral arteries), and systemic veins in the case of paradoxical embolism, in which a venous thrombus can travel to the brain via a patent foramen ovale. In stroke caused by hypoperfusion, reduction in systemic perfusion causes a reduction in cerebral blood flow (CBF), which can be exacerbated when there is preexisting vessel stenosis.

The Ischemic Penumbra

CBF is normally 50 to 60 mL/100 g/min. With reduction in CBF to 20 mL/100 g/min, electrical activity is affected, and when CBF falls to less than 10 mL/100 g/min, there is irreversible injury. In ischemic stroke, there is a core area of the ischemic brain region in which blood flow drops below a critical level, and, therefore, is destined for cell death and infarction. A surrounding *penumbric* area of ischemic tissue may also exist that is physiologically impaired, but not necessarily destined for death. It is believed that restoration of CBF to this penumbra can prevent further cerebral infarction. While the precise duration of brain tissue viability for the penumbra has been debated and may vary among patients, depending on numerous pathophysiologic processes, most clinical and animal studies indicate a declining temporal profile of tissue survival that is on the order of hours. Hence, "time is brain," and the more rapidly cerebral perfusion can be restored, the better the neurologic outcome.

STROKE SYNDROMES

Knowledge of the vascular anatomy of the brain and the effects of specific arterial occlusions is important in determining the location and size of the infarct. Chapters 5 provides detailed clinical and vascular-neuroanatomic descriptions of anterior and posterior circulation stroke syndromes. Most

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stroke syndromes can be divided into (a) anterior circulation syndromes—middle cerebral artery (MCA) and anterior cerebral artery (ACA) syndromes, (b) posterior circulation syndromes, (c) lacunar syndromes, and (d) borderzone (or *watershed*) infarct syndromes. A brief description of each of these syndromes is given in the following text.

Middle Cerebral Syndromes

Occlusion of the MCA will present with contralateral weakness, face and arm more than leg associated with sensory loss, visual field cut, and aphasia when the dominant hemisphere is affected and hemineglect when the nondominant hemisphere is involved.

ACA Syndromes

Occlusion of the ACA will present with weakness, leg more than arm and face, behavioral disturbances such as abulia, mutism, anterograde amnesia, grasping and sphincter dysfunction.

Posterior Circulation Syndromes

Strokes in the posterior circulation can present with dizziness, anisocoria, diplopia, dysphagia, ataxia, hemiplegia, quadriplegia, and coma depending on the location of the occlusion. The major posterior circulation syndromes include posterior inferior cerebellar artery (PICA, also known as "Wallenberg") syndrome, anterior inferior cerebellar artery (AICA) syndrome, and posterior cerebral artery (PCA) syndrome. Wallenberg syndrome presents with ipsilateral facial sensory loss, contralateral body sensory loss, dysphagia, dysphonia, ipsilateral ataxia, Horner's syndrome, and nystagmus. Infarction of the AICA territory usually presents with sudden hearing loss, vertigo, vomiting, ipsilateral facial palsy, ataxia, and contralateral sensory loss. Infarction of the PCA territory can present with multiple symptoms depending on the area affected. The most common symptom is visual field loss, and when there is involvement of the P2 branches, patients present with impaired cognition, amnesia, and changes in personality.

Lacunar Syndromes

Most lacunar infarcts are secondary to occlusion of small penetrating arteries; there are five "classic" lacunar syndromes: pure motor hemiparesis, pure sensory stroke, sensorimotor stroke, dysarthria–clumsy hand syndrome, and ataxic hemiparesis. The most common presentation is pure motor and pure sensory stroke.

Watershed Infarct Syndromes

Watershed infarcts are secondary to severely reduced flow in one or multiple vascular territories that leads to infarction of distal areas lying between two vascular territories. The most common are infarcts in the ACA/MCA watershed region, classically described as the *man-in-a-barrel* syndrome because of the especially proximal upper extremity weakness, although most of the time patients present with heterogeneous symptoms.

STROKE RECOGNITION

Rapid recognition of the signs and symptoms of stroke, and timely access to stroke centers, are crucial to optimizing acute care for stroke. Too often, patients develop signs of stroke and wait hours before seeking care, believing that the deficits will go away if they wait long enough. A study by Feldman in 1993 showed that the median time from onset of symptoms to presentation to emergency departments was 13 hours (1). Only 42% of patients presented within 24 hours. During the course of the National Institutes of Health rt-PA Pilot Study, public education and awareness campaigns were conducted to encourage early hospital arrival. Following this campaign, the mean time from symptom onset to hospital arrival declined significantly (3.2 h vs. 1.5 h). The use of 911 increased from 39% in the first quartile of the study to 60% in the fourth quartile. Community forums have also been successful in creating and extending awareness of the need for immediate action. The five most common symptoms of stroke include:

1. Sudden numbness or weakness of face, arm, or leg, especially on one side of the body
2. Sudden confusion, trouble speaking or understanding
3. Sudden trouble seeing in one or both eyes
4. Sudden trouble walking, dizziness, loss of balance, or coordination
5. Sudden severe headache with no known cause

Public education as to the significance of these symptoms and the importance of early evaluation is the goal of any comprehensive stroke program.

Emergency medicine system protocols are also critical in the early treatment of stroke. Proper training of paramedics allows these frontline personnel to obtain crucial information from family or bystanders. This includes obtaining history regarding time of onset and medications the patient might be taking. This historical information, as well as physical findings such as aphasia, motor deficit, and vital signs, can be called to the hospital emergency department so that a stroke alert protocol can be activated, saving significant time in treatment.

EMERGENCY DEPARTMENT MANAGEMENT OF STROKE

Because of the importance of rapid intervention in treating patients with ischemic stroke, it is important that hospitals develop protocols and order sets to be used when a patient with symptoms of stroke arrives. If the patient is transported by emergency medical services that communicate with the emergency department, the hospital can institute the protocol immediately on arrival, but preferably before. Several criteria should be established in the emergency department regarding minimizing delays, including activation of the

stroke team, timely interpretation of studies, and administration of fibrinolytic therapy.

Patient History and Evaluation

The history should focus on determining whether the symptoms are a result of stroke or other medical conditions that can mimic stroke symptoms. The latter include migraine, seizure, syncope, and hypoglycemia. To determine whether the patient may be a candidate for fibrinolytic therapy, it is essential to establish the time of symptom onset, or, if this is unavailable, the time that the patient was last known to be free of stroke symptoms.

As with other critically ill patients, initial evaluation and management should address the ABCs: airway, breathing, and circulation. Patients with hypoxia should be given supplemental oxygen to maintain oxygen saturation >94%. In the emergency care setting, a rapid but thorough neurological assessment is needed. The National Institutes of Health Stroke Scale (NIHSS), shown in Figure 3.1, is an 11-item scale

Ia. Level of Consciousness (LOC)	0 Alert 1 Not alert but arousable by minor stimulation to obey, answer, or respond 2 Not alert; requires repeated stimulation to attend, or is obtunded and requires strong or painful stimulation to make movements 3 Response only with reflex motor or autonomic effects or totally unresponsive, flaccid, and are flexic
Ib. LOC Questions	0 Answers both correctly 1 Answers one correctly 2 Answers neither correctly
Ic. LOC Commands	0 Performs both tasks correctly 1 Performs one task correctly 2 Performs neither task correctly
II. Best Gaze	0 Normal 1 Partial gaze palsy 2 Forced deviation or total gaze paresis
III. Visual	0 No visual loss 1 Partial hemianopia 2 Complete hemianopia 3 Bilateral hemianopia (blind including cortical blindness)
IV. Facial Palsy	0 Normal symmetrical movements 1 Minor paralysis 2 Partial paralysis 3 Complete paralysis of one or both sides
V. Motor Arm Right arm Left arm	0 No drift; limbs holds 90 (or 45) degrees for full 10 seconds 1 Drift; limb drift down before full 10 seconds, does not hit bed or other support 2 Some effort against gravity 3 No effort against gravity 4 No movement
VI. Motor Leg	0 No drift; limbs holds 90 (or 45) degrees for full 5 seconds 1 Drift; limb drift down before full 5 seconds, does not hit bed or other support 2 Some effort against gravity 3 No effort against gravity 4 No movement
VII. Limb Ataxia	0 Absent 1 Present in one limb 2 Present in two limbs
VIII. Sensory	0 Normal 1 Mild-to-moderate sensory loss 2 Severe to total sensory loss
IX. Best Language	0 No aphasia; normal 1 Mild-to-moderate aphasia 2 Severe aphasia 3 Mute, global aphasia
X. Dysarthria	0 Normal 1 Mild-to-moderate dysarthria 2 Severe dysarthria
XI. Extinction or Inattention	0 No abnormality 1 Visual, tactile, auditory, spatial, or personal inattention in one of the sensory modalities 2 Profound hemi-inattention or extinction to more than one modality

FIGURE 3.1 The NIH Stroke Scale.

that can rapidly quantify the neurological deficits of a stroke patient. The use of standardized assessment tools has proved useful when discussing the patient's condition with the treating primary medical team, and for continuity of rehabilitation care. Training for this, as well as certification for performing the evaluation, can be obtained through several mechanisms such as the American Stroke Association website.

Tissue Plasminogen Activator

Recombinant tissue plasminogen activator (rt-PA) is a serine protease that converts plasminogen to plasmin, a fibrinolytic enzyme (Figure 3.2). Upon administration, rt-PA increases plasmin enzymatic activity, resulting in fibrinolysis. It is used to treat the stroke in the acute stage in an attempt to restore flow to the ischemic area, and should be administered as quickly as feasible, by protocol standards within a 3- to 4.5-hour time period to restore blood supply and optimize recovery.

rt-PA was approved by the FDA in 1996 for the treatment of acute stroke based on findings of the NINDS stroke trial in 1995 (2). This double-blind placebo-controlled trial demonstrated that patients treated with rt-PA within 3 hours of symptom onset had a 30% greater likelihood of having minimal to no disability 90 days following treatment, compared to a placebo-treated group. There was a 6.4% risk of symptomatic intracerebral hemorrhage in the rt-PA treated group, compared to 0.6% in the placebo group. However, even considering the risk of bleeding, the mortality at 90 days was 21% in the placebo group, and only 17% in the rt-PA group. Subsequent analyses have shown that these findings with rt-PA in the NINDS trial hold up for improved outcomes at the one-year time point (3). The benefits of early thrombolytic therapy are corroborated by the results of two European Cooperative Stroke Studies, as well as clinical experience, substantiating the effectiveness of rt-PA when used according to the guidelines of the clinical trials (4).

More recently, the third European Cooperative Stroke Study showed benefit for patients who were treated between 3 and 4.5 hours from symptom onset. Patients treated within this time window were more likely to have a favorable outcome (52.4% vs. 45.2%). However, there was a higher incidence of intracranial hemorrhage in the treatment group. The Food and Drug Administration considered this study to be insufficient to approve the use of rt-PA beyond the three-hour window (5). Current American Heart Association/American Stroke Association guidelines recommend treatment of patients in the 3- to 4.5-hour time period, excluding those who are more than 80 years old, those who are taking oral anticoagulants independent of international normalized ratio (INR), and those with NIHSS > 25, ischemia involving more than one-third of the MCA territory, and those with history of both stroke and diabetes mellitus (6).

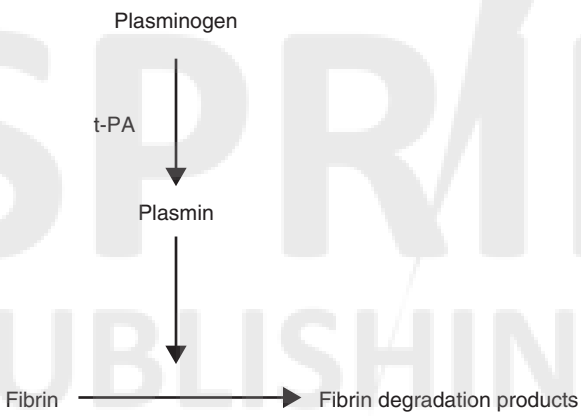

FIGURE 3.2 Diagram showing the site of action of recombinant t-PA to activate plasmin, which mediates fibrinolysis.

If it is determined that a patient's symptoms have been present less than 3 hours, there are other criteria that must be considered to determine if a patient is to be considered for rt-PA administration. These criteria are listed in Figure 3.3. If the patient is brought in between 3 and 4.5 hours after symptom onset, treatment can be considered using the same criteria listed in Figure 3.3 with additional exclusions: age >80 years old, taking anticoagulants, NIHSS > 25, involvement of >1/3 of the MCA territory affected, and history of both stroke and diabetes mellitus.

The consideration of rapidly improving symptoms as they relate to thrombolytic therapy decision making has been somewhat problematic. Improvement over the baseline NIH score is not considered rapid improvement if the patient continues to have a significant deficit. A good rule of thumb has been to assume that the patient is not going to show further improvement in his or her condition. Is the deficit mild enough that the patient can continue to function at a high level? Even mild weakness might be devastating to an individual whose occupation depends on fine motor movements; hence, rt-PA could be a consideration in such patients, even if they have a low NIHSS value. Barber and colleagues noted that one-third of patients deemed to have mild stroke symptoms that excluded them from rt-PA treatment either died or were left in a dependent state (7).

A majority of acute stroke patients have elevated blood pressure at the time of admission and across the initial days after stroke, which must be carefully managed. After rt-PA is administered, the patient should be monitored for at least 24 hours in an intensive care facility. The present recommendations are to keep systolic blood pressure below 185 mmHg and diastolic below 110 mmHg. Labetalol or nicardipine are the recommended agents to lower blood pressure. The lower limits for blood pressure should be a diastolic of 60 mmHg. Serial neurologic examinations are requisite, with appropriate clinical pathways for emergent management of complications such as symptomatic intracranial hemorrhage.

Imaging and Laboratory Studies

Stroke outcome is highly dependent on time; therefore, all eligible patients should be treated with rt-PA within 60 minutes of hospital arrival. Hospitals should determine the delaying steps in their process and work with the different departments to improve the flow.

If any of the following are answered YES, Patient may NOT receive rt-PA

☐ Yes ☐ No Stroke symptom onset more than 3 hours (last time patient was known to be without stroke symptoms)
☐ Yes ☐ No Age 18 or younger
☐ Yes ☐ No Comatose or unresponsive
☐ Yes ☐ No Stroke symptoms clearing spontaneously. Stroke symptoms minor and isolated
☐ Yes ☐ No Intracranial/Subarachnoid hemorrhage (SAH). Clinincal history suggestive of SAH even if CT negative
☐ Yes ☐ No Active internal bleeding or acute trauma (fracture) on examination
☐ Yes ☐ No INR greater than 1.7
☐ Yes ☐ No Platelet count less than 100,000
☐ Yes ☐ No Glucose less than 50
☐ Yes ☐ No HTN uncontrolled despite medication with systolic BP greater than 185 or diastolic BP greater than 110

History of:

☐ Yes ☐ No Active malignancy
☐ Yes ☐ No Recent MI or pericarditis within the past 3 months
☐ Yes ☐ No Recent arterial puncture at noncompressible site within previous 7 days (such as subclavian)
☐ Yes ☐ No Lumbar puncture within 3 days
☐ Yes ☐ No History of GI or urinary hemorrhage within 21 days
☐ Yes ☐ No Pregnancy, lactation, or childbirth within 30 days
☐ Yes ☐ No History of intracranial hemorrhage
☐ Yes ☐ No Major surgery or serious trauma within in past 14 days
☐ Yes ☐ No Seizure with postictal residual neurologic impairment
☐ Yes ☐ No Major ischemic stroke or head trauma within the past 3 months
☐ Yes ☐ No Heparin within 48 hours with PTT greater than upper limits of normal
☐ Yes ☐ No Known AV malformation or aneurysm
☐ Yes ☐ No Known bleeding disorder

FIGURE 3.3 Clinical criteria that must be considered when determining eligibility for rt-PA therapy.

A CT scan should be performed as soon as possible to exclude a hemorrhagic stroke. The CT scan may also demonstrate subtle early signs of infarction. Although the presence of these signs is associated with a poor outcome, this does not preclude the use of rt-PA unless there is evidence of hemorrhage. Only a noncontrast head CT is necessary to treat patients; obtaining advanced imaging is usually associated with delays in treatment.

Further considerations relevant to management in the acute stroke setting include evaluation of glucose, systemic antithrombotic status, and blood pressure. In the acute stroke setting, glucose is important to determine, as hypoglycemia can be associated with focal neurologic deficits, while patients with hyperglycemia have a less favorable prognosis. Partial thromboplastin time (PTT), INR for prothrombin time, and platelet count should be obtained to prevent the use of thrombolytic therapy in patients with coagulation defects. However, for patients without known coagulopathy who are not taking anticoagulants, current guidelines recommend waiting only for finger stick glucose before treatment with rt-PA to avoid delays in treatment (6).

INPATIENT CARE OF ACUTE ISCHEMIC STROKE

Numerous studies have shown that patients admitted to specialized stroke units with multidisciplinary teams have reduced lengths of stay, reduced mortality, and better functional outcomes (8)—findings that have been translated into clinical practice with similar positive results (9). Among the issues that are central to inpatient care are management of blood pressure, blood glucose, fluid balance, close neurologic monitoring to detect any signs or symptoms of clinical deterioration, prevention of common poststroke complications, and initiation of appropriate secondary stroke prevention measures. Early rehabilitation includes assessment for therapy needs with initiation of early mobilization, and comprehensive treatment plans, which should involve the family and caregivers and plans for continuity of care.

Blood Pressure, Fluid, and Glucose Management

Blood pressure management in the acute stroke patient is not the same as for the general population. Normally, cerebral autoregulation results in a constant CBF for mean arterial pressures between 60 and 160 mmHg. However, autoregulation may be lost in the acute stroke setting, and as a result, decreasing blood pressure decreases CBF in the area of ischemia. Extreme hypertension should also be avoided, as it may cause hemorrhagic transformation of the infarct, encephalopathy, and result in systemic complications. The optimal range of blood pressure in the acute stroke setting is not well established. For patients who are not candidates for rt-PA, unless there is a cardiac, renal, or other medical reason for which the pressure must be lowered, the current recommendation is to treat the blood pressure only when it is above 220/120 mmHg. Agents such as

sublingual nifedipine that lower the blood pressure quickly should be avoided. A reasonable decrease in blood pressure would be 15% over 24 hours. For patients who have pre-existing hypertension and are taking antihypertensive medications, it is generally agreed that antihypertensive medications should be temporarily held or reduced, but can be restarted at 24 hours if the patients are neurologically stable, unless a specific contraindication to restarting treatment is known.

Hypotonic and glucose-containing intravenous fluids are not recommended in the acute setting of cerebral infarction. Cytotoxic edema resulting from cellular membrane disruption with resulting swelling of the cell body develops with infarct. The use of these solutions can increase the cellular damage with influx of water into the cell. Normal saline is, therefore, generally utilized in these patients.

Hypoglycemia can mimic stroke symptoms and, if severe, can result in neuronal injury. Blood glucose should be checked immediately in patients presenting with stroke symptoms, with rapid correction of hypoglycemia. Numerous studies have shown that, in addition to hypoglycemia, sustained glucose greater than 140 predicts less favorable stroke outcomes than lower glucose values. Hyperglycemia after acute ischemic stroke has been shown to predict higher mortality and worse 90-day clinical outcomes for individuals with and without preexisting history of type 2 diabetes mellitus (10), and appears to blunt the beneficial effect of early recanalization that accompanies rt-PA therapy (11). Glucose levels should be monitored, and if greater than 140 to 180, treatment with insulin is similar to management in other medical intensive care conditions, with close monitoring to prevent hypoglycemia.

Evaluating and Managing Neurologic Deterioration

Between 15% and 30% of individuals with acute ischemic stroke experience neurologic deterioration during the acute hospitalization period, and this portends a much poorer prognosis (12). Factors linked to early neurological deterioration tend to be neurovascular, including stroke in progression, recurrent stroke, brain swelling, and hemorrhagic transformation (13). Neurologic factors beyond recurrent or progressing stroke that can mediate clinical deterioration in the acute hospital setting include brain swelling with mass effect, herniation syndromes, hemorrhagic transformation of ischemic stroke, and seizures, including subclinical variants that are difficult to diagnose without electroencephalography and can greatly compromise stroke outcomes. A number of other potentially modifiable systemic and medical factors must be considered. They include evaluation of cardiopulmonary and fluid status, glucose and electrolyte status, assessment for infection, and metabolic and toxic abnormalities, as well as consideration of medication side effects. Any neurologic deterioration or signs of fluctuating mental status should trigger rapid assessment for possible etiologies of worsening (12).

Management of Malignant Cerebral Edema

The management of malignant cerebral edema in large infarctions has historically proved problematic. Clinical signs of brain edema from large supratentorial cerebral infarctions typically begin with a decreased level of consciousness, followed by upper brainstem signs and involvement of anterior and posterior cerebral arterial territories. Malignant cerebral edema typically presents within the first 5 days, including one-third of cases within less than 24 hours, and portends a poor prognosis, with fatality approaching 80% regardless of medical management (14–16). Pooled analyses from three European randomized clinical trials showed that decompressive surgery performed within 48 hours of stroke onset reduces mortality (78% vs. 29%) and increases the likelihood of achieving a favorable 1-year outcome, defined as Modified Rankin Score of 4 or less, when compared to usual medical management (75% vs. 24%) (16). To place this in perspective, a modified Rankin of 4 indicates moderately severe deficits: inability to walk or attend to activities of daily living (ADLs) without assistance (17). Early decompressive surgery also led to doubling of chances to recover to a Modified Rankin Score of 3 or less by 1 year; a score of 3 indicates moderate disability, ability to walk without assistance. Notably, chances of surviving with severe disability (Score 5, bedridden, incontinent, requiring constant nursing) were not different for decompressive surgery versus usual medical care (4% vs. 5%). Note that these favorable outcomes for decompressive surgery come from studies that employ strict eligibility and exclusion requirements, including age 60 years or less, NIHSS greater than 15 in the setting of more than 1/2 MCA territory infarction, and with no space-occupying hemorrhagic lesions, fixed dilated pupils, or other major illnesses that could affect outcomes. These factors must be taken into consideration when making decisions regarding early decompressive surgery for individual patients.

Seizures

Any change in mental status, particularly episodic, should trigger evaluation for seizures. Incidence of seizures is reported at 9% for ischemic stroke (18). By contrast, seizures are reported in one-third of intracranial hemorrhage cases, and clinical studies suggest that more than half of these are electrographic only, and are not accompanied by clinical signs or symptoms of seizure (19). Specifically, continuous EEG recording has revealed seizures in up to 36% of lobar intracranial hemorrhage; contrary to conventional thinking, convulsive or nonconvulsive seizures are reported in 21% of subcortical intracranial hemorrhage cases, and they are linked to increased hemispheric mass effect and poorer outcomes (20). Seizures increase cerebral metabolic demands and intracranial pressure; generalized seizures can increase body temperature. All these factors can potentially worsen neurologic status and extend brain infarction in individuals with ischemic or hemorrhagic stroke, conditions in which cerebral autoregulation is already impaired. Hence, seizures must be treated

urgently in the setting of stroke. Likewise, suspicion of subclinical seizures warrants bedside electroencephalography and monitoring, along with rapid and aggressive anticonvulsant therapy, if seizures are diagnosed.

Infection

Infection is known to be a prothrombotic trigger mechanism in as many as 25% to 33% of ischemic strokes, and has long been recognized as an etiology for clinical worsening in the setting of acute stroke (21–23). Therefore, survey for infection is recommended at the time of initial stroke presentation, and comprehensive infection evaluation should be conducted if clinical deterioration occurs. Aspiration pneumonia and urinary tract infections are the most prevalent and must be treated aggressively. Because acute infection is linked to a prothrombotic state, and elevated temperature can accelerate neuroexcitotoxicity, both fever and infection must be aggressively treated in the acute stroke setting to protect the brain from further ischemic damage.

Dysphagia, Aspiration Risk, and Nutritional Management

One of the major dangers following stroke is aspiration, which may be silent, resulting in aspiration pneumonia. Dysphagia occurs in nearly half of hospitalized stroke patients and strongly predisposes to risk for aspiration pneumonia. Notably, the presence of a gag reflex is not indicative of safety in swallowing. Therefore, patients should be kept NPO until a bedside evaluation can be performed. Speech and language therapists play a significant role in this evaluation, and a videofluoroscopy swallowing study is recommended if bedside screening reveals abnormalities. If the patient is deemed to be at risk of aspiration, a dysphagia therapy program should be provided, optimally in consultation with a speech/language professional, as this has been shown to reduce pneumonia in the acute phase of stroke. Individuals at high risk for aspiration pneumonia may require nasogastric feeding tubes or percutaneous endoscopic gastrostomy (PEG). There is controversy regarding which is safer and more effective. While prior reviews provided some initial suggestions that PEG might be more efficacious (24), emerging evidence based on meta-analyses of 15 prospective studies suggests that nasogastric tubes are not associated with higher death rates, as previously believed (25). Hence, best clinical judgment must be used until the results of further clinical research are available. Dysphagia also identifies individuals who are inherently at greater risk for developing malnutrition, which is reported in 15% of stroke cases at the time of initial presentation, and doubles to 30% across the first week of hospitalization (26). Because malnutrition is linked to poorer clinical outcomes, ongoing monitoring of nutritional as well as hydration and electrolyte status becomes an important component of clinical pathways for stroke, particularly in individuals with dysphagia and compromised oral intake (27).

Antithrombotic and Anticoagulant Therapy

Aspirin is the antiplatelet agent that has been most extensively studied in the management of acute stroke. The combined results of two large acute stroke trials demonstrated a modest benefit in mortality and disability when aspirin therapy was initiated within 48 hours of stroke (28,29). This led to a recommendation of instituting aspirin at a dose of 325 mg within the first 48 hours after stroke. For patients who have received rt-PA, aspirin is not recommended within 24 hours of rt-PA administration.

The efficacy of other antiplatelet agents as monotherapy or in combination with aspirin is not well established for acute stroke. A 2007 study compared clopidogrel plus aspirin to aspirin alone given within 24 hours of onset of minor stroke (NIHSS < 4) or transient ischemic attack (TIA) (30). There was a 7% recurrent stroke incidence in the combined group, compared to 11% in the aspirin group. However, this did not reach statistical significance. The recent CHANCE trial demonstrated that the combination of aspirin and clopidogrel initiated within 24 hours of stroke or TIA was superior to aspirin alone in preventing recurrent stroke, without an increase in hemorrhagic complications, in a Chinese population (31). A similar study (POINT) comparing the combination of aspirin and clopidogrel to aspirin alone is currently underway in North America. Combinations of antithrombotic agents are generally not recommended for long-term secondary stroke prevention, as they are linked to increased bleeding risks (32–34).

Anticoagulants are generally avoided in the treatment of acute stroke. Numerous studies have shown that although the use of heparin or heparinoids in the management of acute stroke results in a decrease in the risk of early recurrence of stroke, there is an increased risk of hemorrhagic complications, including symptomatic intracerebral hemorrhage, with the use of anticoagulants (29). An example of this is seen in Figure 3.4. Historically, heparin had often been used acutely in patients with suspected cardioembolic stroke, such as those

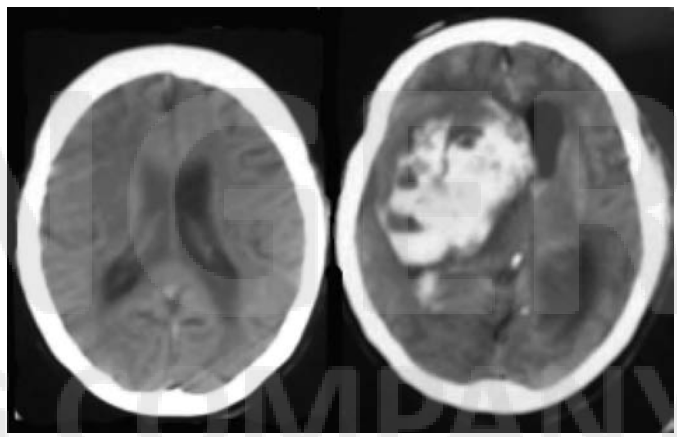

FIGURE 3.4 Patient presents at 10 a.m. with left hemiparesis, and the scan on the left is obtained. Heparin was started. At 4 p.m., the patient becomes obtunded, and the scan on the right is obtained.

with atrial fibrillation, to prevent early recurrence. However, in randomized clinical trials, no subgroup or arterial distribution has been identified in which urgent anticoagulation has demonstrated a significant benefit, when also considering the risk of bleeding. In an observational study, bridging with heparin for patients initiating oral anticoagulant therapy did not reduce the rate of early recurrent stroke (35). Acute anticoagulation may be used in certain high-risk patients, such as those with intracardiac thrombus or intra-arterial thrombus with or without arterial dissection, though the evidence to support its use is limited. As with antiplatelet agents, anticoagulants should not be utilized within 24 hours of rt-PA administration.

Early Rehabilitation Care and Mobilization

Consensus recommendations support early mobilization in appropriate medically stable subjects (36). While medical instability can limit the scope of rehabilitation early on, there are numerous physiological reasons for early care emphasizing mobility, including prevention of deep venous thrombosis, pressure ulcers, autonomic deconditioning, skin and lung infections, contracture formation, and muscular wasting. Muscular wasting can be rapid and devastating for functional recovery, particularly in frail elderly subjects. For those patients incapable of volitional muscle activation because of altered consciousness or severe motor deficits, early range-of-motion exercises and/or appropriate splinting as indicated to reduce contracture development, along with change of body positioning and other strategies to minimize skin pressure and friction, are recommended to minimize common post-stroke complications of contractures and pressure ulcers, respectively. For individuals with cardiopulmonary stability with higher neurologic function, resumption with appropriate supervision and training in basic mobility, self-care, and socialization skills is fundamental to early comprehensive rehabilitation care (36). Involvement of family and caregivers, including provision of structured written materials mapping rehabilitation plans and issues, is strongly recommended.

Prevention of Deep Venous Thrombosis

Patients with stroke often have deficits that impair their ability to ambulate safely, or even cause them to be confined to bed. This immobilization, along with elements of the prothrombotic state that are associated with acute ischemic stroke, increase the risk for deep venous thrombosis and associated pulmonary embolism. Therefore, measures should be taken to prevent this complication. Consensus recommendations strongly support the use of subcutaneous low-dose unfractionated heparin or low molecular weight heparin or heparinoids (37). Some evidence exists that the latter may have greater efficacy. For example, a study by Sherman and Alpers indicated a 43% improvement in venous thromboembolism in patients treated with the heparinoid enoxaparin given 40 mg subcutaneously daily, compared to subcutaneous unfractionated heparin given twice a day (38). This is consistent with meta-analyses concluding that both unfractionated heparin and low molecular weight heparin/heparinoids are partially effective in reducing deep venous thrombosis, but some evidence suggests that low molecular weight heparinoids may be more effective (39). As previously stated, heparin should not be used during the initial 24 hours of postthrombolytic therapy. Intermittent pneumatic compression devices (or elastic stockings) can also be used to help prevent deep vein thrombosis in patients with contraindications to anticoagulants, and for individuals presenting with acute intracranial hemorrhage; stable patients with intracranial hemorrhage may be switched over to low-dose subcutaneous heparin as early as the second day postevent. Aspirin may provide some mild benefit, and is safe to use in combination with low-dose heparin. Regardless of the medical coverage, early mobilization (preferably in collaboration with physical therapy consultation) and walking are important and can significantly reduce the risk for venous thrombosis (37).

Skin Care and Prevention of Pressure Ulcers

Pressure ulcers occur in approximately one-tenth of hospitalized stroke patients and one-fourth of those in nursing homes. Individuals at particular risk are those with mobility deficits of greater severity and medical conditions that compromise skin vascular integrity (including diabetes and peripheral arterial occlusive disease), those with urinary incontinence, and frail elderly patients with low body mass. Nursing pathways for stroke employ daily monitoring of skin integrity, and scheduled care including turning, proper positioning, and other appropriate methodologies to reduce the pressure and friction that propagate pressure ulcer formation (37,40). This includes the use of pressure-relief ankle-foot orthoses as a means to prevent contractures and pressure sore development. Consistent with clinical rehabilitation practice guidelines, early physical therapy assessment and care to optimize recovery of mobilization are also recommended to reduce the longitudinal risk profile for skin breakdown and pressure ulcer development.

Incontinence

Urinary incontinence is a prevalent early problem after stroke, occurring in about half of hospitalized cases, and decreasing in prevalence to 20% in the chronic poststroke recovery period. Factors increasing the predisposition to urinary incontinence are similar to those for pressure ulcers: greater stroke severity, diabetes, and advanced age. Because of the extremely high prevalence of urinary incontinence (and often fecal incontinence) in individuals with moderate to severe stroke, indwelling catheters are often used during the acute stage. This can facilitate fluid management and reduce the risk for skin breakdown. However, continued indwelling catheter usage for more than 48 hours predisposes to infection. During acute stroke hospitalization, assessment for urinary retention should be conducted via catheterization or bladder scan, urinary volume and control assessed, and dysuria documented. Some evidence exists that

silver alloy-coated catheters may have fewer complications. Regardless, it is optimal to discontinue indwelling catheter use after 48 hours, and to employ an individualized bladder training program with prompted voiding training for appropriate cases (37). Similarly, bowel incontinence is common after stroke and can be associated with an increased risk for skin breakdown and infection complications. Patients should be carefully assessed for presence, pattern, and etiology of fecal incontinence, including consideration of mental status and neuromotor control of sphincter function, diarrhea, or constipation with diarrhea around a hardened stool mass, medication, and potential infectious complications that can increase the risk for fecal incontinence. Physical therapy to optimize mobility recovery can be useful, as physical activity can influence gastrointestinal transit time. Maintaining skin cleanliness and integrity of the perineal area is crucial, along with attention to dietary fiber content, and implementation of a time-structured regular bowel program and associated medications as clinically indicated.

Cognitive Function and Communication

Global alterations in mental status, as well as a spectrum of specific neuropsychologic syndromes, are highly prevalent during the acute phase of stroke. Approximately one-third of stroke patients have a globally altered mental status during their acute hospitalization that can influence all other cognitive and communication assessments and limit early rehabilitation participation. The first item of the NIHSS categorically documents consciousness level. Those with stupor (or coma), or who fluctuate between drowsiness and stupor, regardless of cardiopulmonary stability, are best managed in a more intensive care setting, with frequent examinations documenting the specific stimuli needed to produce arousal. This enables a more rapid detection of fluctuating or progressing strokes and triggers urgent evaluation pathways. All patients with adequate alertness require evaluation for visual, motor, and sensory hemineglect syndromes, aphasia and apraxia, memory deficits, and impaired executive function—all factors that influence acute and longitudinal rehabilitation care pathways.

Some symptoms, such as denial of deficit and hemineglect syndromes, particularly in visual and motor domains, also lead to challenges for the therapist and safety concerns, as the patient may not realize there is a dysfunction. These and other prevalent poststroke neuropsychologic syndromes should optimally be identified during the acute hospitalization period and their significance explained to caregivers and future rehabilitation providers to optimize continuity of care. Assessment of communication skills, including speech, comprehension, repetition, reading, and writing, with speech/language therapist consultation is a standard of care. Early initiation of speech therapy, including visual communication aids, may be useful to facilitate patients' interaction with staff for routine care, and for socialization with family.

Other elements of neurocognitive health that are often overlooked during the acute hospitalization stage are mood and sleep integrity. Approximately one-third of stroke survivors develop some form of depression, which in many cases can be identified even during acute care hospitalization. Early recognition and management of depression is requisite to optimizing long-term rehabilitation outcomes. Sleep disordered breathing is also highly prevalent after stroke, particularly during the acute and subacute stroke recovery period, where fragmented sleep architecture and/or apnea have been reported in more than half of patients (41,42). A particular concern is obstructive sleep apnea that is linked to increased stroke risk and prothrombotic state, and may be associated with or exacerbate other neuropsychologic issues such as fatigue, depression, and memory impairment: factors that can complicate rehabilitation and recovery (43,44). Individuals fitting the profile for sleep disordered breathing may be screened using nocturnal pulse oxymetry, or further evaluated by polysomnography as clinically indicated. Many acute stroke patients have a disturbed sleep–wake cycle, particularly when in intensive care units. Approaches to improving sleep hygiene include transferring the patient from the intensive care unit as soon as possible, and providing a quiet environment with dark during the night and sunlight during the day to facilitate return of more normal circadian patterns. Selected medications properly timed may be used to facilitate sleep (e.g., trazadone, chloral hydrate), to try to avoid regular use of major sedative-hypnotics and antipsychotics, which can contribute to confused states, particularly in the elderly, and may further alter sleep architecture. Because abnormal sleep architecture is common in acute stroke, and given increasing evidence suggesting that sleep is critical to memory consolidation and, hence, may facilitate sensorimotor recovery in the rehabilitation setting, careful attention to sleep hygiene should be addressed early on (42–44).

In summary, a diversity of neurocognitive and communication deficits, as well as sleep disturbances, can complicate early stroke management and ongoing rehabilitation care. A summary of all cognitive and communication deficits and neuropsychologic syndromes, including depression and sleep disorders, that are diagnosed during acute hospitalization should be discussed with the family and outlined to subsequent care providers to optimize continuity of stroke care.

Screening for Risk Factors

Risk factors for stroke include hypertension, which increases both small and large vessel arterial atherothrombotic risk, atrial fibrillation, and selected other cardiac arrhythmias, extracranial carotid and intracranial large vessel stenosis, cardiomyopathy, hyperlipidemia, vasculitis, cigarette smoking, hypercoagulable states, diabetes, syphilis, elevated C-reactive protein, and elevated homocysteine levels. A timely evaluation of these risk factors is recommended in patients with acute stroke and TIA. Here we present a brief overview of a few of these risk factors and secondary stroke prevention measures, which are covered in more detail in later chapters.

Carotid artery stenosis is an important cause of ischemic stroke. Carotid ultrasound may be used for screening patients, as it has a sensitivity of approximately 85%, compared to digital arteriography. In combination with MR angiography, the sensitivity of detecting carotid stenosis improves to close to 100%. CT angiography is also helpful in assessing carotid lesions, with a sensitivity of 88% to 98% depending on the study. If a question remains regarding the lesion, catheter arteriography may be necessary. These studies are also needed to evaluate for less common conditions such as arterial dissection.

In patients with carotid stenosis greater than 70%, the North American Symptomatic Carotid Endarterectomy Trial indicated that carotid endarterectomy reduced the risk of ipsilateral stroke from 26% to 9%, compared to medical management at 2 years (45). There was no significant change between the groups for less severe stenosis. The surgical/arteriographic risk for these procedures was less than 3%. For patients who are at higher risk, the benefits of endarterectomy compared to medical therapy would be less, perhaps indicating that medical management would be preferable. The greatest benefit occurred when surgery was performed within two weeks of symptom onset.

Carotid artery stenting is an alternative, less invasive method of revascularization. The CREST trial compared stenting to endarterectomy in patients with asymptomatic and symptomatic carotid stenosis, and found no difference in the composite endpoint of stroke, myocardial infarction, or death (46). There was a higher risk of stroke in the stenting group, and a higher risk of myocardial infarction in the endarterectomy group. Notably, younger patients had fewer events with stenting, whereas older patients did better with endarterectomy. Carotid artery stenting is also suitable for patients who have contraindications to surgery, such as prior radiation treatment to the neck or lesions that cannot be approached surgically.

Hyperlipidemia is a risk for cardiovascular disease and, to a lesser degree, cerebrovascular disease. Current guidelines recommend treatment with HMG-CoA reductase inhibitors (statins) for patients with clinical atherosclerotic cardiovascular disease, including stroke or TIA. High-dose atorvastatin has been shown to decrease the risk of recurrent stroke (47). The benefit of statins after stroke may not be due solely to cholesterol reduction, as they also have effects on CBF, endothelial function, and anti-inflammatory properties. The use of statins for neuroprotection is currently being investigated in humans.

Cardiac monitoring is essential for stroke patients for detection of atrial fibrillation and other cardiac arrhythmias, at least for the first 24 hours after stroke. The risk of atrial fibrillation increases with age and comorbid conditions such as congestive heart failure, hypertension, and diabetes. More prolonged monitoring on an outpatient basis increases the chances of detecting paroxysmal atrial fibrillation. The use of anticoagulants significantly decreases the risk of thromboembolism in patients with atrial fibrillation. Warfarin decreases the risk of thromboembolic events by two-thirds (48), and the newer oral anticoagulants, such as dabigatran, rivaroxaban, and apixaban, have similar, or reduced, rates of thromboembolic events compared to warfarin (49–51). Aspirin decreases the risk slightly, but is significantly less effective than warfarin.

Cigarette smoking is another major modifiable risk factor. All smokers should receive counseling and education regarding the importance of smoking cessation. Several agents and techniques are available to help patients with this endeavor. They include nicotine patch and gum, hypnosis, and pharmacological agents such as varenicline and bupropion.

DISPOSITION AND DISCHARGE PLANNING

Decisions regarding the level of care for ongoing rehabilitation, particularly whether intensive inpatient rehabilitation is needed, should be made by the primary medical or neurologic team in consultation with rehabilitation providers. Three criteria influence the triage decision:

1. The premorbid and current functional statuses of the stroke survivor
2. The psychosocial and financial systems to support the stroke survivor in the community
3. The conditions of third-party reimbursement

The first criterion is heavily weighted by the recommendations of the physical, occupational, and speech/language therapists. Consideration must be given to whether the candidate has adequate physical and neurocognitive capacity to perform basic ADL functions, including mobility with safety using the appropriate assistive device and/or orthosis. For individuals with mobility deficits and elevated fall risk, a home assessment may be recommended to optimize safety and facilitate ADL functionality. Some individuals may require the capacity to maintain their own instrumental ADL functions, such as banking, shopping, and cooking, for independent functioning. This involves higher levels of communicative and cognitive skills for home management, community living, health management, and the ability to react safely and correctly to emergency situations. Hence, instrumental ADL status must be ascertained prior to discharge, and a follow-up plan for repeated assessment made in the event of discharge to the community.

Psychosocial and financial systems are essential to support the stroke survivor if he or she wishes to return to the community. If the caregivers are ready, willing, and able to assist or supervise the stroke survivor in the community, the stroke survivor may be admitted to an inpatient rehabilitation facility. If the stroke survivor has inadequate support systems to return to the community, it may be prudent to transfer him or her to a less intensive environment, to give the individual more time for spontaneous improvement. If the stroke survivor remains at an assisted functional level

that cannot be supported in the community, he or she will ultimately be transferred to a long-term care facility.

The final component of the rehabilitation triage decision rests, ultimately, upon the type of third-party payer policy under which the stroke survivor is covered. Although most insurance policies carry contingencies for different levels of rehabilitation care, some may limit the amount of inpatient and/or outpatient coverage per diagnosis. Some may not have provisions for specific levels of rehabilitation. Some may force the stroke survivor to pay for a portion of his or her rehabilitation hospital bills. Some may limit their networks to specific inpatient rehabilitation facilities. In any case, it is imperative for the stroke survivor and his or her caregiver to review the insurance policy to ensure proper coverage in the event of a catastrophic event such as stroke. It is equally essential for the case manager to review the policy and confirm benefits before transferring a stroke survivor to an inpatient rehabilitation facility, to ensure that the third-party payer will pay for the rehabilitation stay and to minimize the financial liability for the stroke survivor and caregiver.

A comprehensive rehabilitation follow-up plan should be set in motion before any community discharge. Attention should be given to therapeutic modalities and prevention of poststroke complications. Other factors such as return to work, driving, sexual function, adaptive equipment, social adjustments, and planning free-living physical activity and health-promoting exercise are generally managed in the outpatient environment and are dealt with in other chapters.

TRANSIENT CEREBRAL ISCHEMIA OR MILD STROKE SYMPTOMS

TIAs were previously defined as stroke symptoms that subsided within 24 hours. With the advent of rt-PA treatment, which requires treatment within 3 hours, that definition has been modified. Indeed, MRI studies with diffusion weighted imaging have indicated that more than half of the patients whose symptoms lasted more than 60 minutes actually have areas of infarction despite resolution of symptoms. Although the clinical symptoms in TIA may have subsided, it is important that the patient be thoroughly evaluated. Emerging guidelines for evaluation and acute medical management of TIA are now moving toward paralleling those of acute ischemic stroke (52). This approach toward the rapid management of TIA is being driven by an increasing recognition that many clinical events formerly classified as TIAs do, indeed, result in structural damage to the brain, and because the cerebrovascular event rate following TIA is dangerously high (52,53). Hence, TIA should be considered a medical emergency, with an imperative to optimize comprehensive secondary prevention strategies immediately.

Meta-analyses of 11 prospective studies suggest that, following a TIA, the risk for recurrent stroke is 3.5%, 8%, and 9.2% at 2, 30, and 90 days post-TIA, respectively (53). Twenty-one percent of these strokes are fatal, with another 64% resulting in disability. Rapid evaluation and management of patients with TIA, therefore, offer an opportunity to intervene and prevent a significant number of strokes. Indeed, studies from Paris and Oxfordshire, United Kingdom, have indicated that early evaluation may decrease the risk of stroke in the 90-day period by as much as 80% (54). Notably, the mean time to comprehensive clinical evaluation in the EXPRESS prospective study of stroke prevention following TIA was less than one day, which underscores the importance of rapid care (54). The development of dedicated clinics that see the patient immediately and institute the evaluation of the TIA patient has been possible in some communities. This approach also allows for the timely evaluation and institution of appropriate treatment, but is not widely available.

CONCLUSIONS

The efficient management of acute stroke requires emergent and structured protocols for efficient patient management. When the patient has had an ischemic stroke, early treatment can result in improved clinical outcomes. Proper medical management, even in patients who are not candidates for thrombolytic or neurointerventional procedures, results in better outcomes. Studies have demonstrated a significant decrease in the number of patients with severe disability when treated in a dedicated stroke unit, compared to those treated in a general medical ward. Many hospitals are now developing programs such as Primary and Comprehensive Stroke Centers, and accreditation for these programs has been established. These programs also stress early rehabilitation plans for the patient. Evaluation of dysphagia to prevent aspiration, nutritional assessment and planning, early patient mobilization, cognitive and communication assessment and speech/language therapy, and measures to prevent skin breakdown and deep vein thrombosis are important components of these programs. The institution of timely rehabilitation measures can improve daily living function for the stroke patient.

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4

Neuroimaging of Acute Stroke

Daniel J. Boulter, Govind Mukundan, and Pamela W. Schaefer

For acute care of stroke patients, a number of computed tomography (CT) and magnetic resonance (MR) techniques are essential. Noncontrast CT excludes other causes of acute neurologic deficits and intracranial hemorrhage. CT and MR angiography can identify intravascular clots, and the CT angiography source images improve detection of acute infarction over plain CT. Diffusion MRI estimates the size, location, and age of infarcted core more precisely, and perfusion imaging estimates the ischemic penumbra. These new modalities play a critical role in determining which patients should undergo thrombolytic therapy.

Acute stroke imaging is rapidly advancing. Twenty years ago, state-of-the-art CT and MRI techniques were insensitive in detecting early acute stroke, and the diagnosis was usually presumptive. In the 1990s, diffusion-weighted MRI provided the first highly sensitive technique for visualizing acutely ischemic brain tissue. More recently, the development of CT and MR perfusion imaging has allowed the visualization of additional hypoperfused tissue at risk of infarction. The development, in concert, of CT and MR angiography has allowed highly reliable detection of proximal intravascular thrombus. Concomitant advances in stroke treatment provide a unique opportunity to direct and revolutionize stroke triage and management through imaging (1).

In this chapter, we review how conventional and advanced CT and MR imaging techniques are used to provide four types of information that are essential to the care of acute stroke patients (Table 4.1):

1. They establish the diagnosis of ischemic stroke and exclude other potential causes of an acute neurologic deficit.
2. They identify intracranial hemorrhage.
3. They identify the vascular lesion responsible for the ischemic event.
4. They provide additional characterization of brain tissue that may guide stroke therapy by determining the viability of different regions of the brain and distinguishing between irreversibly infarcted tissue and potentially salvageable tissue.

NONCONTRAST COMPUTED TOMOGRAPHY

CT is based on the measurement of x-ray beam attenuation through a region of interest, which is proportional to its density. Its low cost and accuracy in the detection of acute intracranial hemorrhage still make it the first-line diagnostic examination of choice in the emergency room setting in the United States. In addition to being performed to exclude hemorrhage, noncontrast CT (NCCT) is obtained primarily to exclude hypodensity in more than one-third of the middle cerebral artery territory and to exclude other causes of acute neurologic deficits, such as an intracranial mass lesion that would preclude the patient from receiving anticoagulation, thrombolytic therapy, or aggressive hypertensive therapy. One large study found that, among patients with symptoms of acute stroke, NCCT achieved a sensitivity and specificity of 90% and 99%, respectively, in detecting intracranial hemorrhage (2).

Noncontrast CT findings of acute stroke syndrome are subtle when present and include: loss of cortical, basal ganglia, or insular gray–white matter differentiation; loss of cortical sulci and reduction in sylvian fissure and basal cistern size caused by mild swelling; subtle parenchymal hypodensity; and hyperdensity within an intracranial vessel, such as the MCA, from acute thrombus (3) (Figure 4.1, Table 4.2). CT hypodensity is, in general, thought to be secondary to increased total tissue edema. Cytotoxic edema develops within 30 minutes of an acute embolic event caused by failure of Na^+K^+-ATPase and other ion pumps. Vasogenic edema develops at approximately four to six hours, secondary to disrupted endothelial tight junctions and reperfusion. Because cytotoxic edema results in net shift of water from the extracellular to the intracellular space, not an increase in total water, and CT hypodensity may appear before the onset of vasogenic edema, some authors have proposed that decreased blood volume causes early CT hypodensity (4).

Reported sensitivities of NCCT in the detection of acute infarction vary widely in the literature, secondary to dependence on time between symptom onset and imaging, the vascular territory involved, the generation of CT scanner, CT technique, viewing methodology, knowledge of clinical

TABLE 4.1 Critical Questions in the Imaging Evaluation of Acute Stroke

1. Is there hemorrhage?
2. Is the proximal intravascular thrombus a target for therapy?
3. Is there an infarct (or core) of irreversibly ischemic tissue?
4. Is there severely ischemic, but potentially salvageable, tissue (the penumbra)?

TABLE 4.2 NCCT Findings in Acute Ischemic Stroke

Parenchymal hypodensity
Hyperdense vessel sign
Loss of gray–white matter differentiation
Mild sulcal effacement
Exclusion criteria for receiving thrombolytic therapy
Intracranial hemorrhage
Hypodensity in greater than one-third of the MCA territory
Predictors of intracranial hemorrhage
Hypodensity in more than one-third of the MCA territory
ASPECTS score < 7

history, and reader experience. In one large retrospective study, in which the mean time from symptom onset to scanning was 2.3 hours and neuroradiologists blinded to clinical history interpreted the scans, the sensitivity in detecting acute infarction was 38% (5). The sensitivity improved to 52% when clinical history was provided. In another study of 30 patients, the sensitivity in detection of acute ischemia was 57% using standard windows (window 40 HU, level 80 HU) but improved to 71% with narrow windows (window 36 HU, level 30 HU) (5). (Radiodensity in CT is defined in Hounsfield Units—HU.) Reported specificities are high, ranging from 89% to 95% (6). In addition, one study found that the hyperdense middle cerebral artery sign was 100% specific for middle cerebral artery occlusion, but only 27% sensitive (7).

The hypodensity in NCCT has a number of important clinical implications. Multiple studies have confirmed that hypodensity on NCCT in the acute stroke setting almost always represents infarcted tissue. One study demonstrated that hypodense tissue on NCCT becomes necrotic with a probability of 97% (8). Hypodensity on NCCT correlates with stroke severity (8). The ECASS study demonstrated that hypodensity in more than one-third of the MCA territory correlates with an increased risk of hemorrhage following the administration of intravenous TPA; hypodensity in more than one-half of the MCA territory is associated with brain herniation (9).

The Alberta Stroke Program Early CT Score (ASPECTS) represents one effort to improve intra- and inter-rater reliability, by partially quantifying the extent of hypodensity on NCCT scans (10). In ASPECTS, 10 regions in the MCA territory are assigned a binary score of zero or one depending on the presence (one) or absence (zero) of hypodensity, and the total number of ischemic regions is subtracted from ten.

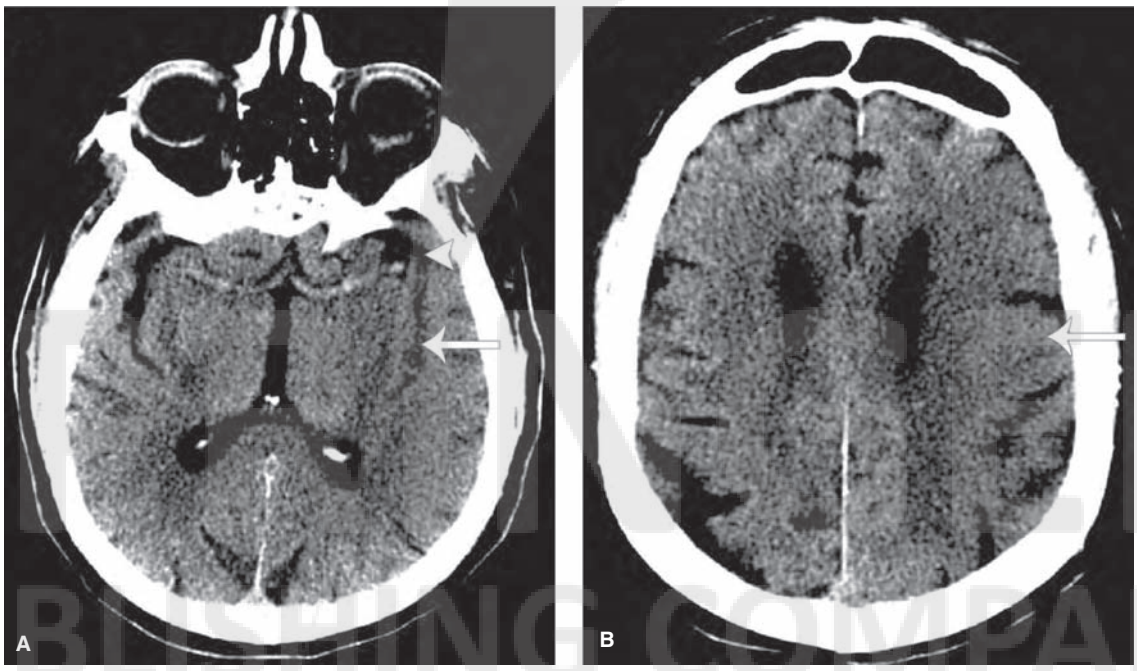

FIGURE 4.1 Early left MCA infarction. Sixty-year-old female with onset of left hemiparesis and aphasia four hours prior to imaging. There is hypodensity, loss of gray–white differentiation, and mild sulcal effacement throughout the visualized MCA territory (arrows). There is hyperdensity in the left MCA stem, consistent with acute thrombus (arrowhead).

ASPECTS may be helpful in deciding whether thrombolytic therapy should be initiated. One large study found that ASPECTS scores of seven or less are associated with a substantially increased risk of thrombolysis-related parenchymal hemorrhage (11). Reanalysis of data from another large study, the Pro-Urokinase for Acute Cerebral Thromboembolism II (PROACT-II) trial of patients randomized to intra-arterial thrombolysis within six hours of symptom onset, revealed that patients with an M1 or M2 occlusion and ASPECTS score greater than seven were three times more likely to have independent functional outcome compared with controls; patients with ASPECTS scores of seven or less were less likely to benefit from treatment (12). Neurointerventionalists who use NCCT to triage patients for intra-arterial reperfusion therapy typically do not treat patients with an ASPECTS score of less than five.

CONVENTIONAL MR IMAGING

T2 and FLAIR images, like NCCT, are capable of detecting parenchymal changes caused by vasogenic edema in acute ischemic stroke. However, because little vasogenic edema is present in the first six hours after stroke onset, parenchymal hyperintensity may be weak or absent. Furthermore, volume averaging of ischemic parenchyma and CSF can obscure small lesions. In one study, the sensitivity of T2 weighted images in the first 6 hours was only 18% (13). By suppressing the CSF signal, FLAIR has improved detection of infarctions in brain parenchyma adjacent to CSF such as cortex and periventricular white matter. The sensitivity of FLAIR imaging in the detection of parenchymal injury, however, is still as low as 29% in the first 6 hours (14). Besides parenchymal hyperintensity, other signs of acute stroke on MRI include the following: in T2 weighted images, loss of vascular flow voids; in FLAIR images, arterial hyperintensity in the clot and in collateral vessels because of slow flow; in gadolinium-enhanced T1-weighted images, vascular contrast enhancement in collateral vessels caused by slow flow; in gradient echo/T2* and susceptibility-weighted images (SWI) images, intravascular susceptibility (blooming) in the region of the acute thrombus; in SWI, prominent asymmetric hypointense cortical veins within the acutely ischemic region; and effacement of sulci, cisterns, and ventricles caused by mild swelling (Table 4.3, Figure 4.2). Gradient echo/T2* images and SWI are also highly sensitive in detecting hemorrhage.

TABLE 4.3 Appearance of Acute Arterial Infarcts on Conventional MRI

1. T2—loss of *arterial* flow void, subtle parenchymal hyperintensity
2. FLAIR—increased arterial signal, subtle parenchymal hyperintensity
3. Gradient echo/T2*—intravascular blooming in the region of the thrombus and hemorrhage
4. Susceptibility-weighted imaging—asymmetrically increased hypointensity of cortical draining veins, intravascular blooming in region of thrombus and hemorrhage
5. T1 postcontrast—arterial enhancement without parenchymal enhancement

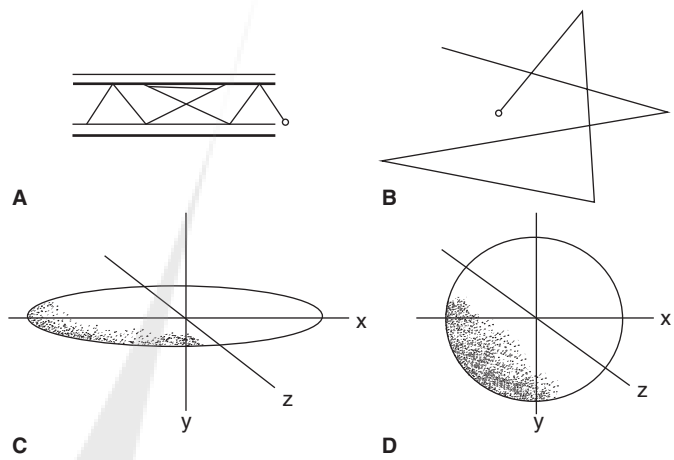

FIGURE 4.2 Anisotropic and isotropic diffusion of water molecules. Diagrammatic path of a water molecule within highly organized tissue such as white matter (A) and the associated three-dimensional representation of diffusion of water molecules in this system (C). Diagrammatic path of water in a non-bounded environment (B) and the associated three-dimensional representation of diffusion of water molecules in this system (D).

MRI DIFFUSION-WEIGHTED IMAGING

Diffusion-weighted imaging is an MR sequence with image contrast dependent on the magnitude of the relative motion or diffusion of water molecules. This property is particularly useful in the setting of acute strokes. Acute ischemia induces a cascade of metabolic and molecular changes that, within minutes, ultimately act to decrease the relative mobility of tissue water molecules in the affected parenchyma (15,16). The decrease in energy metabolism that leads to the failure of Na^+/K^+ ATPase and other ion pumps (15) results in loss of ionic gradients and net translocation of water from the extracellular to the intracellular compartment, where water movement is relatively more restricted. With cellular swelling, there is also a reduction in the extracellular space volume and increased tortuosity of extracellular space pathways (17). In addition, there are significant reductions in intracellular metabolite apparent diffusion coefficients (ADCs) that may be caused by increased intracellular viscosity from dissociation of microtubules and fragmentation of other cellular components, increased tortuosity of the intracellular space, and decreased cytoplasmic mobility.

Physical Principles and Diffusion MR Maps

MR is based on the principle of adding energy to the spins of hydrogen atoms in water molecules (referred to as *spins*)

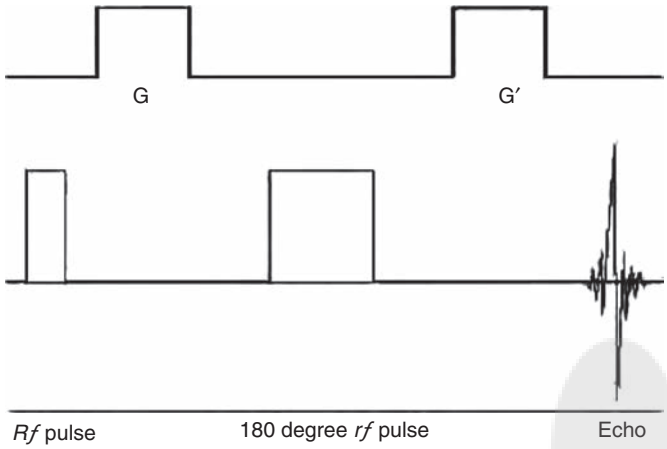

FIGURE 4.3 Fundamental Stejskal-Tanner diffusion MR scheme. During the first gradient lobe (G), the proton spins acquire phase shift. The 180-degree radio frequency (rf) pulse inverts all the spins. The second gradient lobe (G′) induces a second refocusing phase shift that is opposite to the first (caused by all spins inverted). Water protons that have not translocated have their phase shifts cancelled and lose no net signal (bright on image). Water protons that have migrated in space result in incomplete refocusing and incomplete cancellation of phase shift leading to loss of signal (dark on image).

and listening to the energy that is emitted back as the spins relax from their higher energy state to a lower basal state. The basic diffusion pulse sequence (Figure 4.3) consists of two equal applications of magnetic gradients with a 180-degree refocusing pulse in between (18). The first gradient causes the spins to go out of phase and lose signal. The 180-degree pulse inverts the phase of the spins. The second gradient refocuses the spins. Because the magnitudes of the gradients are identical, relatively immobile spins such as those in ischemic parenchyma are exposed to equal but opposite gradient-induced phase shifts, leaving their initial signal intact. This results in a relatively larger signal on the resultant diffusion-weighted MR image. However, the more the spins wander between the two gradient applications (e.g., with the diffusion of water in normal brain parenchyma), the more unequal the cancellation of their accumulated phase, resulting in loss of signal. Thus, normal parenchyma appears relatively hypointense compared to ischemic tissue.

Image Interpretation

Diffusion-weighted images (DWIs) and exponential images or apparent diffusion coefficient (ADC) maps should be available for review (Figure 4.4). It is important to understand that the DWIs indicate T2 signal differences as well as differences in diffusion. To remove the T2 contrast (called "shine-through"), the DWI can be divided by the echoplanar T2 image (or b 0 image) to give an exponential image. Alternatively, an ADC map, whose signal intensity is equal to the magnitude of the ADC, can be created. On DW images, regions with decreased diffusion (as in acute ischemia) are hyperintense. Regions with elevated diffusion (as in vasogenic edema) may be hypointense, isointense, or hyperintense, depending on the strength of the diffusion and T2 components. On exponential images, regions with decreased diffusion are hyperintense whereas lesions with elevated diffusion are hypointense. On ADC maps, regions with decreased diffusion are hypointense, whereas regions with elevated diffusion are hyperintense. For lesions with decreased diffusion, the DW images have superior lesion conspicuity. However, because hyperintense signal abnormality on DWI could result from the T2 component rather than from abnormal diffusion, review of the ADC maps or the exponential images is important.

Regardless of the mechanism, DWIs are highly sensitive and specific in the detection of hyperacute and acute stroke (19–21). Reported sensitivities and specificities are in the greater-than-90% range. The rare infarcts not identified on DWIs are typically very small lacunar brainstem or deep gray nuclei infarctions. False-positive DWIs may occur in patients with a subacute or chronic infarction because of T2 shine-through. In such cases, a lesion appears hyperintense on the DWI because of an increase in the T2 signal. This pitfall is easily avoided by interpreting the DWI in combination with ADC or exponential images (as described earlier). False-positive DWIs can also occur with decreased diffusion as a result of ion pump failure (seizures or hypoglycemia), high viscosity (abscess), dense cell packing (some tumors), and myelin vacuolization (Creutzfeldt Jakob disease, demyelinative lesions, or diffuse axonal injury). When these lesions are reviewed in combination with routine T1, T2, and gadolinium-enhanced T1-weighted images and clinical history, they can usually be readily differentiated from acute ischemic infarctions.

The DWI lesion is thought to represent tissue that is destined to infarct. Indeed, reversibility (abnormal on initial DWI but normal on follow-up images) of DWI hyperintense lesions is very rare and usually seen only in the setting of very early reperfusion following intravenous thrombolysis and/or intra-arterial recanalization procedures (22,23). Even with intravenous thrombolysis and intra-arterial recanalization procedures, the amount of DWI abnormal tissue that recovers is usually relatively small and typically more often involves white matter than gray matter. However, judging whether tissue with a diffusion abnormality is normal at follow-up is complicated. Such lesions may appear normal on follow-up DW, ADC, or T2-weighted images, but this may not reflect complete tissue recovery. Kidwell et al. reported a decrease in size from the initial DWI abnormality to the follow-up DWI abnormality immediately after IA thrombolysis in 8 of 18 patients (22). However, despite the initial apparent recovery, a subsequent increase in DWI lesion volume was observed in five patients. Furthermore, a number of studies have demonstrated that ADCs are significantly higher in DWI reversible tissue compared with DWI abnormal tissue that progresses to infarction. Mean ADCs

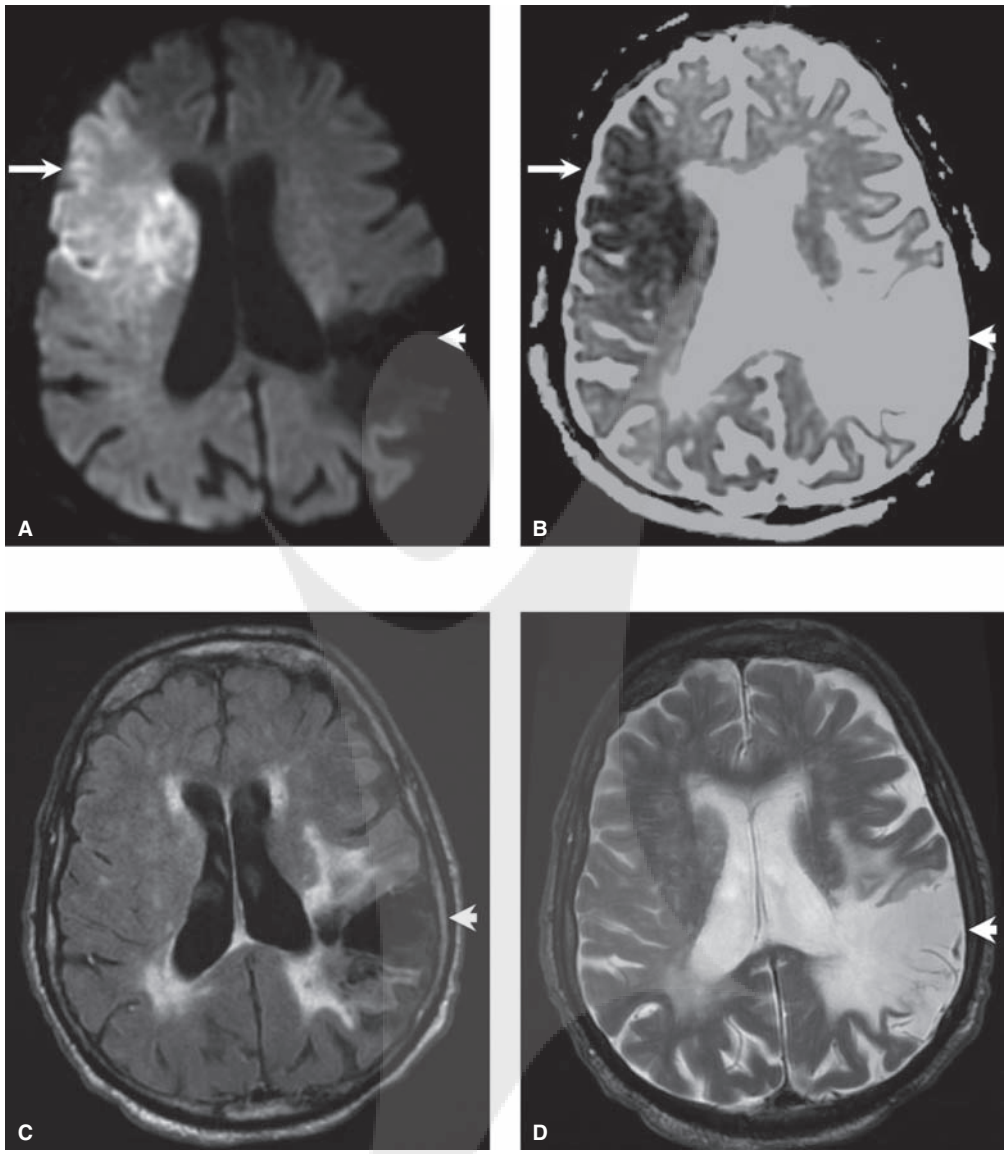

FIGURE 4.4 Acute and chronic infarction. Eighty-six-year-old male with atrial fibrillation with sudden onset of left hemiparesis four hours prior to MR imaging. There is restricted diffusion consistent with acute right MCA infarction, which is hyperintense on DWI (A) and hypointense on ADC map (B) images (arrows). FLAIR (C) and T2-weighted images (D) demonstrate no definite parenchymal abnormality in the region of the acute infarction. There is a chronic left parietal infarction, characterized by tissue cavitation and gliosis (arrowheads).

range from 663 to 732 × 10^{-6} mm^2/sec in DWI reversible regions, compared with 608 to 650 × 10^{-6} mm^2/sec in DWI abnormal regions that progress to infarction (22,24).

The temporal evolution of acute infarcts on DW imaging is of paramount importance, from both diagnostic and therapeutic standpoints (Figure 4.5, Table 4.4). The literature reports appreciable reduced diffusion as early as 30 minutes after an ischemic event. The ADC then decreases until it reaches a nadir at one to four days. This is reflected in marked signal hyperintensity on DWIs and exponential images, and marked signal hypointensity on ADC maps. Thereafter, with cell membrane disruption and the development of vasogenic edema, the diffusion coefficient begins to rise and returns to baseline at one to two weeks. At this point, a stroke is usually mildly hyperintense from the T2 component on the DWI and isointense on the ADC images (25). Thereafter, the ADC values continue to rise because of gliosis and/or cavitation with increased extracellular water. There is hypointensity, isointensity, or hyperintensity on the DWI (depending on the strength of the T2 and diffusion components) and increased signal intensity on ADC maps. Whereas multiple variables, including patient age, type of infarct, and infarct location, can influence the general time course of these ADC changes, it is generally true that infarcts with low ADC and little or no associated abnormality on T2-weighted images are less than approximately six hours in age. Recent evidence suggests

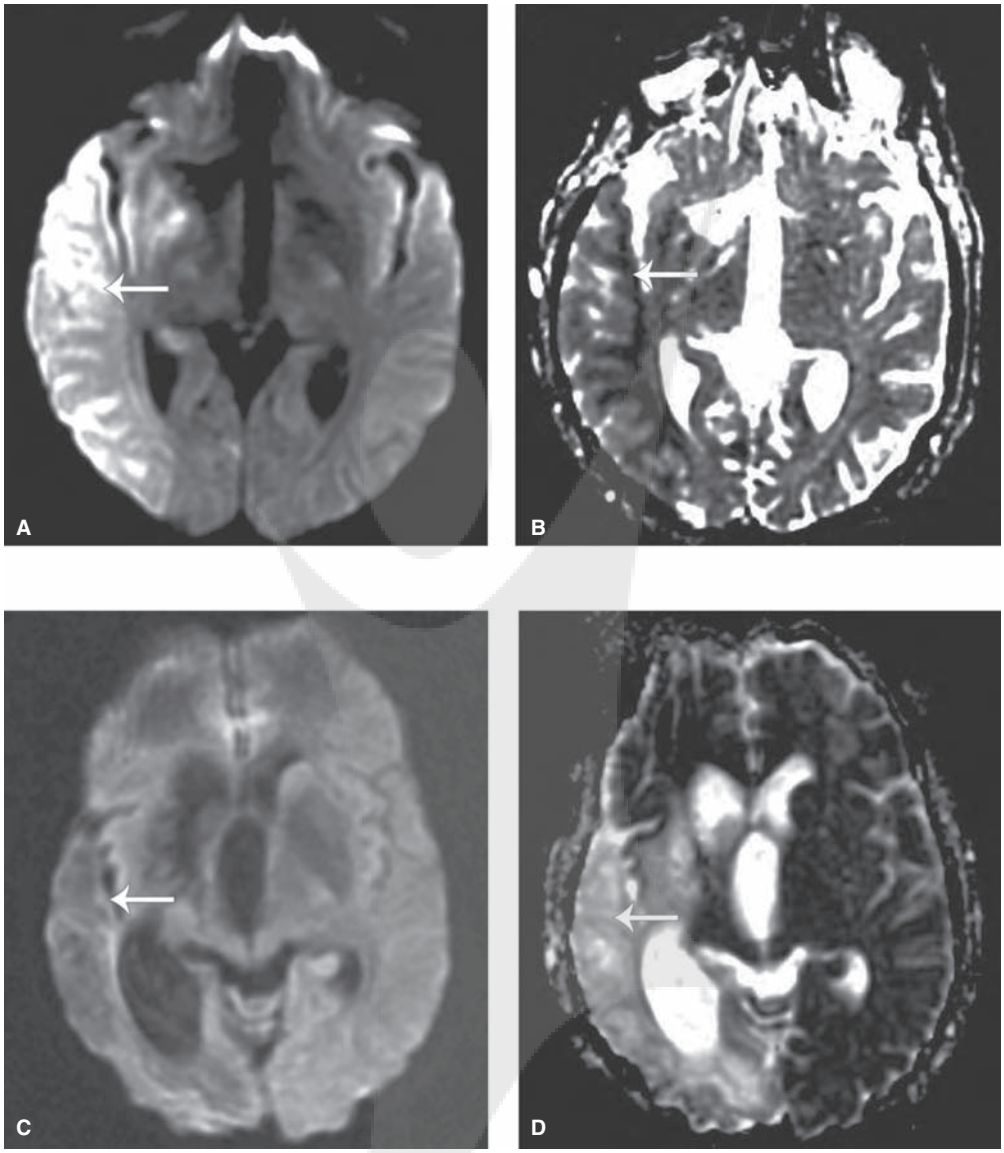

FIGURE 4.5 Evolution of DWI changes in an infarction. Sixty-four-year-old female with sudden-onset left facial drop, left-sided weakness, and slurred speech. In the acute stage, the infarction (arrow) is hyperintense on DWI (A) and hypointense on ADC (B) maps from decreased diffusion. In the chronic stage two years later, the infarction is characterized by tissue cavitation and volume loss with associated dilatation of the lateral and third ventricles. There is now more free movement of water molecules, with elevated diffusion characterized by decreased signal on the DWI (C) and increased signal on the ADC (D) maps.

TABLE 4.4 Temporal Changes in DWI, ADC, and Exponential Maps

PULSE SEQUENCE	HYPERACUTE (0–6 HOURS)	ACUTE (6–24 HOURS)	EARLY SUBACUTE (1–7 DAYS)	LATE SUBACUTE (1–4 WEEKS)	CHRONIC
Reason for ADC change	Cytotoxic edema	Cytotoxic edema	Cytotoxic edema + smaller vasogenic edema component	Cytotoxic and vasogenic edema	Vasogenic edema and then gliosis and neuronal loss
DWI	Hyperintense	Hyperintense	Hyperintense	Hyperintense (mostly T2 component)	Isointense to hypointense
ADC	Hypointense	Hypointense	Hypointense	Isointense	Hyperintense
EXP	Hyperintense	Hyperintense	Hyperintense	Isointense	Hypointense

that this phenomenon may be a useful imaging surrogate for estimating infarct age in patients with "wake-up" strokes of unclear onset times, who have traditionally been precluded from thrombolytic therapy. One study found that DWI hyperintense infarcts with little or no FLAIR hyperintensity predicted a symptom onset within 4.5 hours with a sensitivity of 62%, a specificity of 78%, and a positive predictive value of 83% (26). In addition, infarcts that are FLAIR hyperintense but have lower-than-normal ADC are usually less than approximately two weeks in age (27,28).

DWI lesions have been found to be highly predictive of patient outcomes and of likelihood of response to treatment. Larger DWI lesion volumes are strongly associated with poor patient outcomes, and may help predict which patients are unlikely to benefit from recanalization therapy. In one study, all patients with DWI lesion volumes greater than 70 mL had a poor outcome despite recanalization therapy (29). Another study found a diminishing effect of recanalization with increasing baseline DWI lesion size, with little treatment benefit for lesions more than 25 mL (30). Lesion location is also likely an important determinant of outcome, because not all brain regions contribute equally to clinical deficits. One study showed that a location-weighted, atlas-based method provided better prediction of clinical deficit severity than volume-based estimates alone in the subacute period (31).

CT ANGIOGRAPHY

Information about the intracranial and cervical vessels is an important part of the imaging evaluation because the bulk of acute stroke therapy targets intraluminal thrombus. However, thrombolytic therapy carries a significant risk of intracranial hemorrhage, so it is important to exclude patients with conditions that do not benefit from therapy, such as lacunar infarcts or postseizure deficits.

CTA has many attractive features that have made it the first-line diagnostic test for imaging intracranial vasculature in patients with signs and symptoms of acute stroke. CTA is widely available in the emergency setting and is a quick extension of the nonenhanced CT scan. Fast, high-resolution CTA techniques have become possible largely because of the advent of the helical CT scanner and the multidetector design of the scanner array. Helical scanning technology, developed in the 1990s, uses 360-degree rotation of the x-ray tube, scanning continuously with table progression. This results in the acquisition of a three-dimensional helical ribbon of data. The development of multislice or multidetector CT has led essentially to the acquisition of a larger ribbon of data per gantry rotation, allowing larger coverage at higher speeds. Thus, with a single bolus of contrast, high-resolution angiographic images of the major vessels from the arch to the vertex can be obtained within a minute.

Furthermore, the required postprocessing can be performed rapidly. For example, three-plane, orthogonal, maximal intensity projection (MIP) images can be reconstructed at the scanner by a technician in less than three minutes. The combination of the source axial images and the three-plane MIPS nearly always allows adequate evaluation of the arterial vasculature for the purposes of triage for thrombolytic therapy. In addition, the speed of CTA makes CTA images relatively resistant to degradation by artifact related to patient motion. With CT scanners, unlike MRI scanners, it is safe to bring metallic equipment into the scanner room, permitting easier monitoring of potentially unstable acute stroke patients. A significant percentage of stroke patients have cardiac diseases that require pacemakers, and they cannot undergo MR scanning. Also, CTA is less susceptible to other artifacts often encountered in MR angiography, including susceptibility artifact from calcified atherosclerotic plaque, air (e.g., within the petrous apices and sinuses), and metal clips.

Multiple studies have shown that CTA can detect large vessel intravascular clots with a sensitivity and specificity of greater than 95% (32) (Figure 4.6). Thus, CTA plays a critical role in directing acute therapy by detecting occlusion of proximal intracranial arteries that are accessible by endovascular microcatheterization and may be treated by intra-arterial thrombolysis or mechanical clot disruption. Indeed, studies using CTA suggest that proximal occlusions should be treated with intra-arterial recanalization procedures rather than, or in addition to, intravenous thrombolysis, because intravenous thrombolysis is less effective in treating proximal lesions than in treating distal ones (33,34). Also, detection of large vessel clots may be important in determining prognosis. One CTA study found that occlusion of a large intracranial artery was one of two factors that independently predicted poor outcome in acute stroke patients (The other was poor initial neurologic status.) (35). Another found a four-and-a-half-fold increased odds of death and a three-fold reduction in odds of good outcome in patients with large vessel occlusion (36). From worst outcome to best were occlusions of the basilar artery, internal carotid artery, M1, and M2 segments. The presence of large vessel occlusion is also highly correlated with mismatch on perfusion imaging (37), suggesting that it may be useful in selecting for reperfusion therapy. Indeed, in a post hoc analysis of perfusion mismatch selected patients from the desmoteplase in acute stroke (DIAS), desmoteplase in acute ischemic stroke (DEDAS), and DIAS-2 trials (described in more detail later), the presence of a proximal arterial occlusion on CTA was associated with a clinically beneficial effect of intravenous administration of the plasminogen activator desmoteplase (38). An additional CTA study showed that in the setting of proximal arterial occlusion, the recanalization status determines which clinical parameters are most important in determining clinical outcome; time was most important in patients with complete recanalization, whereas NIHSS was more important in those who incompletely recanalize (39). CTA has also been shown to predict the need for advanced neurointerventional services (40).

The Boston Acute Stroke Imaging Score (BASIS) is an instrument developed to integrate the useful information gained from CTA with that of NCCT and represents

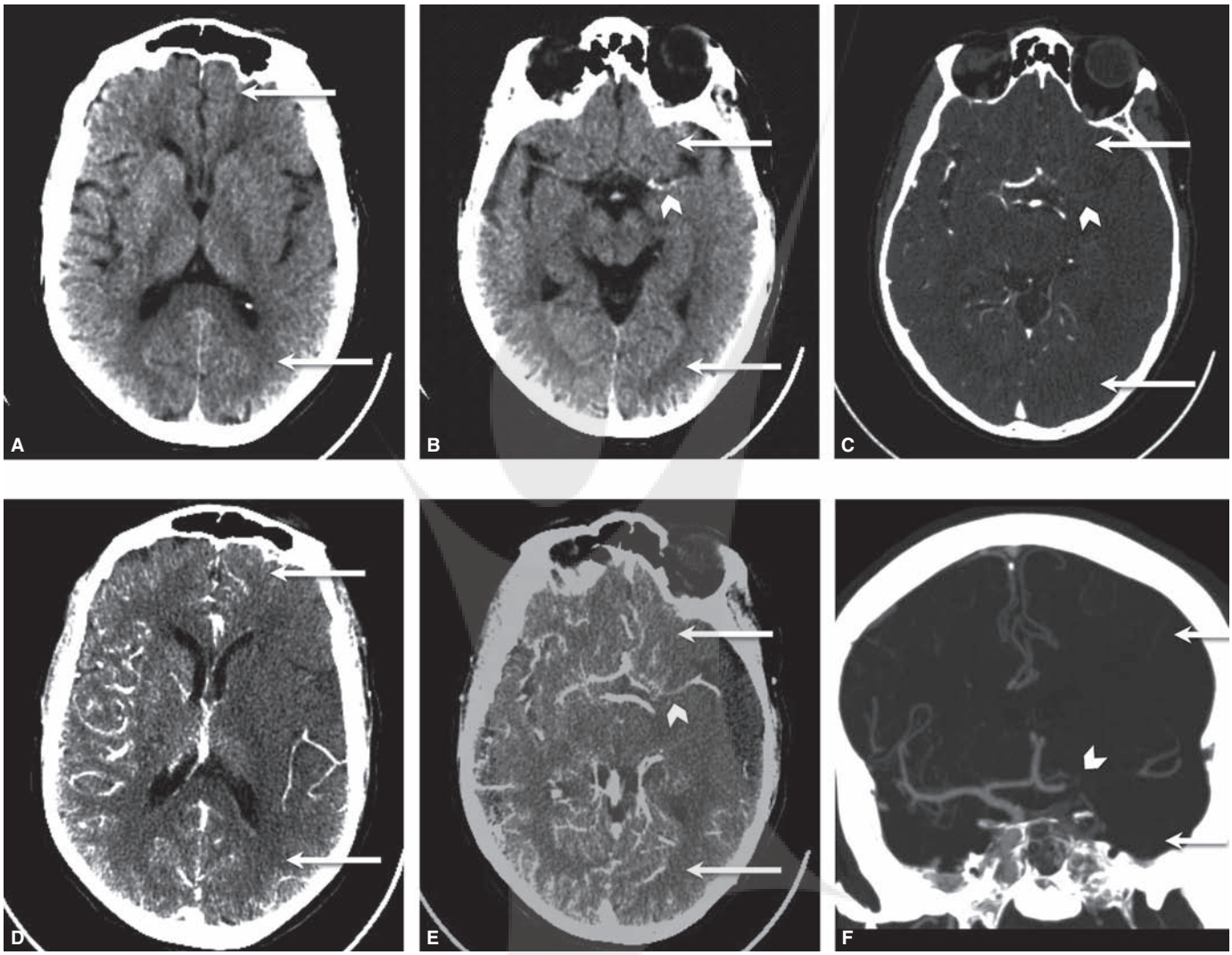

FIGURE 4.6 Embolic left MCA occlusion. Sixty-two-year-old male with known left ventricular thrombus following myocardial infarction awoke with right hemiparesis and aphasia, last seen normal 13 hours prior to imaging. Noncontrast CT (A and B) reveals a hyperdense clot in the left MCA stem (arrowhead), with subtle sulcal effacement and loss of gray–white matter differentiation throughout a large portion of the left MCA territory (delineated by arrows). Thin-section CTA source images (C) show absent enhancement within the occluded left MCA stem (arrowhead) as well as the distal left MCA branches and arterial collaterals (delineated by arrows). Thick-section (5 mm) CTA source images (D and E) more clearly demonstrate a large area of hypoperfused brain tissue in the left MCA territory (delineated by arrows). Coronal MIP CTA image (F) clearly depicts the absent enhancement of the left MCA stem caused by embolic occlusion (arrowhead), as well as the absent enhancement in the distal left MCA branches and arterial collaterals. (*Continued*)

an augmentation of the ASPECTS noncontrast CT scoring system that is superior in predicting outcomes (41). In one large trial, the Improved Outcome Prediction Using CT Angiography in Addition to Standard Ischemic Stroke Assessment (STOPStroke) study, BASIS+ was one of two independent outcome predictors; the other was NIHSS (42). In this trial, patients were classified as BASIS+ if proximal anterior circulation artery occlusions were observed on CTA or if the NCCT ASPECTS score was seven or less in patients without proximal artery occlusions.

CTA has a number of other advantages. In the neck, it allows evaluation of stroke etiology (Figure 4.7). CTA can demonstrate atherosclerotic plaque with thrombus at the internal carotid artery bifurcation. It can differentiate thrombosis from hairline residual lumen, and it can identify dissection. In the head, CTA source images (CTA-SIs) greatly improve the detection of subtle, early parenchymal ischemic changes compared to NCCT (43,44) (Figure 4.6). In the early days of CTA, a steady-state level of contrast was reached during scanning and the CTA-SIs could be considered whole-brain perfused blood volume images. Furthermore, the CTA-SI lesion size correlated with the DWI lesion size and could help to identify the infarction core. However, with current, faster CTA protocols, a steady state is not reached, the CTA-SI are more blood

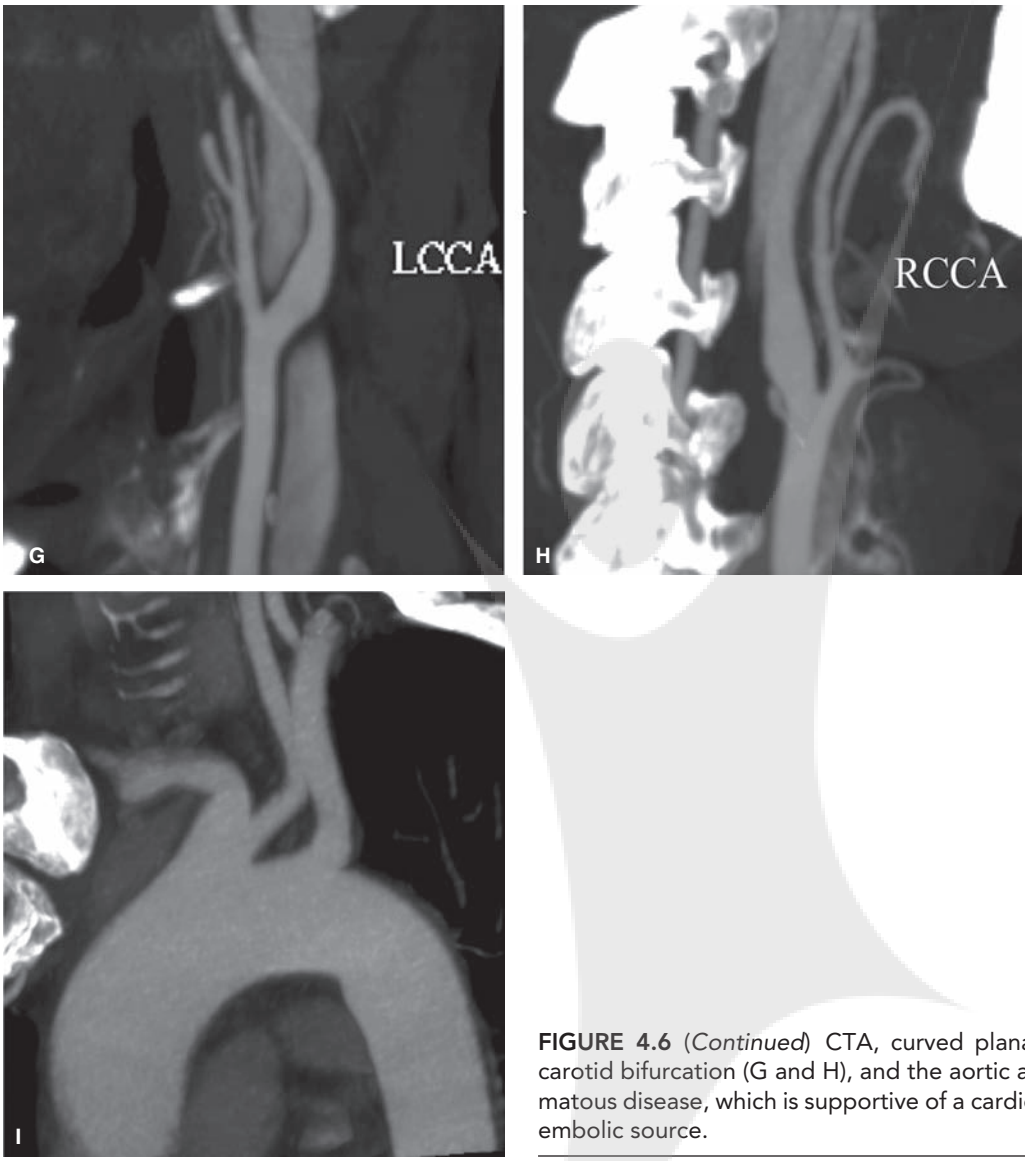

FIGURE 4.6 (*Continued*) CTA, curved planar reformats of the left and right carotid bifurcation (G and H), and the aortic arch (I) reveal no significant atheromatous disease, which is supportive of a cardioembolic rather than a large vessel embolic source.

flow weighted, and they frequently overestimate infarct core relative to the DWI lesion volume (45). The CTA-SI technique may also be important in risk stratification and in determining patient prognosis. In one study, CTA-SI increased the utility of the ASPECTS metric in predicting the clinical outcomes of acute stroke patients (46). In another, the degree of hypoattenuation on CTA-SI correlated with the likelihood of hemorrhagic transformation (47).

The extent of leptomeningeal arterial collateral supply can be noninvasively assessed in the acute setting using CTA (48). A robust collateral circulation supports the tissue surrounding the infarct core and decreases the extent of final ischemic injury in stroke patients with large vessel occlusion. Several studies have identified a malignant profile of collateral circulation on CTA that stratifies patients who are likely to do poorly (49,50). One study found that a malignant collateral profile in the setting of a proximal arterial occlusion was highly specific for large admission DWI lesion size and poor functional outcome (49), while another found high mortality and poor outcome despite early intravenous thrombolysis (50). Studies have also shown that the extent of CTA collaterals can predict both the final infarct volume following (51), and the clinical response to, endovascular therapy (52).

CTA does have some disadvantages. One of the most significant is the risk of contrast nephropathy (53,54). This is especially heightened in patients with reduced renal function, diabetes, or both. However, a recent large study of acute stroke patients who received CTA and CT perfusion (CTP) within 24 hours of admission found no increased risk of contrast-induced nephropathy compared with unexposed patients (55). These findings support the practice in many institutions of deferring a creatinine level in order to save valuable time for patients being considered for urgent intra-arterial recanalization procedures. In addition, a risk of contrast-induced allergic reactions does exist. Although

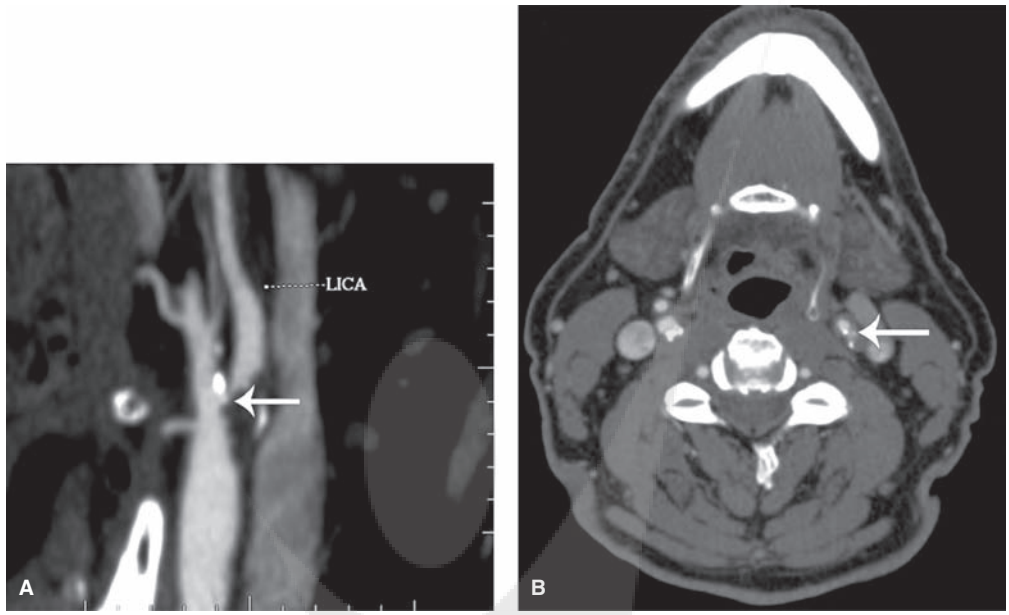

FIGURE 4.7 Carotid stenosis on CTA. Sixty-four-year-old male presenting with acute left hemiparesis. CTA, sagittal reformatted (A), and axial source (B) images demonstrate a large hypodense asymmetric plaque at the left carotid bifurcation extending into the proximal left ICA, causing severe stenosis (arrows). This disease was likely the site of the patient's embolus.

nonionic contrast agents have decreased the overall risk of contrast-induced reactions, there is a 0.03% risk of an anaphylactic reaction for nonionic, iodinated contrast agents (56). CTA also imparts a radiation dose, a particularly important fact to consider when imaging children and pregnant women. Multiple CTA examinations can result in a large cumulative dose.

MR ANGIOGRAPHY

MR angiography (MRA) techniques utilized in stroke imaging include noncontrast-enhanced time-of-flight (TOF) imaging as well as gadolinium-enhanced MRA. The physical principles underlying both techniques are complicated and are beyond the scope of this chapter. Briefly, TOF techniques utilize a gradient-echo sequence that saturates signal from the stationary spins within a volume of tissue. This is accomplished by multiple radio frequency pulses, followed by dephasing and rephasing gradients. Thus, the only unsaturated spins (signal) are within blood flowing from outside into the volume of interest. Generally, the contrast is proportional to the velocity of flow (57). A saturation band decreases signal from venous flow, which is usually in the opposite direction from the arterial flow. Two-dimensional TOF MRA is generally performed for evaluation of the cervical arterial vasculature with the acquisition of multiple, contiguous, thin slices of tissue. Three-dimensional TOF MRA is usually used to evaluate the intracranial vasculature. This technique, as its name implies, acquires a volume of tissue and, with an additional phase-encoding step, partitions the volume into thin slices (Figure 4.8).

Three-dimensional TOF MRA provides an increased signal-to-noise ratio and a higher spatial resolution versus the two-dimensional TOF technique. However, the volume covered is restricted by vascular saturation artifact, thus limiting it largely to the intracranial vasculature. Both techniques, particularly the two-dimensional TOF technique, are susceptible to signal loss from turbulent flow. From a diagnostic standpoint, this tends to cause overestimation of vascular stenoses. A combination of the two techniques called multiple overlapping thin slab acquisition (MOTSA) exists. It allows larger volumes of coverage with decreased saturation effects and increased spatial resolution.

Phase contrast techniques, based on quantitation of the differences in the transverse magnetization between stationary and moving spins, are not typically performed in the evaluation of stroke patients because of the much longer acquisition times that make this technique vulnerable to motion artifact. However, this technique can be used for the evaluation of flow in collateral vessels because, unlike TOF MRA, the technique can measure flow direction.

Contrast-enhanced MRA techniques, based on a short rapid gradient-echo sequence, image a bolus of intravenous gadolinium contrast in the arterial phase. The contrast agent shortens the T1 within vessels. This allows good separation of vessels from surrounding longer T1 soft tissues (57). Compared to TOF techniques, contrast-enhanced MRA provides coverage of a larger volume with a shorter acquisition time and less vulnerability to patient motion. In addition, this technique generally provides better signal-to-noise ratios than TOF techniques and has fewer artifacts related to dephasing from turbulence and saturation effects. For these

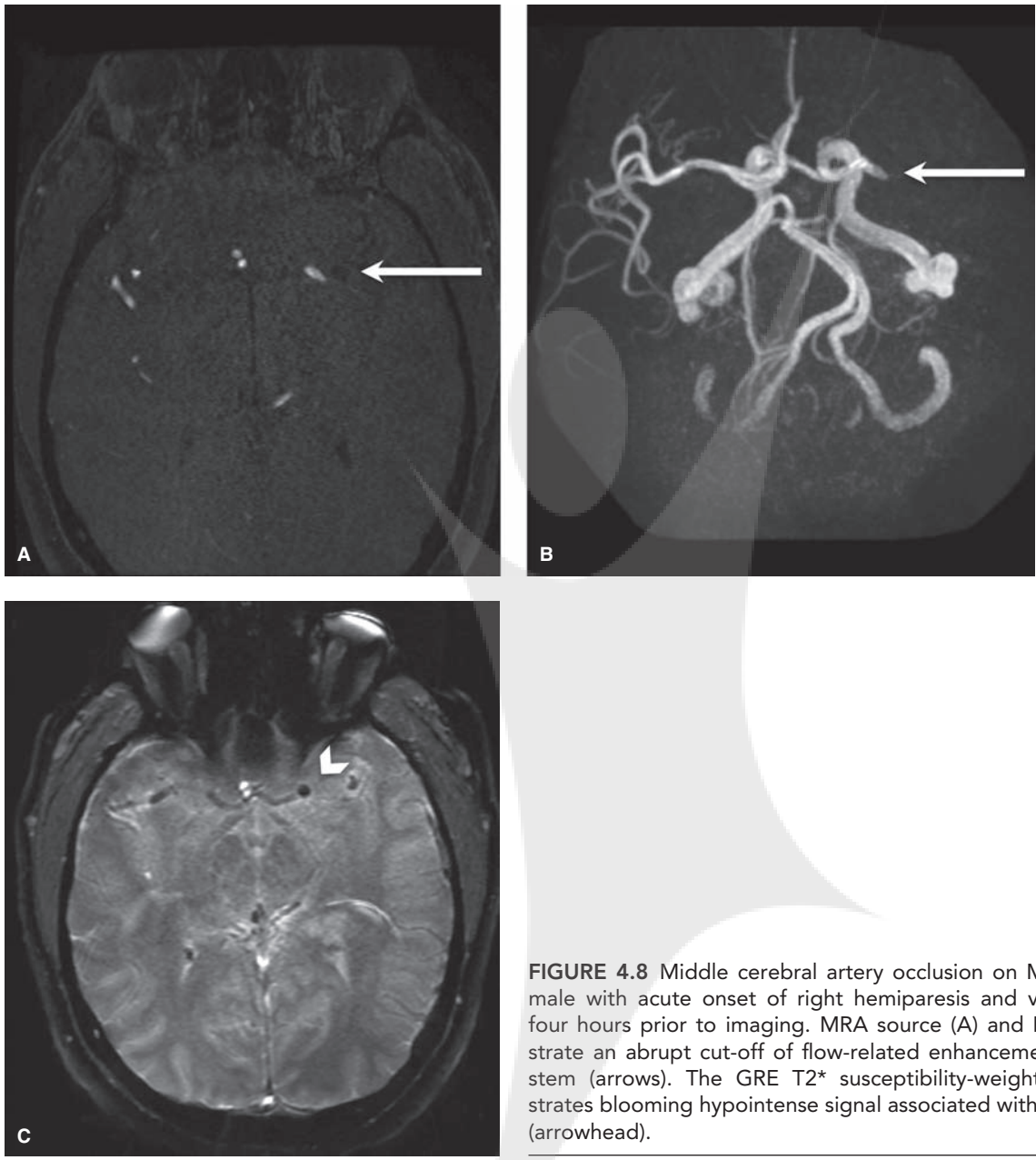

FIGURE 4.8 Middle cerebral artery occlusion on MRA. Forty-five-year-old male with acute onset of right hemiparesis and verbal unresponsiveness four hours prior to imaging. MRA source (A) and MIP (B) images demonstrate an abrupt cut-off of flow-related enhancement within the left MCA stem (arrows). The GRE T2* susceptibility-weighted image (C) demonstrates blooming hypointense signal associated with the left MCA thrombus (arrowhead).

reasons, contrast-enhanced MRA is often used to image the arteries of the neck (Figure 4.9). This can be accomplished in approximately one to two minutes. However, contrast-enhanced MRA has worse spatial resolution compared to noncontrast MRA, making the technique less suitable for imaging the smaller vessels of the head.

Multiple studies have demonstrated that contrast-enhanced MRA is highly accurate in differentiating surgical from nonsurgical carotid artery stenoses (58). Other studies have suggested that MRA is also highly accurate in detecting proximal intracranial occlusions (59,60). However, from a practical standpoint, MRA images of the head and neck are generally inferior to CTA images for scanning acute stroke patients on an emergency basis because motion artifact is a common problem (Table 4.5). Also, compared to CTA, contrast-enhanced MRA images have a narrower window for acquiring images during peak contrast enhancement. Consequently, inadequate arterial enhancement and venous contamination are common problems. Thus, in the acute stroke practice at the Massachusetts General Hospital, MRA is generally utilized only to evaluate patients with allergies to CT contrast agents, patients with renal failure, and patients such as children and pregnant women who are particularly vulnerable to radiation. However, gadolinium-enhanced MRA techniques cannot be used in patients with renal failure because of the increased risk of their developing nephrogenic systemic fibrosis (NSF) (61). Also

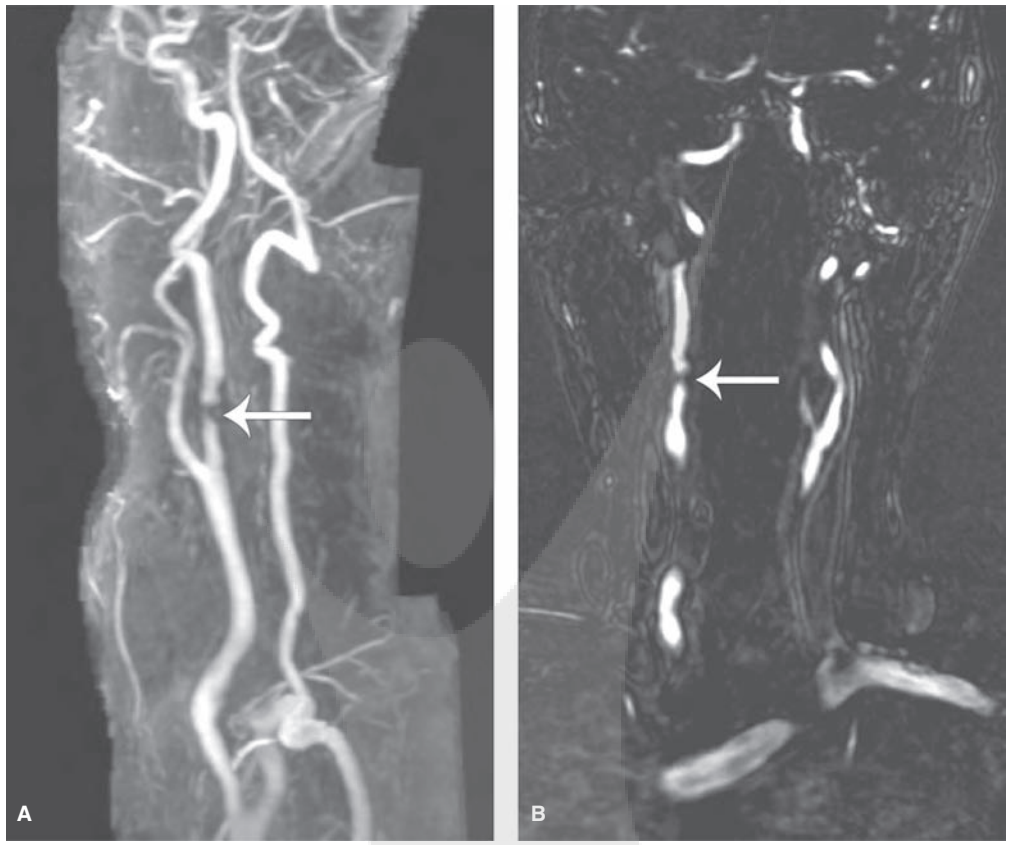

FIGURE 4.9 Carotid stenosis on MRA. Gadolinium-enhanced MRA of the neck MIP (A) and source (B) images demonstrate signal dropout, consistent with a focal severe stenosis of the proximal right internal carotid artery (arrow).

TABLE 4.5 CTA and MRA Comparison in the Acute Stroke Setting

	CTA	MRA
Advantages	• Rapid acquisition speed, resulting in decreased motion artifact and greater coverage • Cost and availability: Cheaper physical plant and wider dissemination in the acute setting • Accuracy: Nonflow-dependent technique with higher spatial resolution • Higher accuracy for detection of proximal vessel occlusion • Better collateral flow assessment • CTA source images of value in infarct detection • Can be utilized where MR is contraindicated, for example, patients with non-MR-compatible implantable devices	• Good for patients with allergic contraindications to iodinated contrast • Can provide velocity and flow direction data
Disadvantages	• Contrast-dependent techniques in patients with allergies and renal failure • Radiation dose cumulative effect, especially in repeated imaging	• More susceptible to motion artifact • High cost and less accessibility of equipment • Inferior accuracy • Contrast-dependent techniques in patients with renal abnormalities, such as nephrogenic systemic fibrosis (NSF) (56)

present is a relative contraindication to gadolinium contrast utilization in pregnant patients (62).

In addition, gadolinium contrast agents are associated with a small (0.01% or less) risk of anaphylactic reactions (63), although the risk is lower than for iodinated contrast agents in CTA.

CONVENTIONAL ANGIOGRAPHY

Although potentially a front-line diagnostic tool, the risks associated with this invasive procedure, such as stroke, the relatively long preparation time, and relative cost preclude the use of this modality in most diagnostic acute stroke evaluations. However, catheter-guided therapy using digital subtraction angiography has an important role in acute stroke management. The use of intra-arterial thrombolytic agents, mechanical clot disruption, and clot retrieval for the treatment of acute stroke are discussed in subsequent chapters.

PERFUSION IMAGING

The circulation of blood through a vascular bed defines tissue perfusion. In the acute stroke setting, perfusion imaging is generally performed with a bolus tracking technique in which a contrast agent is injected rapidly (5–7 cc/sec) into a peripheral intravenous catheter and images are obtained repeatedly as the contrast agent passes through the brain. The technique takes approximately one to two minutes and is performed such that it is sufficient to track the first pass of the contrast bolus through the intracranial vasculature without recirculation effects. The images obtained in the examination are converted by a computer to contrast agent concentration versus time curves. The cerebral blood volume (CBV) is proportional to the area under the curve. The cerebral blood flow (CBF) and mean transit time (MTT) are computed by deconvolution using an arterial input function. Cerebral perfusion parameters are related according to the central volume theorem, that is, MTT = CBV/CBF. Other frequently used transit time parameters are T_{max} (the time at which the deconvolved residue function reaches its maximum) and time to peak contrast concentration (TTP).

Several variants of MR perfusion broadly employing endogenous and exogenous labeling of blood exist (Figure 4.10). The primary method is a dynamic susceptibility (T2*) contrast sequence that relies on the decrease in signal caused by the magnetic susceptibility effects of gadolinium as it passes through the intracranial vasculature (64). Because blood passes through the brain parenchyma rapidly, the most commonly used sequence is a single-shot gradient-echo echo-planar sequence (EPI) capable of multiple slice acquisition from a single repetition time (TR). Approximately 60 images are obtained for each 5-mm brain slice, and the whole brain is covered. Historically, the arterial input was typically chosen from the ipsilateral or contralateral MCA, but currently is frequently chosen automatically using cluster analysis (65).

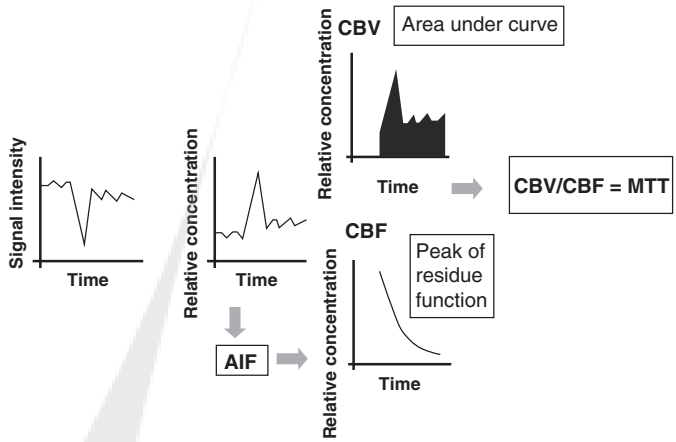

FIGURE 4.10 MR perfusion scheme. For each pixel in each image slice, a graph of signal intensity as a function of time is converted into a change in rate of susceptibility (T2* effect) caused by gadolinium, which is proportional to the gadolinium contrast agent given. This curve can then be used to compute relative CBV, which is proportional to the area under the curve. Using a deconvolution technique, where an arterial input function (AIF) that describes the contrast left in the arteries is used, cerebral blood flow (CBF) can be calculated. CBV/CBF gives mean transit time (MTT).

For CT, brain tissue increases and then decreases again in density as an iodine-based contrast agent passes through the brain. Briefly, the technique utilizes a standard cine protocol that obtains approximately 60 sequential images for each scan location over a given volume of coverage (slab). The slab is 4 cm for 64 detector scanners and up to 16 cm for the latest 256 and 320 detector scanners. On current-generation scanners, the volume of coverage can also be increased above the physical detector limit, on the order of 6 to 16 cm, through the use of vendor-specific techniques such as adaptive spiral scanning or simultaneous scanning of two slabs in a single acquisition (shuttle mode). The volume of tissue imaged is divided into 5-mm-thick slices. The arterial input function is usually chosen from the anterior cerebral artery or the top of the internal carotid artery, or may be automatically chosen by the vendor software using a summation of large vessels. The venous output function, which is required for CT but not for MRI, is usually chosen from the superior sagittal sinus.

A number of studies have demonstrated that lesion volumes on CT perfusion (CBV, CBF, and MTT) maps correlate highly with those obtained from similar MR perfusion maps (66,67). However, the degree of correlation depends strongly on the volume of anatomical coverage of CTP (68). Compared to MRP, CTP offers wider availability in the acute setting, lower cost, higher speed of acquisition, higher spatial resolution, and quantitative perfusion estimates. Also, CTP can be readily performed in patients with contraindications to MR imaging, such as pacemakers. Compared to CTP, however, MRP generally offers a larger volume of coverage and avoids a relatively large dose of radiation.

In addition, MRP avoids iodinated contrast-related risks, including contrast allergy and contrast-induced nephropathy, particularly important in older patients at higher risk for stroke syndromes.

CBV, CBF, and MTT relate to acute ischemia as follows. With the onset of acute ischemia, loss of cerebral perfusion pressure (CPP) exceeds the autoregulatory capacity of the cerebral vasculature, and CBF begins to fall. There is compensatory vasodilatation and capillary recruitment that increases the effective vascular cross-sectional surface area, resulting in a lower blood velocity and an increase in MTT. A decrease in the velocity of blood as it passes through the capillaries is adaptive, as it allows time for a greater oxygen extraction fraction (OEF). With a modest impairment of blood flow, this mechanism allows for preservation of blood volume and of oxidative metabolism without alteration in electrical function. However, when CPP and, therefore, CBF are sufficiently low, OEF reaches a maximum and cannot increase further. Brain tissue ceases to function electrically, resulting in a neurologic deficit. If the oxygen supply falls low enough, the tissue dies. The amount of time it takes for tissue to suffer irreversible damage is inversely related to the severity of the ischemic insult. Tissue that is completely deprived of blood will die within a few minutes, but less severely hypoperfused tissue may survive for many hours and may be saved by therapeutic intervention.

It has been suggested that when CPP becomes very low, microvascular collapse occurs and CBV falls. However, the early studies on which the current understanding of cerebral hemodynamics is based offer little direct evidence of decreased CBV. These studies focused more often on the CBV/CBF ratio (i.e., MTT), rather than CBV itself (69). In fact, early studies often found that CBV was elevated, although these measurements were usually made in subacute infarcts (70–72).

Imaging the Infarct Core and Ischemic Penumbra

In the clinical setting, radiologists and neurologists evaluate the diffusion and perfusion images to determine the infarct core and ischemic penumbra (Table 4.6). Operationally, for MRI, the DWIs (depicting changes from cytotoxic edema) are thought to represent the infarct core or tissue that is severely ischemic, is irreversibly damaged, and is unlikely to survive in spite of acute intervention. For CT, definition of the infarct core is controversial. Some investigators choose thresholded CBV maps to represent infarct core. Others have shown that CBV can be elevated or decreased in infarct core and choose thresholded CBF maps to represent the infarct core.

With proximal emboli, MTT and other transit time (T_{max}, TTP) lesion volumes are generally much larger than the DWI or thresholded CBV/CBF lesions. Tissue that appears normal on the DWIs and thresholded CBV/CBF images but abnormal on the MTT and other transit time images is thought to represent the ischemic penumbra. The ischemic penumbra usually surrounds the core where collateral vessels supply some residual perfusion. The penumbra represents tissue that may progress to infarction or may recover, depending on the timing of reperfusion and the degree of collateralization. It is tissue that can potentially be salvaged with reperfusion therapy.

TABLE 4.6 Summary of Perfusion-Weighted Parameters and Prediction of Tissue Viability

PARAMETER	INFORMATION
DWI	Infarct core, generally irreversible and highly predictive of final infarct volume
CBV	Thresholded CT CBV used by some investigators to define infarct core. Thresholds vary depending on vendor
CBF	Thresholded CT CBF used by some investigators to define infarct core. Thresholds vary depending on vendor Nonthresholded CBF yields operational penumbra. For proximal occlusions, nonthresholded CBF is usually much larger than DWI
MTT, T_{max}, TTP	Yield operational penumbra. Thresholded maps may separate benign oligemia from tissue at risk. For proximal occlusions, MTT, T_{max}, and TTP are usually much larger than DWI

A number of investigators have tried to establish CT and MR perfusion parameter thresholds that define the infarct core and penumbra. Unfortunately, reported thresholds are highly variable, as highlighted in a recent article by Dani et al., who reviewed 20 CT perfusion and 49 MR perfusion studies. CT perfusion parameter ranges for penumbra included MTT 6.53–7.0 seconds; relative MTT 1.45–2.2; and relative CBF 0.50–0.63. MR perfusion parameter ranges for penumbra were MTT 1.78–8.1 seconds; TTP 4–7 seconds, and relative CBF 0.58–0.61 (73). Recently, authors and trials evaluating MR-PWI as a selection criterion for thrombolytic therapy have used various MR-T_{max} thresholds, with values ranging from more than 2 seconds to more than 6 seconds for penumbra and more than 6 seconds to more than 10 seconds for infarct core (74–79).

The variability in perfusion thresholds likely results from a number of different factors. Most importantly, the data obtained represent only a single time point in a dynamic process. In addition, postprocessing techniques are inconsistent between manufacturers and introduce a significant source of variability in defining appropriate and generalizable thresholds. For example, one CTP study found that CT-CBF maps most closely approximated the DWI lesions, but that the thresholds varied up to two-fold among various postprocessing software (80). Another found that CT-MTT maps best distinguished benign oligemia from tissue at true risk; however, the precise thresholds depended upon whether the postprocessing software used a delay-corrected or standard algorithm (81). Yet another source of variability appears to be the timing of reperfusion therapy relative to initial perfusion imaging. One study found lower CBF thresholds for infarction in tissue that was reperfused earlier (82). Jones et al. demonstrated that both severity and duration of CBF reduction of

up to four hours define an infarction threshold in monkeys (83). The CBF threshold for tissue infarction with reperfusion at 2 to 3 hours was 10 to 12 mL/100 g/min, while the threshold for tissue infarction with permanent occlusion was 17 to 18 mL/100 g/min. Another factor is that normal average cerebral blood flow in human parenchyma varies greatly, from 21.1 to 65.3 mL/100 g/min, depending on age and location in gray matter versus white matter (84,85). Indeed, one study demonstrated variable regional ischemic vulnerability of the brain to hypoperfusion on CTP, suggesting that location-specific rather than whole-brain thresholds may provide a more accurate assessment of infarct core and penumbra (86). Other factors include variability in initial and follow-up imaging times, and in postischemic tissue responses.

Although somewhat controversial, the assumption that the DWI-MTT mismatch (MR perfusion) and the thresholded CBV/CBF-MTT mismatch (CT perfusion) represent the ischemic penumbra implies that patients with a large mismatch are most likely to benefit from intravenous thrombolytic therapy and endovascular procedures because they have the largest volume of threatened tissue that may be salvaged (Figures 4.11–4.14, Table 4.7). If these patients cannot be treated with intravenous thrombolytic therapy or intra-arterial procedures, then they should be treated aggressively

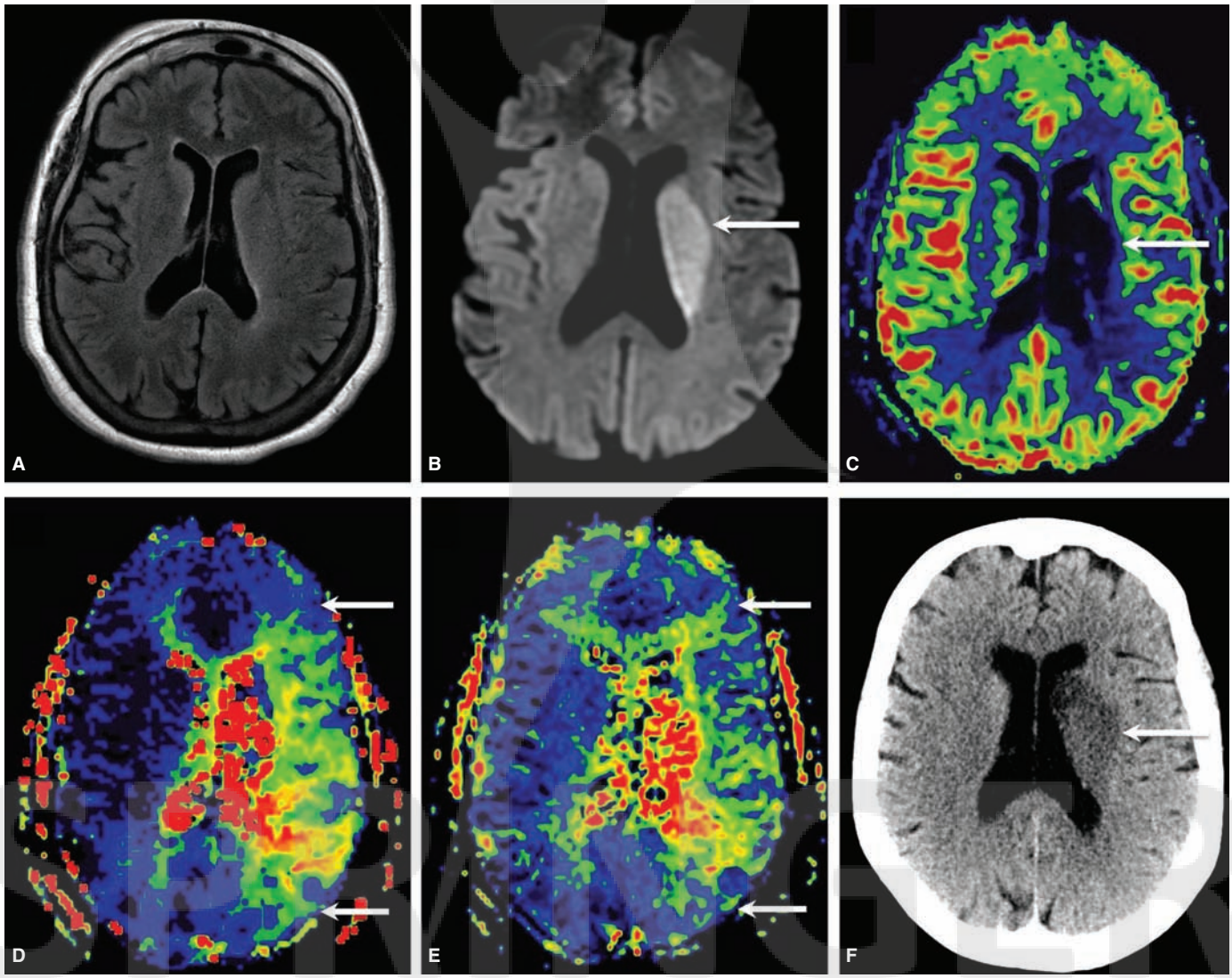

FIGURE 4.11 A 71-year-old male developed acute-onset aphasia and right hemiparesis two hours prior to MR imaging. There are no significant parenchymal findings on FLAIR (A) to suggest a completed infarction. DWI (B) shows restricted diffusion within the left basal ganglia and corona radiata (arrow), consistent with acute infarction. MR perfusion CBF map (C) shows severely decreased blood flow within the left basal ganglia (arrow) corresponding to the area of acute infarction on DWI. There is increased T_{max} (D) and MTT (E) within a large portion of the left MCA territory (delineated by arrows), without corresponding abnormality on diffusion. The large area of diffusion–perfusion mismatch within the left MCA territory suggests tissue at risk for infarction without recanalization (penumbra). A follow-up CT (F) performed 48 hours following successful intra-arterial recanalization of the occluded left MCA reveals hypodense infarct that matches the area of acute infarction on the admission MRI, suggesting salvage of the ischemic penumbra.

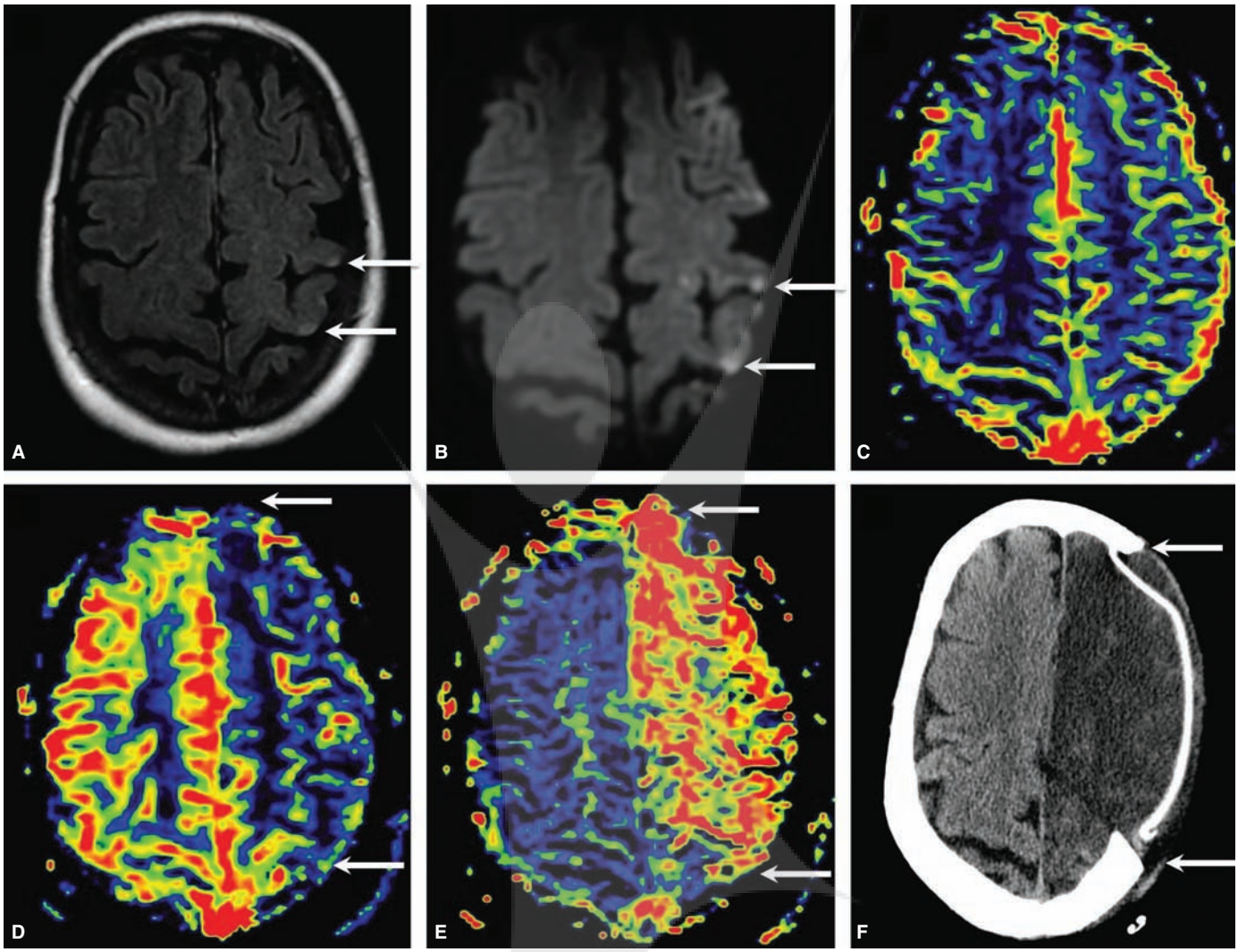

FIGURE 4.12 A 76-year-old woman developed acute-onset right hemiparesis 2.5 hours prior to MR imaging. There are a few tiny foci of FLAIR hyperintensity (A) and restricted diffusion (B) within the left precentral and middle frontal gyri (arrows), consistent with acute infarction. MR perfusion shows markedly decreased CBF (D) and increased MTT (E) within the entire visualized left MCA and ACA territories (delineated by arrows), involving a much larger area than the diffusion abnormality. CBV (C) is approximately symmetric. The extensive area of diffusion–perfusion mismatch is suggestive of tissue at risk for progressing to infarction without treatment. CTA (not shown) demonstrated thrombosis of the left internal carotid artery and proximal anterior and middle cerebral arteries. Attempted intra-arterial recanalization was unsuccessful. Follow-up head CT performed one week after symptom onset shows hypodense infarction of the entire left MCA and ACA territories (delineated by arrows), with postsurgical changes related to left hemi-craniectomy and duraplasty performed for cerebral edema. This is an example of a large diffusion–perfusion mismatch with subsequent infarction of tissue at risk.

with hypertensive therapy. Conversely, patients with little or no diffusion–perfusion mismatch should not receive aggressive therapies because their infarctions are unlikely to increase in size, and they should be spared the associated risk of hemorrhage (Figure 4.15).

The concept that the mismatch represents the ischemic penumbra and should be used as a selection criterion for intravenous thrombolysis and endovascular procedures is supported by studies demonstrating that patients with larger mismatches have more lesion growth (87). More importantly, a number of studies have shown that intravenous thrombolysis may be beneficial more than three hours after stroke onset, provided that only patients with a significant diffusion–perfusion mismatch are treated. Ribo et al. found that patients with a more than 50% diffusion–perfusion mismatch could be treated safely and effectively with IV-tPA in the three- to six-hour time period (88). In phase II of the DIAS trial, patients with diffusion–perfusion mismatch were treated with desmoteplase up to nine hours after stroke onset and showed better outcomes than patients given placebo, with only a minimal incidence of symptomatic hemorrhage (89). Similar success was achieved in the same time window

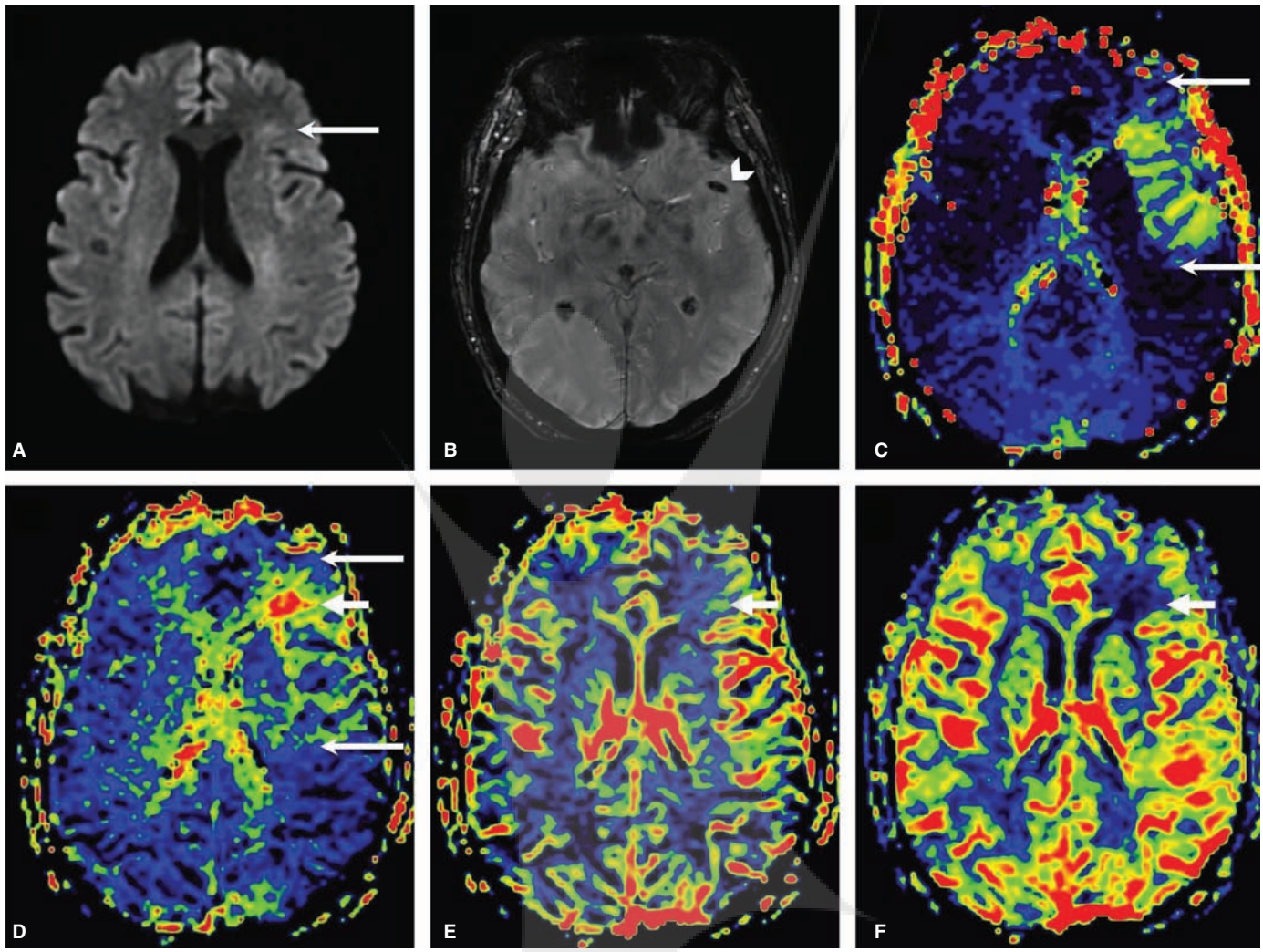

FIGURE 4.13 A 77-year-old man developed acute-onset aphasia and right hemiparesis five hours prior to MR imaging. DWI (A) shows mild focal hyperintensity within the left frontal operculum consistent with early ischemia (arrow). Susceptibility-weighted image (B) shows focal blooming hypointense signal, consistent with embolic clot within a proximal left M2 branch of the MCA (arrowhead). There is transit time delay with prolonged T_{max} (C) and MTT (D) involving a large portion of the left MCA territory (delineated by arrows), which corresponds to the territory supplied by the occluded left M2 branch. Within this region, there is a smaller area of more severely elevated MTT, mildly increased CBV (E), and decreased CBF (F) (short arrow), which corresponds to the region of diffusion abnormality. (*Continued*)

by the dose escalation study of DEDAS (90). In contrast, these early positive results were not replicated in the larger DIAS-2 phase III trial that followed, in which patients with diffusion–perfusion mismatch treated with desmoteplase between three and nine hours after stroke onset showed no benefit compared with placebo (91). The study authors speculate that the unexpectedly high placebo response rate may have been because of a higher proportion of mild strokes than in the previous trials, with smaller DWI lesion volumes, fewer proximal vessel occlusions, and lower NIHSS. In addition, a post hoc analysis of pooled data from DIAS, DEDAS, and DIAS-2 showed a positive treatment effect of desmoteplase in both the pooled sample and in the DIAS-2 patients when a mismatch volume of 60 mL or greater was used, rather than the visually apparent mismatch criteria (approximately >20% mismatch) used in these trials. The study showed no treatment effect relative to placebo for patients with mismatch volumes less than 60 mL in both DIAS-2 and pooled data, suggesting that higher minimum mismatch volumes may be required to detect treatment benefits in future trials (92).

Additional more recent trials also support the DWI/PWI mismatch model for selection of patients for reperfusion therapies. In both the diffusion and perfusion imaging evaluation for understanding stroke evolution (DEFUSE) trial and the DEFUSE-2 trial, patients receiving reperfusion therapy (intravenous tPA and endovascular therapy, respectively) between three to six hours were stratified based on predefined DW-PW imaging profiles, and both showed a favorable clinical response in the patients with "target mismatch" that had early reperfusion relative

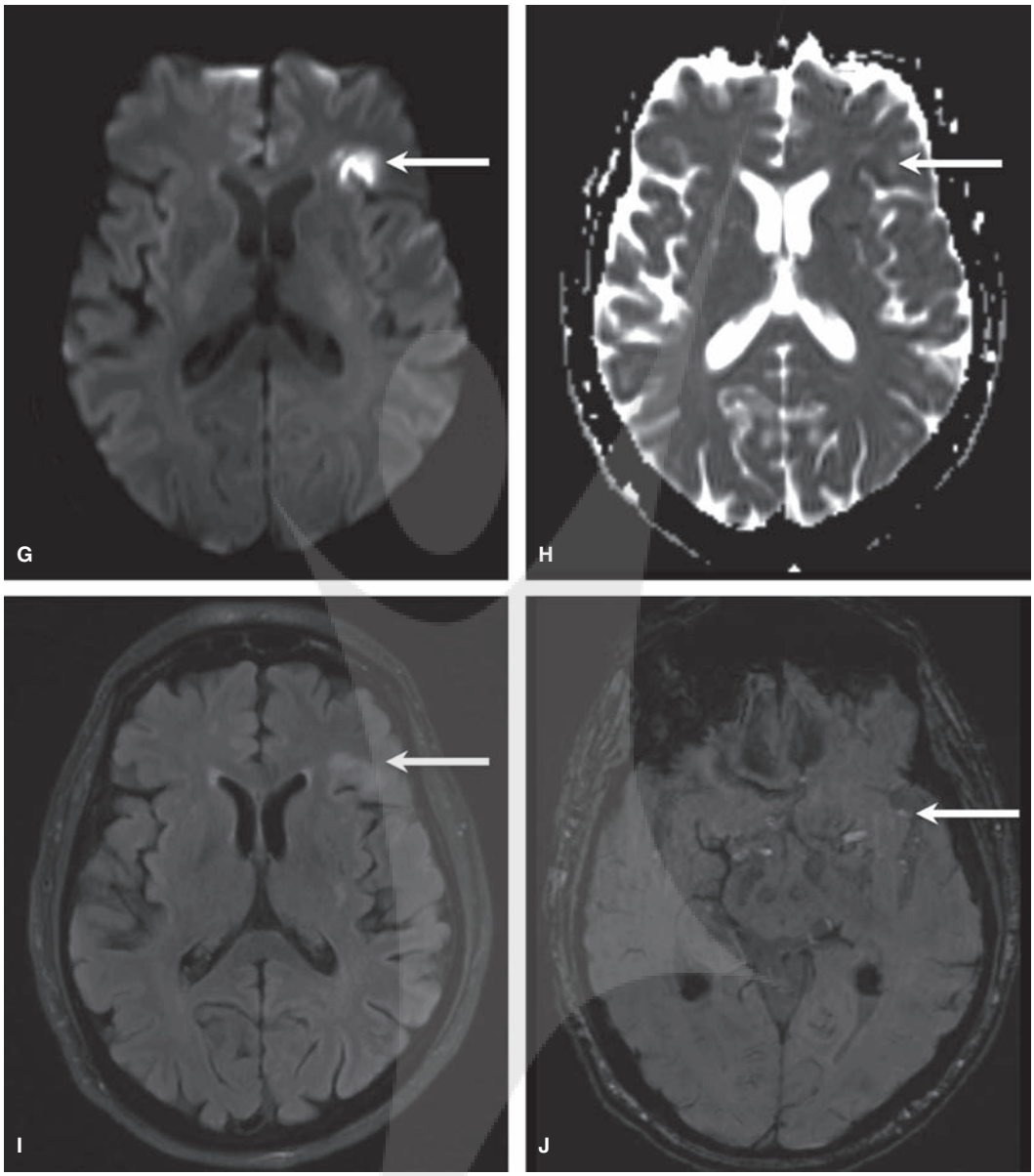

FIGURE 4.13 (*Continued*) The combination of findings suggests a small area of early infarction in the left frontal operculum, with a larger area of diffusion–perfusion mismatch suggesting tissue that may be at risk for progressing to infarction without recanalization. Follow-up MRI performed three days following symptom onset shows acute infarction on DWI (G), ADC map (H), and FLAIR (I) images (arrows) involving the region of most severely increased MTT on the initial MRI scan, with preservation of the remaining diffusion–perfusion mismatched tissue that was at risk for infarction. Follow-up susceptibility-weighted image (J) shows interval recanalization of the left MCA, with resolution of the blooming hypointense clot seen on the initial MRI scan (arrow).

to those with "no mismatch" or "malignant" profiles (78,79). In the more recent DEFUSE-2 trial (endovascular therapy), a "target mismatch" profile was defined as (a) a ratio between the volumes of critically hypoperfused tissue (T_{max} > 6 s) and an ischemic core (ADC < 600 × 10^{-6} mm^2/s) of 1.8 or more, with an absolute difference of 15 mL or more; (b) ischemic core volume less than 70 mL; and (c) less than 100 mL of tissue with severe delay in bolus arrival (T_{max} > 10 s). Early reperfusion was defined as more than 50% reduction in volume of the perfusion lesion (T_{max} > 6 s) between baseline and early follow-up. The adjusted odds ratio for a favorable clinical response associated with reperfusion was 8.8 in the target mismatch group, and only 0.2 in the no target mismatch group. These studies raise the possibility that, one day, imaging-based treatment protocols may allow for intravenous thrombolysis and endovascular reperfusion therapies in selected patients well outside the now-accepted three- and six-hour time windows, respectively, and could allow treatment of a much larger number of patients.

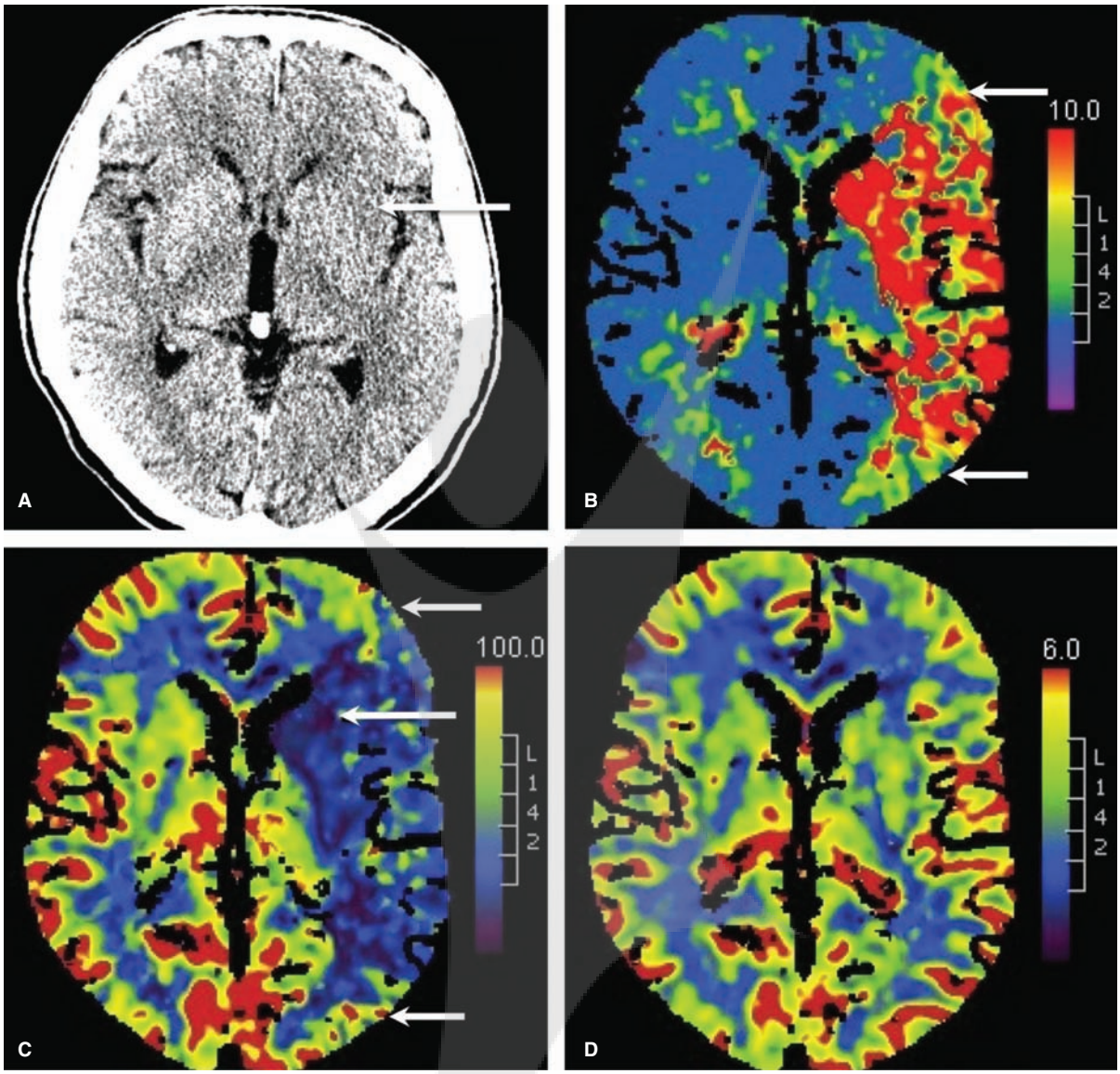

FIGURE 4.14 Fifty-seven-year-old female presented with right hemiparesis and aphasia, last seen normal 2.5 hours prior to imaging. Noncontrast CT (A) reveals subtle loss of gray–white matter differentiation within the left lateral putamen (arrow), which is faintly visible with narrow window level settings. CT perfusion maps reveal a large area of increased MTT (B) and decreased CBF (C) involving the entire left MCA territory (delineated by short arrows), with preserved CBV in this region (D). There is a small focal area of more severely decreased blood flow (C) within the anterior left putamen (long arrow), which was confirmed to represent infarction core on follow-up MRI (not shown). The large mismatched region with increased MTT and decreased CBF, but normal CBV and noncontrast CT findings, may represent the penumbra, ischemic but viable, tissue at risk for infarction.

Even when an acute stroke patient is not a candidate for intravenous thrombolytic or endovascular therapy, perfusion-weighted imaging should be considered. For patients who cannot undergo MR imaging, CTP increases the detection of acute ischemia. In one study, CTP increased the sensitivity in detecting acute stroke by 18% compared with NCCT alone, and by 12% compared with NCCT and CTA-SI (93). For patients with an acute neurologic deficit and a normal DWI, perfusion imaging can help determine whether or not the acute deficit is ischemic; a wedge-shaped perfusion deficit suggests that the patient has ischemic but viable tissue, whereas normal perfusion suggests a nonvascular etiology for the patient's symptoms. In a patient with a DWI abnormality in one vascular territory, perfusion imaging can help determine stroke etiology; for example, PWI demonstrating abnormalities in multiple vascular territories suggests a cardioembolic or vasculitic etiology. Perfusion imaging also contributes to general patient outcome prediction models. One study including patients who received heparinization alone or intravenous thrombolytic and/or endovascular therapy showed that a combination of MR-MTT and DWI lesion volumes improved outcome prediction over NIHSS alone, with MTT volume less than 47 mL and

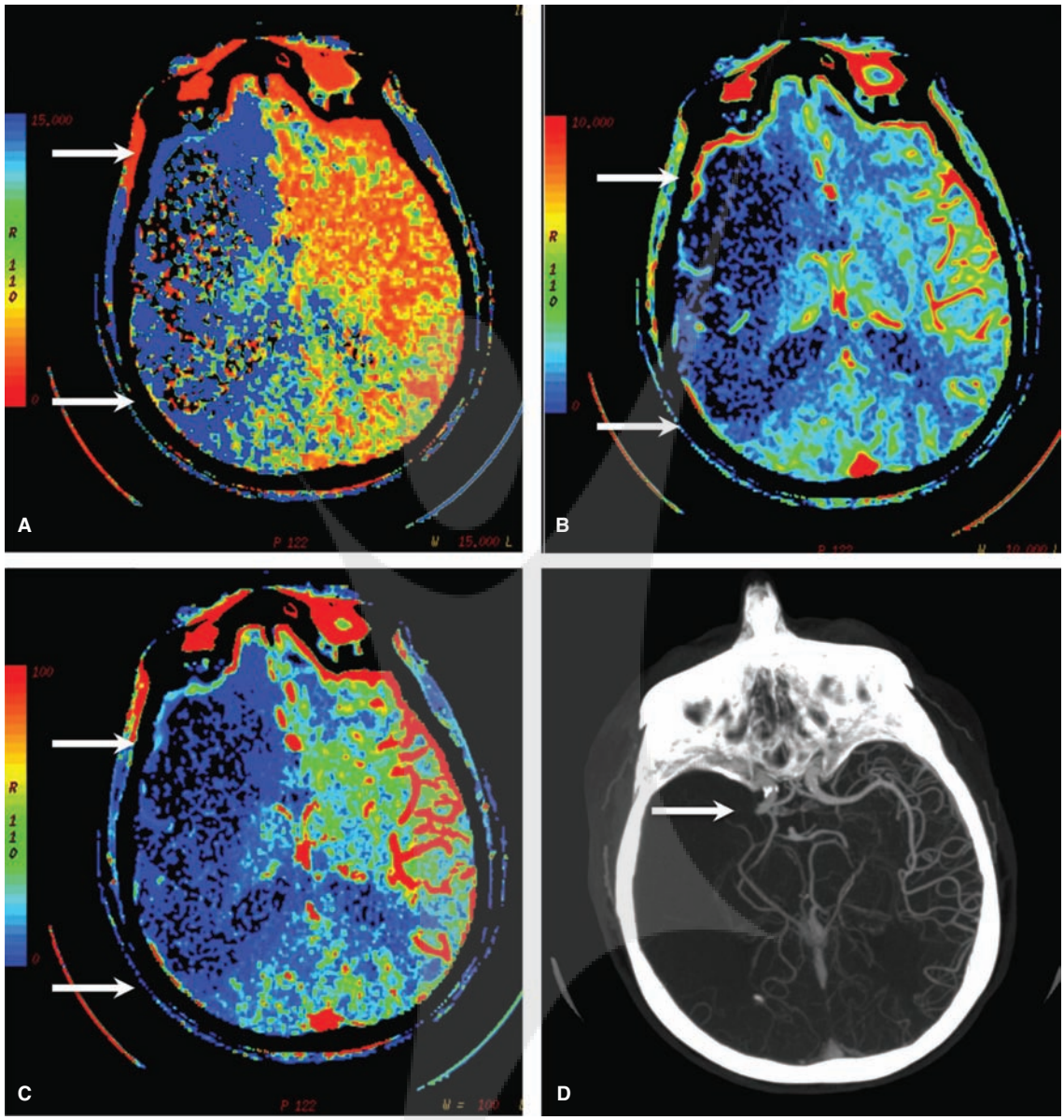

FIGURE 4.15 Eighty-eight-year-old female with atrial fibrillation with sudden onset of left hemiparesis, 1 hour and 20 minutes before imaging. CT perfusion maps demonstrate severely decreased CBV (B) and CBF (C) throughout the visualized right MCA territory, consistent with infarction core. There is also prolonged MTT (A) throughout the same region. There is no mismatch between the MTT images and regions of severely decreased CBV and CBF, suggesting that there is no tissue that is at increased risk for further infarction. The CTA MIP image (D) demonstrates occlusion of the right M1 segment of the MCA without significant collateral vasculature.

NIHSS less than 8 predicting good patient outcome and DWI volume more than 72 mL and NIHSS more than 20 predicting poor outcome (94). Perfusion imaging may also predict malignant middle cerebral artery territory infarction, as was demonstrated in one CTP study that showed an association between the area of increased blood–brain barrier permeability and those patients ultimately requiring hemicraniectomy (95). In addition, preliminary studies have demonstrated that location-weighted CT perfusion analysis may be helpful in predicting motor and language recovery (96,97).

HEMORRHAGIC TRANSFORMATION OF ACUTE STROKE

Hemorrhagic transformation is a major complication of acute stroke. It is commonly thought that reperfusion into severely ischemic tissue leads to hemorrhagic transformation (Figures 4.16 and 4.17). However, some investigators have shown that it can occur distal to permanently occluded vessels and suggest that collateral flow into ischemic tissue can lead to hemorrhage (98). Furthermore, thrombolytic agents increase the risk of hemorrhage. They are thought

TABLE 4.7 DWI and PWI Lesion Volumes and Associated Prediction of Ischemic/Infarct Tissue Behavior

PATTERN	CAUSE	COMMENT
MTT but no DWI	Frequently, proximal occlusion or critical stenosis with penumbra perfused via collaterals	DWI abnormality may develop, depending on collateral supply and timing of reperfusion. Good candidate for reperfusion therapy.
MTT > DWI	Frequently, proximal occlusion or critical stenosis with penumbra perfused partially by collaterals	Infarct may expand into part or all of the MTT abnormality, depending on collateral supply and timing of reperfusion. Good candidate for reperfusion therapy.
MTT = DWI	Usually, distal occlusions or lacunar infarcts, but can involve proximal occlusions as well	Entire territory has infarcted. No additional tissue at risk and no need for aggressive therapy.
MTT < DWI	Proximal, distal, or lacunar infarct	Ischemic tissue has reperfused. No additional tissue at risk and no need for aggressive therapy.
DWI but no MTT	Proximal, distal, or lacunar infarct	Ischemic tissue has reperfused. No additional tissue at risk and no need for aggressive therapy. Also, tiny infarcts below resolution of perfusion imaging.

to aggravate microvascular damage by activation of the plasminogen-plasmin system with the release of metalloproteinases that cause degradation of the basal lamina (99,100).

CT is considered the gold standard for detecting hemorrhagic transformation. However, T2* sensitive gradient-echo MR sequences (GRE) that have increased sensitivity to blood breakdown products, because of their paramagnetic properties, are as sensitive as CT in the detection of hemorrhage associated with acute stroke (101) (Figure 4.17). Furthermore, following thrombolysis, both contrast extravasation and hemorrhage are hyperdense and may be difficult to differentiate on CT. GRE images can easily differentiate between the two. Hemorrhage has susceptibility effects, whereas iodinated contrast does not.

Estimation of blood–brain barrier permeability (BBBP) with MRI or CT perfusion imaging may help predict the likelihood of hemorrhagic transformation. Permeability can be estimated from the standard dynamic susceptibility (T2*-based) MRI perfusion by measuring the relative recirculation of contrast. In one study of 84 patients, pretreatment BBBP derangement was 98% specific for hemorrhagic transformation, although it was only 29% sensitive (102). CT perfusion can also be used to assess permeability by measuring the rate of contrast material extravasation from the intravascular to the extravascular space through a disrupted BBB. An early study used a first-pass 60-second acquisition CTP protocol and found a sensitivity of 100% and specificity of 89% for prediction of hemorrhagic transformation (103). Subsequent studies, however, found that first-pass CTP data overestimate true tissue permeability (104), and that longer acquisition times of at least 210 seconds are required to generate accurate permeability values with CTP (105). In one recent study using a delayed-acquisition CTP protocol, a permeability surface product threshold of 0.23 mL × min^{-1} × 100 g^{-1} had 77% sensitivity and 94% specificity for detection of HT (106).

A number of additional imaging parameters have been found to be predictive of hemorrhagic transformation. These parameters are thought to reflect more severe ischemia and breakdown of the blood brain barrier and include the following:

1. Hypodensity in more than one-third of the MCA territory on CT (107)
2. Early parenchymal enhancement on gadolinium-enhanced T1-weighted images (108)
3. Larger volume of the initial DWI abnormality (compared to infarctions that do not hemorrhage) (109)
4. A higher percentage of pixels with ADC less than 550×10^{-6} mm^2/sec (compared to infarctions that do not hemorrhage) (110)
5. A more severe decrease in CBV and CBF versus the entire perfusion abnormality (compared to infarctions that do not hemorrhage) (111)
6. A relative CBF value less than 0.48 or relative MTT more than 1.3 compared to the contralateral side (112)
7. At least 126 voxels with CBV less than 5% of contralateral normal gray matter in patients who received intravenous tPA (113)

Conversely, it has been shown that preexisting microbleeds detected on T2* gradient echo do not signify risk for hemorrhagic transformation following thrombolytic therapy (114).

THE FUTURE: EMERGING TRENDS AND TECHNIQUES

The techniques and modalities employed in imaging acute stroke patients are rapidly evolving. Multidetector CT scanners with larger numbers of detectors have shortened scanning times, increased perfusion CT coverage, and require smaller contrast boluses. In addition, higher field strength MR magnets coupled with parallel imaging coils promise even faster, higher signal-to-noise ratio MR images

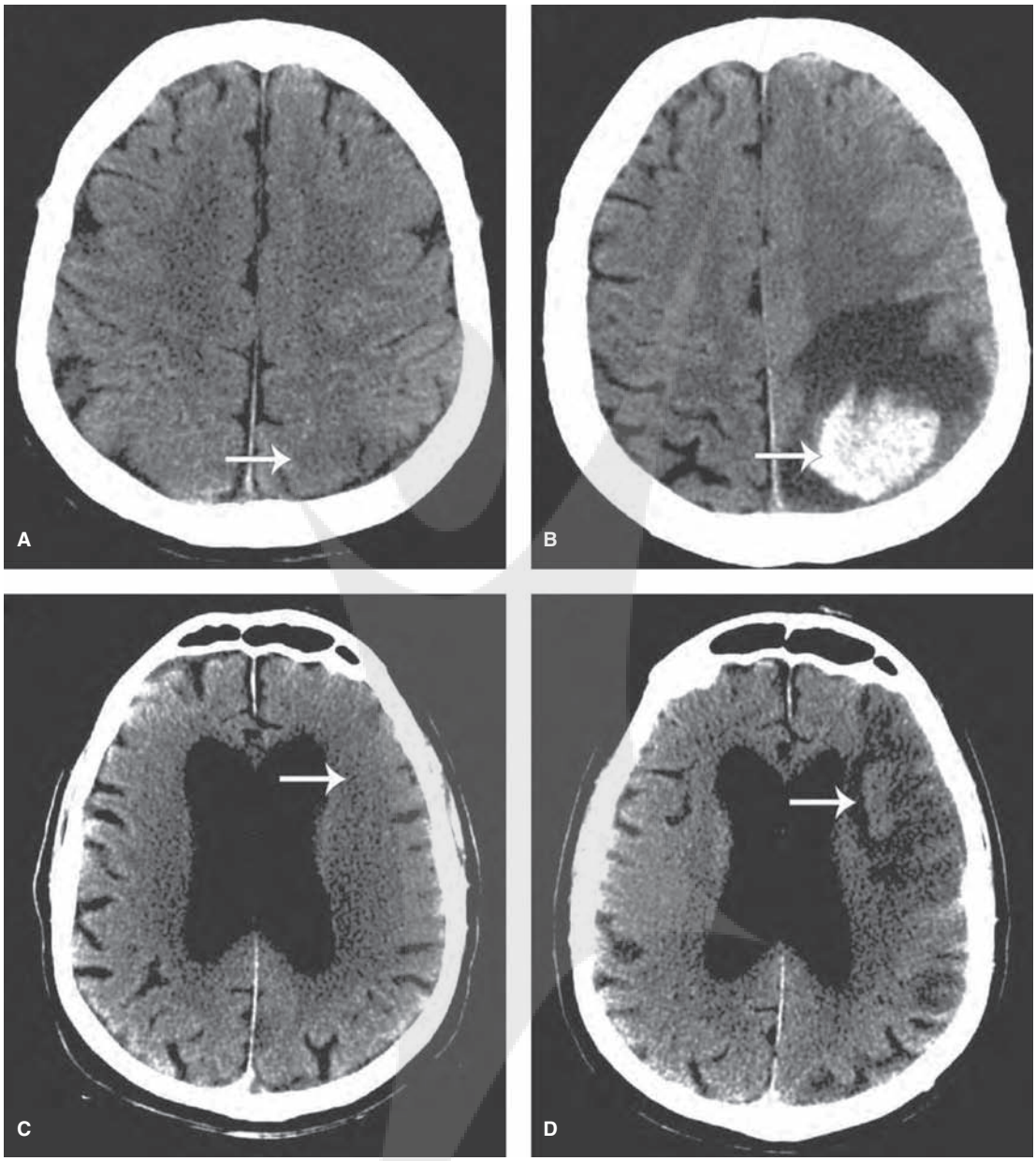

FIGURE 4.16 Hemorrhagic transformation on CT. Fifty-year-old male shown below. Initial noncontrast CT examination (A) demonstrates a small infarction within the left parietal region (arrow). On the follow-up study 14 days later (B), there is expansion of the infarction with a relatively large intraparenchymal hemorrhage (PH2 by ECASS classification scheme) (arrow). In a second patient with right hemiparesis, initial noncontrast CT (C) demonstrates a left MCA infarction (arrow). On follow-up CT (D), there is petechial hemorrhage within the infarction (HI1 by ECASS classification scheme) (arrow).

and MR angiograms. The physiologic evaluation of the acute stroke patient is moving from a largely subjective to an objective quantitative approach.

The search for imaging biomarkers and profiles that can individualize treatments based on specific physiology, rather than a generalized guideline or time window, has intensified. Sodium concentration in brain tissue can be calculated with high field strength MR scanners. In the unperturbed state, brain tissue maintains sodium ion homeostasis via energy-dependent mechanisms. This homeostasis is disrupted in ischemia, and there is evidence that tissue sodium concentrations can be used as a tool to predict ischemic tissue viability (115). Optical imaging (near-infrared spectroscopy) is being used to study both infarct progression and neuroplasticity following ischemia. Blood oxygen level-dependent (BOLD) MRI has been used to assess the cerebral metabolic rate of oxygen ($CMRO_2$), a marker of brain function that may enable a more precise evaluation of tissue at risk for progressing to infarction (116,117). MRI pH-weighted imaging is sensitive and specific for tissue

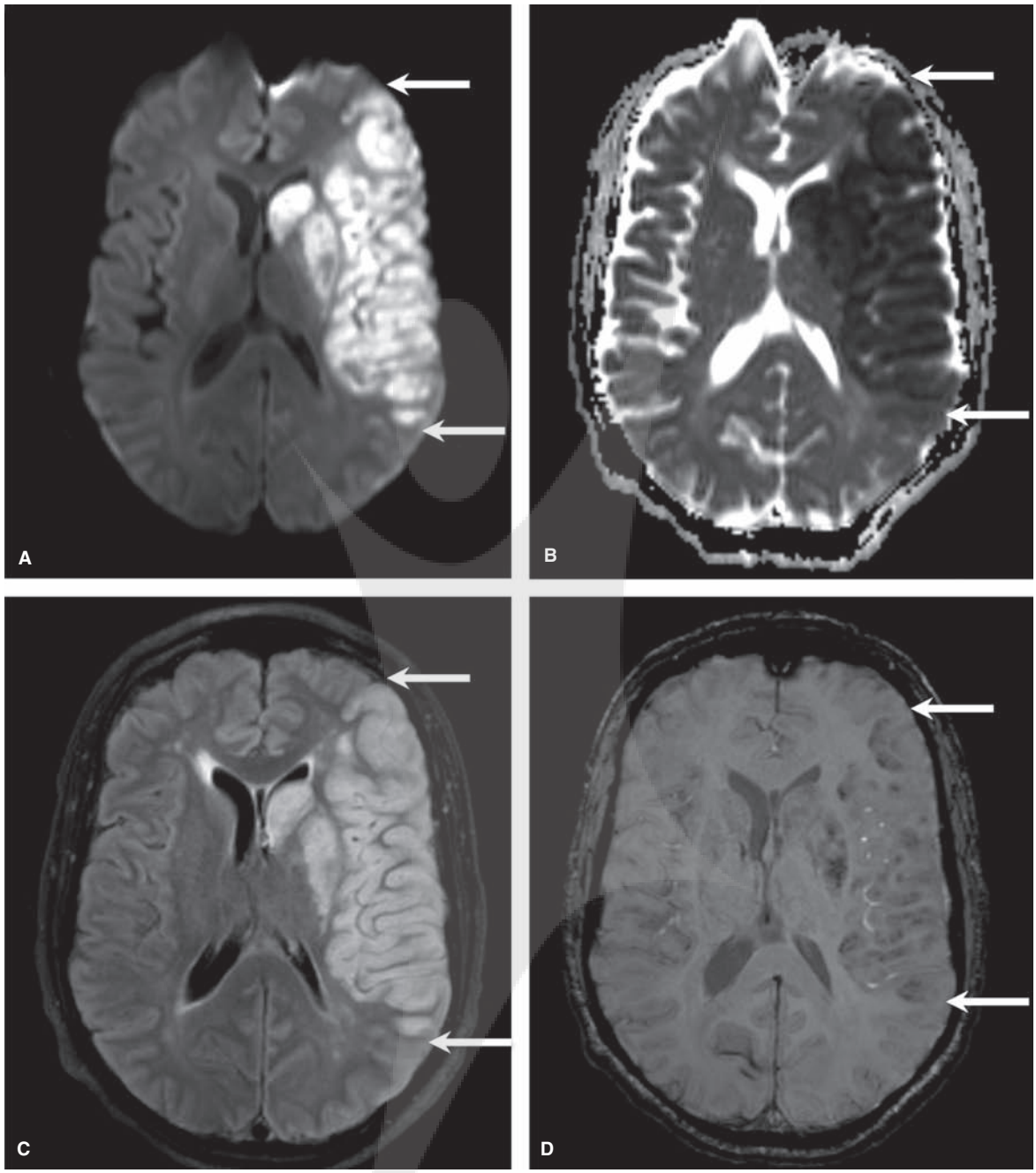

FIGURE 4.17 Hemorrhagic infarction on MRI. Follow-up MRI of the patient depicted in Figure 4.6 confirms infarction in the majority of the left MCA territory, which is hyperintense on DWI (A), hypointense on ADC (B) maps, and hyperintense on FLAIR (C) (delineated by arrows). Susceptibility-weighted images (D) reveal multifocal patchy hypointense signal throughout the area of infarction (delineated by arrows), consistent with confluent petechial hemorrhagic infarction (HI2 according to ECASS classification scheme).

lactic acidosis and is also under investigation as a way to quantify ischemic tissue at risk for infarction (118). Diffusion kurtosis imaging is an advanced diffusion imaging technique that may improve our understanding of the microstructural changes that occur during acute stroke. One recent article suggested that diffusion kurtosis lesions might more accurately define the infarct core versus diffusion-weighted imaging (119).

CONCLUSION

This chapter hopes to inform the reader about the current state of the art and future of acute stroke imaging and its impact on stroke triage. The advent of evaluation of the stroke patient using physiologic stroke parameters, in concert with the advances in stroke therapy, promises better clinical outcomes in the near future.

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5

Cerebral Stroke Syndromes

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The main purpose of the neurologic examination in stroke rehabilitation is to identify physical, cognitive, and communicative impairments, and to determine their impact on functional activity. By understanding these activity limitations, meaningful therapeutic goals can be derived. This contrasts with the neurologic examination performed in acute care, which informs the diagnosis and localizes the injury. In the rehabilitation setting, the lesion location is usually known, so the neurologic examination focuses on identifying *expected* impairments characteristic of a particular stroke syndrome. Understanding stroke syndromes helps target the examination, which improves the practitioner's efficiency and the accuracy of the neurologic assessment.

This chapter covers the stroke syndromes that occur in brain regions above the tentorium, including the anterior cerebral artery (ACA), middle cerebral artery (MCA), posterior cerebral artery, and others. In addition, the lacunar syndromes characteristic of infarcts within the territories of subcortical branches originating from these main arteries are reviewed. The syndromes described are those typical of arterial and branch occlusions rather than hemorrhagic rupture. This chapter is not intended to be an exhaustive review of cerebrovascular and neurologic anatomy, but rather a general anatomical overview that facilitates understanding of common clinical stroke syndromes.

CLINICAL NEUROANATOMY

The two cerebral hemispheres are divided, by convention, into four lobes: frontal, parietal, occipital, and temporal (Figure 5.1).

The frontal lobe is separated from the parietal lobe by the central sulcus. All behavioral motor output, including mobility, object manipulation, directional eye movement, and verbal expression, originate in the frontal lobe and are assisted by the basal ganglia and cerebellum. In contrast, processing of all sensory input, including visual, auditory, and somatosensory, is integrated by the thalamus, and the parietal, occipital, and temporal lobes. However, there is rich neural integration between frontal lobe systems and primary sensory areas. There are also significant interconnections between the primary motor cortex and somatosensory cortex, premotor and ventral motor areas, as well as connections from the thalamus to the motor cortex and the motor cortex to basal ganglia, superior and inferior colliculi, and cerebellum.

Cortical Areas of the Frontal Lobe

Primary Motor Cortex (M1)

The primary motor or M1 cortex is located in the precentral gyrus, just anterior to the central sulcus, in both hemispheres. It extends from the medial portion of the frontal lobe at the paracentral lobule, around the lateral convexity, and into the frontal operculum (the frontal lobe cortical surface tucked within the sylvian fissure). The motor cortex contains large pyramidal neurons (Betz cells) that constitute the "upper motor neurons" of the primary motor system and that supply axons for the cortical spinal tract. It is somatotopically organized in the form of the classic "homunculus" described by Penfield, where motor control for the feet is located in medial frontal regions; shoulder, arm, and hand are located along the superior lateral convexity; and face, tongue, and throat are located along the inferior convexity and the operculum (Figure 5.1). Lesions of the M1 cortex result in hemiplegia, often without spastic dystonia.

Broca's Area

Named after Paul Broca (1824–1880) (1), Broca's area is one of the two primary cortical language areas. Broca's area is located in the inferior lateral convexity and within the operculum of the dominant (usually left) frontal lobe (2,3). Interestingly, it is located in the premotor area anterior to M1 cortical representation for face, mouth, tongue, and throat. Thus it makes sense that lesions in this area would result in impaired oral motor communication, characterized by nonfluent speech production, apraxic errors, and problems with syntax. However, lesions in Broca's area often result in mild to moderate loss of auditory comprehension, characterized by failure to understand the syntax of complex sentences. Broca's area is important for facilitating the production of motor activity given on command, especially commands given verbally. Injury to Broca's area results in limb apraxia in both right and left limbs (4).

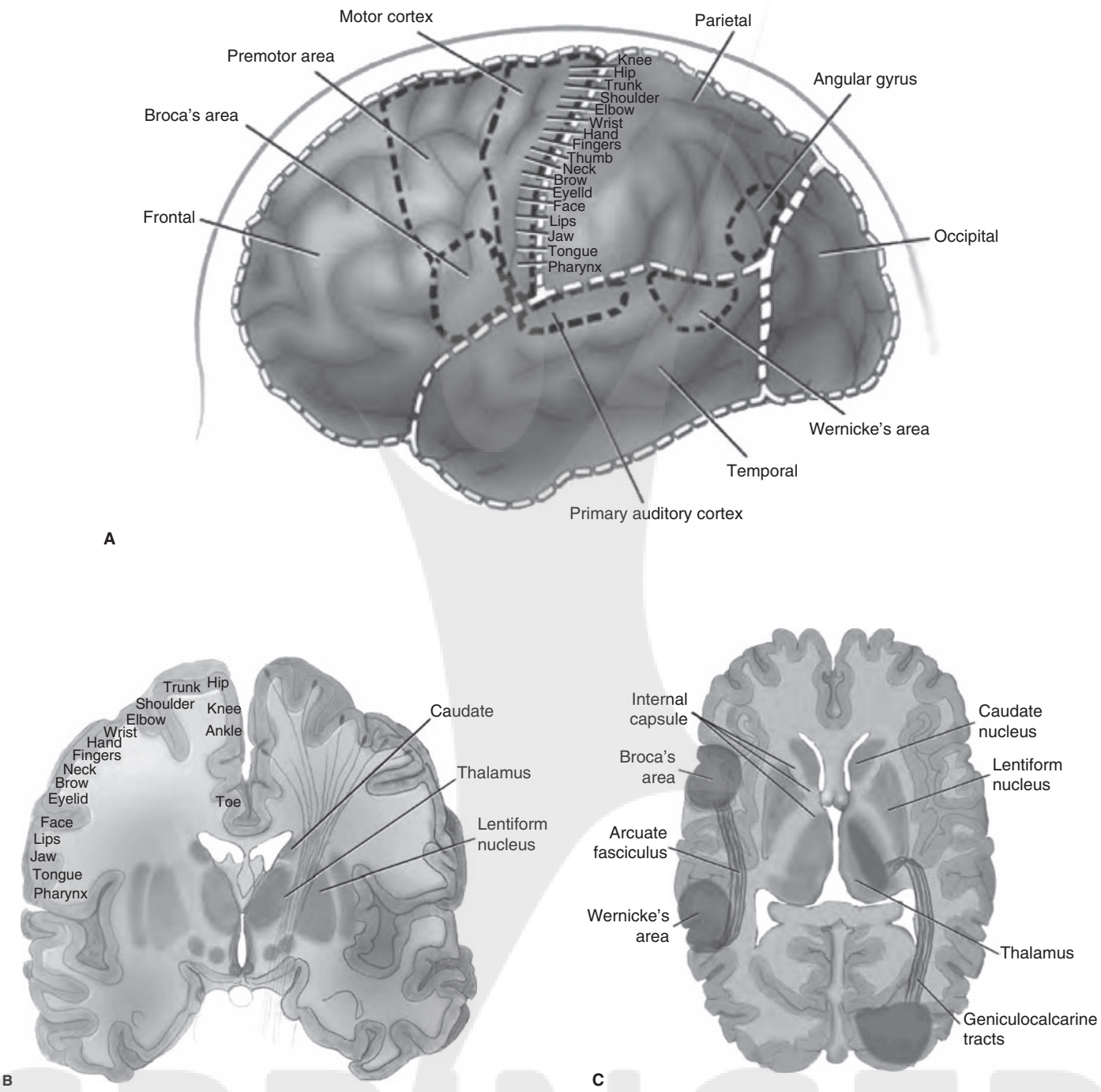

FIGURE 5.1 Cortical and subcortical neuroanatomy of the human brain. (A) Lobes of the cerebral hemisphere and identified cortical structures. (B) Coronal view of frontal lobe. (C) Horizontal view with highlighted language and visual areas and associated tracts.

Frontal Eye Fields

Although the prefrontal area of the frontal lobe is complex and poorly understood, it is accepted that this area plays an important role in executive decision making. Within this context, there are cortical regions in the prefrontal area that are important in directional and exploratory eye movements, called the frontal eye fields. Within each hemisphere are located two eye fields. One is known as the "eye field of the dorsomedial frontal cortex," and the other, located dorsolaterally, is the "frontal eye field" (5). A unilateral lesion of either eye field causes a gaze preference and frequently head-turning toward the side of the lesion, away from the hemiplegic side. Patients with such lesions have reduced saccadic gaze and visual pursuit toward the contralateral visual field. Often these symptoms are transient, but sometimes they may be long-lasting. In addition, injury to the nondominant (usually

right) prefrontal area impairs exploratory eye movements to the left and contributes to the attentional deficits seen in neurologic neglect syndrome (6). Head- and eye-turning associated with nondominant prefrontal lesions is often more persistent, whereas these symptoms usually resolve within days to a few weeks with dominant lobe lesions.

Primary Cortical Sensory Areas

Primary Somatosensory Cortex (S1)

The postcentral gyrus is located anteriorly in the parietal lobe, behind the central sulcus, and contains primary somatosensory representation. Like M1, it is somatotopically organized with roughly the same anatomic organization as the primary motor cortex. Lesions in S1 result in loss of two-point discrimination and stereognosis in the contralateral body. If subcortical sensory structures such as sensory tracts and thalamus are involved as well, there may also be loss of pain, temperature, and joint position sense.

Primary Visual Cortex

Located on the medial surface of the occipital lobe, within the longitudinal fissure, is the calcharine or primary visual cortex, a critical structure for vision. Unilateral hemispheric lesions of the visual cortex result in a contralateral homonymous hemianopsia, meaning loss of half the visual field to an equivalent extent in both eyes. Symptoms of homonymous hemianopsia are not limited to lesions of the primary visual cortex; they may also occur with lesions involving subcortical structures of the temporal lobes. This is because visual tracts extend from the ventral posterior lateral thalamus, radiate posterolaterally into the temporal lobes, and then arch medially to the occipital cortex (Figure 5.1). Any lesion along this tract will also cause a contralateral homonymous hemianopsia.

Primary Auditory Cortex

Pure tone recognition is processed in the primary auditory cortex, located on the superior temporal gyrus in the temporal lobe. This is also known as Heschel's gyrus and is more prominent in the dominant hemisphere (7). Auditory cortex is tonotopically organized by sound frequency (8,9). A lesion to the superior temporal lobe on or near Heschel's gyrus does not result in deafness; however, in the dominant hemisphere, such a lesion can cause complex auditory perceptual problems, such as pure word deafness (10).

Cortical Sensory Association Areas

Cortical association areas are local networks connected by extensive reciprocal monosynaptic connections to other cortical areas, as well as to certain subcortical structures. These interconnected local networks make up large-scale networks for distributed processing of neurocognitive activities such as attention, language, and memory. Thus, lesions in associated areas can negatively affect complex perceptual, cognitive, and communicative behaviors (6).

Posterior Parietal Cortex

Located behind the primary somatosensory cortex, the posterolateral parietal area integrates neural information from somatosensory, visual, and auditory cortices to construct a cohesive perception of three-dimensional space and the body's position within the surrounding environment (11). Current theory suggests that in humans, the nondominant parietal cortex is oriented to bilateral space, whereas the dominant hemisphere is strongly oriented to the contralateral (usually right) hemispace. As such, lesions in the left parietal cortex usually cause only transient right hemineglect syndrome. In contrast, lesions in the right parietal cortex cause clinically significant left hemineglect syndrome. The neglect syndrome is characterized by reduced recognition of and attention to visual, somatosensory, and auditory stimuli in the contralateral hemispace. In addition, patients with lesions in the right parietal hemisphere have visual perceptual deficits resulting in spatial disorientation. Clinically, they are unable to draw figures accurately, to use blocks to build a simple structure, and to orient their clothing to their body while dressing (12). Clinical terms such as *constructional apraxia* and *dressing apraxia* have been applied to this syndrome. However, it is important to note that these problems result from deficits in perception and are not true motor apraxias.

Wernicke's Area

Named after Carl Wernicke (1848–1905) (13), Wernicke's area is located posteriorly to Heschel's gyrus in the dominant hemisphere and is a language-association area functioning as a local neural network, situated between the primary auditory and visual cortices. Wernicke's area processes spoken and written symbolic language into meaning and comprehension (2,3). Along with Broca's area in the frontal operculum, Wernicke's area participates in a larger network for distributed processing of language (6). Lesions in Wernicke's area result in impaired language comprehension and a fluent aphasia mixed with multiple paraphasic errors. Patients with Wernicke's aphasia lack insight about their comprehension deficits, which can complicate care and participation in rehabilitation.

Angular Gyrus

Immediately posterior to Wernicke's area, in the posterior superior temporal lobe, is the angular gyrus, which receives visual input from the occipital lobe and the posterior inferior temporal lobe (14). The angular gyrus is an important region for processing written language; lesions here can cause alexia (3).

Subcortical Structures

Posterior Limb of the Internal Capsule

Axons that constitute the cortical spinal tract descend from the M1 cortex subcortically into the internal capsule. The anterior portion of the posterior limb, beginning at the genu,

contains these fibers. This portion of the internal capsule passes between the thalamus and the globus pallidus, into the cerebral peduncle, and then into the midbrain as the ventral crus cerebri (Figure 5.1). The posterior limb of the internal capsule is somatotopically organized with face, hand, arm, and shoulder anterior to trunk, thigh, leg, and foot. Lesions in the internal capsule result in contralateral hemiplegia.

Thalamus

Located between the third ventricle and the posterior limb of the internal capsule, the thalamus functions as a sensory hub for somatosensory, visual, and auditory inputs (Figure 5.1). Lesions here can result in mild hemiplegia or hemiataxia, sensory deficits, pain syndromes, mild aphasia, and neglect syndrome.

Arcuate Fasciculus

Another important structure in the large-scale language network is the arcuate fasciculus, which is a cortico-cortical white-matter tract passing reciprocally between Wernicke's and Broca's areas along an arched pathway (6). Lesions along the arcuate fasciculus can cause problems with repetition of language as well as limb apraxia bilaterally (3,4).

Corpus Callosum

The large arch-shaped bundle of white matter connecting the two cerebral hemispheres is the corpus callosum (Figure 5.1). Lesions within this structure can contribute to a disconnection between the right and left hemisphere, resulting in various clinical manifestations depending on the location of the lesion.

CEREBROVASCULAR ANATOMY

The Circle of Willis

In his book *Cerebri Anatome*, published in 1664, Thomas Willis provided the first complete description of the cerebral arterial circle, now commonly known as *the circle of Willis* (15). The circle is supplied by three intracranial arteries. The right and left internal carotid arteries supply the circle anteriorly, and the basilar artery provides the posterior supply (Figure 5.2).

The last branch of each internal carotid before entering the circle of Willis is the ophthalmic artery, which passes into the orbit and supplies the retinal tissue. Small branches of the ophthalmic artery anastomose with branches from the external carotid. After releasing the ophthalmic artery, the internal carotid artery enters the circle of Willis at the point where the posterior communicating artery (PComA) branches posteriorly. The internal carotid then provides a deep perforating cerebral artery, the anterior choroidal artery (AChA), before bifurcating into the middle cerebral artery (MCA) and the anterior cerebral artery (ACA). The basilar artery bifurcates into both posterior cerebral arteries (PCA). The circle is completed by anastomosis of the PComA with the PCA, and the anterior communicating artery (AComA) with both ACAs (Figure 5.2).

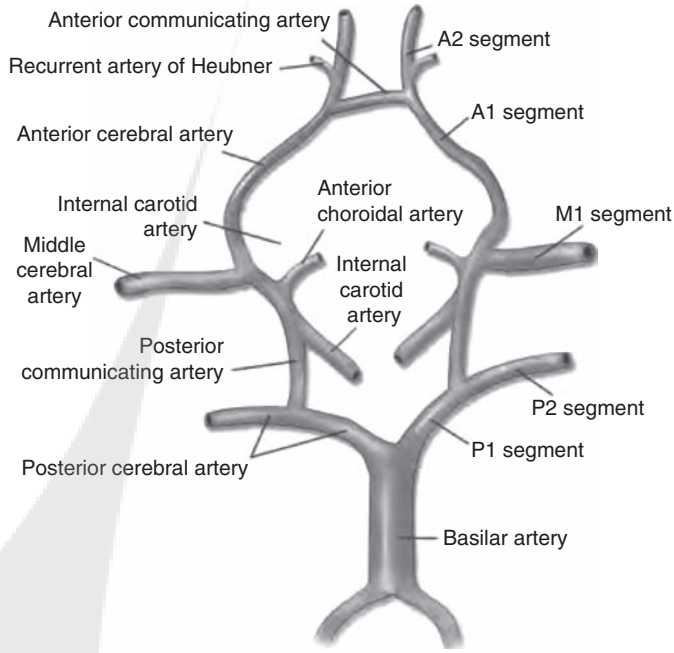

FIGURE 5.2 The circle of Willis and associated branches.

This "typical" anatomy of the circle is present in only 35% of human specimens. Anatomical variations are numerous, including hypoplastic portions of the circle as well as absent portions, the most common being an absent PComA on one side. In the presence of atherosclerotic disease, the intact circle of Willis can provide important collateral supply of blood flow to the ACA, MCA, PCA, and deep perforating arteries. Another important collateral supply to the circle of Willis, in the presence of atherosclerotic occlusion of an internal carotid, is retrograde blood flow from the external carotid artery through the ophthalmic artery. Finally, leptomeningeal arteries provide another helpful, but limited, source of collateral blood supply to the cerebral cortex.

The Anterior Choroidal Artery

The last branch of the internal carotid artery before the MCA–ACA bifurcation is the AChA. It is a major deep perforating artery that supplies the optic tract, globus pallidus, anterior hippocampus, and parts of the thalamus including a branch to the lateral geniculate nucleus (16,17). In addition, the AChA provides blood supply to the deep white matter of the temporal lobe, including the geniculocalcarine tract and the lower portion of the posterior limb of the internal capsule in the cerebral peduncle. As the name of the AChA implies, the terminal branches supply the choroid plexus of the temporal horn.

The Anterior Cerebral Artery

The ACA originates from the carotid bifurcation and extends in an anteromedial direction to the anastomosis of the AComA. This portion of the circle of Willis is called the A1 segment. The A2 segment continues after the AComA anastomosis, along the medial frontal lobe within the medial longitudinal fissure between the cerebral hemispheres (Figure 5.3).

It then passes superiorly and posteriorly around the corpus callosum to supply the medial frontal lobe, the corpus callosum, the cingulate gyrus, the paracentral lobule, and portions of the medial parietal lobe (18). Tributaries from the ACA transverse over the convexity of the cerebral hemisphere and anastomose with tributaries from the MCA in a watershed region.

The recurrent artery of Heubner (RAH) was first described by Johann Otto Leonhard Heubner in 1872 (19). This artery is the largest of a group of deep perforating arteries known as the lenticulostriate, which supply the basal ganglia as well as the intervening internal capsule and other surrounding white matter. The RAH originates either from the proximal A2 segment of the ACA or from anywhere along the A1 segment. Specifically, the RAH supplies the anterior caudate nucleus, the anterior third of the putamen, the tip of the outer segment of the globus pallidus, and the anterior limb of the internal capsule. Within the dominant hemisphere, the RAH supplies subcortical tissue near Broca's area in the frontal operculum.

Middle Cerebral Artery

The MCA supplies the largest volume of the cerebral hemisphere, including the basal ganglia, the internal capsule, and the visual radiations from the thalamus. The mainstem of the MCA originates from the carotid bifurcation and turns laterally toward the insular cortex. Along this route, it supplies a series of lenticulostriate branches to subcortical structures. Once at the insular cortex, deep in the sylvian fissure, the MCA divides into an upper and lower division. The segment from the carotid bifurcation to the MCA divisions is named M1. The M2 segment constitutes the upper- and lower-division branches within the sylvian fissure. The M3 segment includes the branches to the opercula, and the M4 are the branches overlying the cerebral convexities (Figure 5.3).

The superior division of the MCA supplies the frontal operculum, the lateral convexity of the frontal lobe, and, to a varying extent, the parietal lobe. The inferior division of the MCA supplies the temporal operculum, the lateral convexity of the temporal and occipital lobes, and, to a varying extent, the parietal lobe.

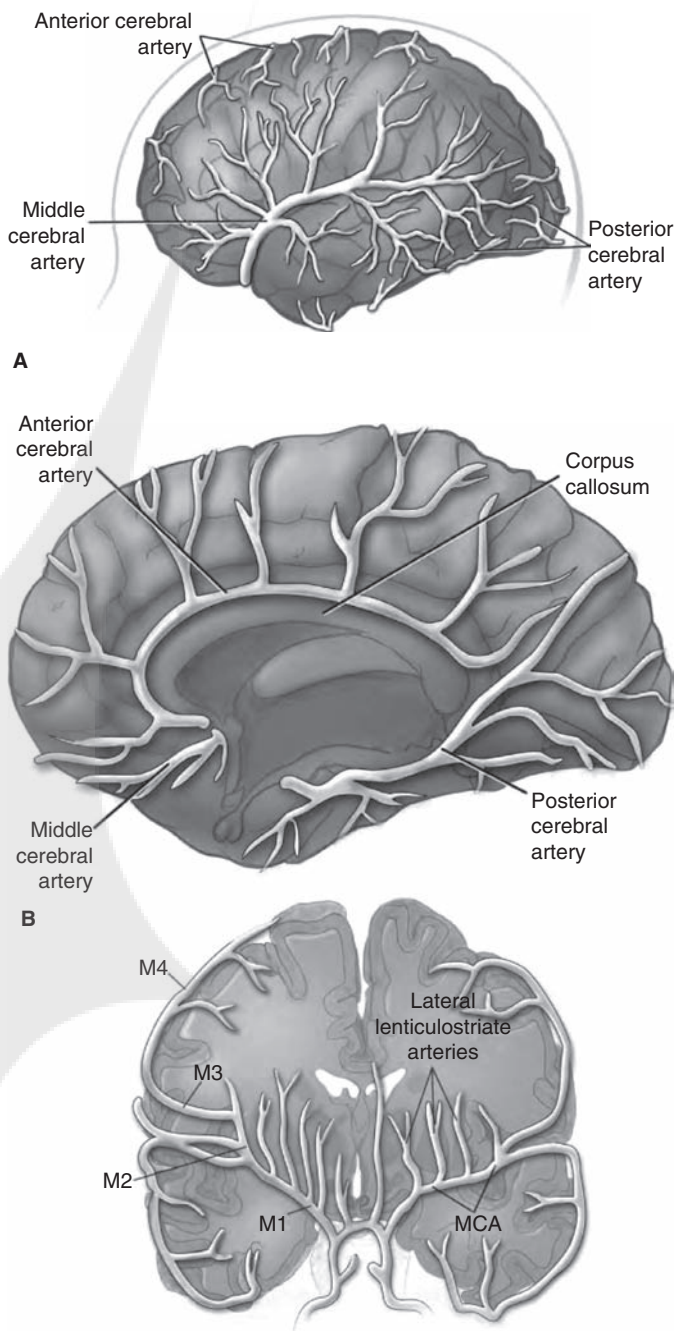

FIGURE 5.3 Vascular supply to cerebral hemisphere of the human brain. (A) Vascular supply to the lateral convexity of the cerebral hemisphere. (B) Vascular supply to the medial portions of the cerebral hemisphere. (C) Distribution of the middle cerebral artery and the subcortical branches of the lenticulostriate arteries.

The Posterior Cerebral Artery

The two PCAs divide at the top of the basilar artery and pass posterolaterally toward the medial temporal lobes. The P1 segment constitutes the section from the basilar artery to the branch of the PComA. The PCA then continues as the P2 segment to supply the medial occipital lobe within the longitudinal fissure, the posterior corpus callosum, and the medial temporal lobes, including portions of the hippocampi. Branch tributaries pass over the convexity of the cerebral

hemisphere and anastomose in a watershed region with MCA tributaries. Other tributaries within the longitudinal fissure anastomose with those of the ACA in the region of the medial parietal lobe (Figure 5.3).

CEREBRAL STROKE SYNDROMES

The stroke-related neurologic syndromes associated with major cerebral artery occlusion are predictable when one understands the neuroanatomy and cerebrovascular anatomy described in the first part of this chapter. In the context of cerebrovascular embolism or thrombosis, ischemic infarct can occur in all or a portion of the vascular bed supplied by the artery, depending on whether occlusion is total or incomplete. Immediate or delayed, intrinsically or extrinsically induced thrombolysis may also influence the extent of damage. The presence of atherosclerotic or small-vessel disease can affect the quality of tissue perfusion in watershed regions of major arteries. Thus, patients may experience all the components of a stroke syndrome, but more often only some of the signs and symptoms. Some of the neurologic impairment may be significant, whereas other impairments may be mild.

The following section includes a description of the most common clinical signs and symptoms associated with major cerebral stroke syndromes. However, it should be understood that individual cases seen in clinical practice may vary somewhat from the classic syndromes. Still, given the history and evidence on imaging of an infarct within a certain vascular distribution, the clinician should look for all signs and symptoms associated with that particular syndrome.

Carotid Artery Syndromes

A thrombus in the common carotid or internal carotid artery is associated with atherosclerotic carotid artery disease. Infarcts can occur from an occlusive carotid thrombus or thromboembolism to distal cerebral arteries (most commonly the MCA). Watershed infarcts in the distal MCA distribution can occur, presenting with partial contralateral hemiplegia and a sensory deficit affecting the shoulder more than the hand and leg. Carotid thrombosis often presents with a transient ischemic attack (TIA), which by definition lasts less than 24 hours and usually lasts only minutes. Amaurosis fugax, which is a transient monocular blindness, is a symptom that is peculiar to carotid TIAs. This phenomenon is typically caused by thromboembolism from the carotid to the ophthalmic artery with immediate thrombolysis. Often described as a "curtain dropping over the eye and rising again," amaurosis fugax more often presents as a visual obscuration, clouding, or fogginess variably affecting the whole, or part, of the visual field in one eye. On rare occasions, a completed stroke from carotid thrombosis will result in ipsilateral monocular blindness and contralateral hemiplegia.

AChA SYNDROME

The AChA syndrome was first described by Foix in 1925 and more thoroughly evaluated by Abbie in 1933 (16,20). Ischemic injury in the territory of the AChA causes a contralateral hemiplegia, because of injury to the posterior limb of the internal capsule. Hemianopsia can also occur, which varies depending on the structures involved. Injury to the optic tract can result in a contralateral hemianopsia and reduced pupillary reaction. A lesion to the geniculocalcarine tract in the medial temporal lobe can also cause a contralateral hemianopsia. If the lateral geniculate nucleus is injured, a contralateral hemianopsia with median horizontal sparing can occur and is diagnostic of an AChA occlusion (21). Visual sparing in the horizontal plane results because a portion of the lateral geniculate is supplied by the lateral choroidal artery. AChA strokes usually cause no language deficit if the infarct is in the dominant hemisphere, but nondominant injuries may cause a left hemineglect syndrome.

ACA Syndrome

The ACA stroke is an uncommon stroke, constituting 3% or fewer of all strokes. Still, patients with ACA stroke present with complex physical and cognitive deficits and usually require comprehensive neurorehabilitation services (22). Patients with a unilateral ACA infarct present with contralateral hemiplegia that is worse in the leg and shoulder than in the arm, hand, and face, because of injury to the medial M1 cortex at the paracentral lobule. If facial weakness is noted, it is likely that the RAH is occluded as well (19). Sensory loss is minimal, usually impaired two-point discrimination if present, and in the same distribution as the motor impairment.

Patients with ACA infarcts, whether in the right or left cerebral cortex, often have limb apraxia that is limited to the left side. This is because the ACA supplies the anterior corpus callosum, which is a main pathway of transcortical interconnectivity between the frontal lobes. Infarcts in either the right or left ACA disconnect the right premotor and M1 cortex from the left language network. This disconnection results in apraxic errors of the left upper limb when the patient is given a command (4,14). However, because the left motor cortex is adjacent to Broca's area, ACA strokes do not affect motor performance on command in the right upper limb. These patients usually perform better with the left upper limb if given visual cues to follow.

In cases of injury to the eye fields of the dorsomedial frontal cortex, head and eye deviation ipsilaterally (away from the hemiplegia) is observed (5). Prefrontal lobe injury is also associated with the grasp reflex of the affected hand as well as some paratonia, which is a kind of limb rigidity that becomes more prominent with an increase in effort by the examiner during muscle stretches (force-dependent rigidity). Other "frontal release" signs such as palmomental or snout reflexes can be seen in some cases.

Medial frontal injury involving the supplementary motor area and cingulate gyrus can also result in reduced initiation and, if severe, in psychomotor bradykinesia. Patients with ACA stroke may be very slow to respond to questions or commands; however, it should be kept in mind that they are often impulsive and may show no impediment in impulsive actions (such as climbing out of bed in an attempt to get to the restroom). Psychomotor bradykinesia can be severe enough to cause reduced verbal expression or even mutism that may be difficult to differentiate from aphasia (3). Executive cognitive functioning that can have a negative impact on independent performance of instrumental activities of daily living is also impaired with injury to the prefrontal cortex.

Patients with ACA strokes can present with aphasia when the infarction includes the vascular supply of the left RAH (19). This usually infarcts subcortical tissue in the region extending between the supplementary motor area and Broca's area, injuring white-matter portions of the language network (23). This most commonly causes a transcortical motor aphasia with reduced fluency, some apraxic errors of speech, and intact repetition (2,3).

MCA Syndromes

Mainstem MCA (M1 segment): Occlusion of the MCA within the M1 segment can cause ischemic injury in the entire MCA distribution, which includes most of the lateral convexity of the cerebral hemisphere. In addition, a substantial injury to subcortical structures—including the internal capsule, visual radiations, and thalamocortical white matter—results from hypoperfusion of the lenticulostriate arterial branches off the M1 segment. Large MCA distribution infarcts can produce significant edema and increased intracranial pressure, which can cause contralateral cerebral injury, uncal herniation, and death. Those who survive a large mainstem MCA stroke will have significant neurologic impairment.

A patient with a mainstem MCA infarct has complete contralateral hemiplegia from injury to the M1 cortex and the entire internal capsule. Contralateral hemisensory loss or even hemianesthesia can result from substantial injury to the subcortical sensory tracts and the S1 cortex, although the thalamus itself may be spared. Infarct of the ipsilateral frontal eye fields in the lateral prefrontal area causes head and eye deviation toward the lesion (away from the hemiplegia) (5). Deep infarction to the geniculocalcarine tract causes homonymous hemianopsia in the contralateral visual field.

If the infarct is in the dominant MCA distribution, there is damage to the language network, including Broca's area, Wernicke's area, the angular gyrus, and the arcuate fasciculus. The patient will have a global aphasia, with reduced fluency, severely impaired comprehension, and an inability to repeat, read, or write.

A nondominant MCA stroke causes severe visual and perceptual deficits, with disrupted spatial body orientation, dressing apraxia, and constructional apraxia. Survivors of nondominant MCA strokes also have a severe left hemineglect syndrome, contributed in part by reduced left attention (from parietal injury) and reduced exploration (from frontal injury) of the left hemispace. There is severe inattention to the left body as well, such that patients may even deny they have a stroke or stroke-related impairments (anosognosia).

Superior-Division MCA

Occlusion of the MCA at the origin of the superior division results primarily in a cortical infarct of the frontal lobe convexity, sparing the medial frontal lobe and subcortical tissue. Symptoms include a contralateral hemiplegia affecting the arm and hand more than the leg. Sensory deficits are mild, usually loss of two-point discrimination, in the same distribution as the weakness. These patients may have transient head and eye deviation toward the lesion (away from the hemiplegia). Visual fields are usually spared.

When the dominant hemisphere is affected, the patient has Broca's aphasia with decreased fluency of speech, apraxic errors, inability to repeat, and minimally impaired comprehension (2,3). These patients have bilateral limb apraxia from injury of the frontal-lobe language network (necessary for carrying out motor commands in either upper limb) (4). Patients often struggle to follow motor commands even with visual cues.

Patients with superior-division MCA strokes in the nondominant (usually right) hemisphere have a hemineglect syndrome, with reduced exploration of left hemispace and mildly reduced attention to left-sided stimuli (11). They often have deficits in visual spatial perception. Oral expression is altered in that patients may have less prosody in their speech, lacking the normal inflections that emphasize the meaning, importance, or emotional content of a sentence. Aprosodia is seen with nondominant frontal-lobe injuries (24,25).

Inferior-Division MCA

Occlusion in the inferior division of the MCA results in a primarily cortical infarct of the lateral convexity of the parietal, occipital, and temporal lobes. Patients with infarction in this region have no motor or somatosensory deficits. They may have a partial contralateral hemianopsia because of partial injury to the visual radiations in the temporal lobe.

Injury to the dominant hemisphere from an inferior division MCA stroke causes a Wernicke's aphasia, with fluent speech that is filled with paraphasic errors and poor comprehension of spoken and written language. Patients with nondominant injuries have a hemineglect syndrome, with reduced attention to the left hemispace and perceptual deficits (12). They may also have a *sensory aprosodia*, also known as an affective agnosia, in which the individual has difficulty in comprehending the prosody in another's speech (24–26).

Posterior Cerebral Artery Syndromes

If an occlusion occurs in the proximal PCA (P1) segment, hypoperfusion occurs in the distal PCA and the thalamoperforant arteries supplying the thalamus. This infarct results in

a contralateral sensory syndrome, with hypoesthesia, a feeling of heaviness in the limbs, and, in some cases, dysesthesia (called Déjerine–Roussy syndrome) (27). The PCA distribution stroke also causes a contralateral homonymous hemianopsia from direct injury to the primary visual cortex in the medial occipital lobe. Injury to the medial temporal lobe and structures of the hippocampus following PCA occlusion have been reported to cause an amnestic disorder in a few cases, but this is not commonly seen with unilateral infarct.

On rare occasions, a PCA infarct in the left occipital lobe can result in *alexia without agraphia* (3,14). These patients are not able to read, but can write. The infarct includes the left primary visual cortex, causing a right homonymous hemianopsia. It also includes the posterior corpus callosum, which disconnects the right primary visual cortex from the language network. Thus the patient can see words in the left hemispace but cannot transfer visual images to the language centers. Writing is not affected because there is no disconnection between the language network and motor cortex (14). Patients with this lesion may have some left neglect syndrome as well (28).

Thromboembolism to both PCAs is uncommon, but is the most common cause of cortical blindness. Other causes include hypertensive encephalopathy, hypoperfusion injury, or trauma. If the infarct includes the primary visual cortices and adjacent visual association areas, the patient may present with blindness and visual anosagnosia, or Anton's syndrome. This syndrome was named after Gabriel Anton, who described a series of such patients in 1899. Anton's syndrome is characterized by denial of visual loss associated with confabulation in the setting of severe loss of vision. These patients will fervently deny that they are blind, but will walk into walls if not guided to avoid them (29). The prognosis for recovery of visual loss is good when the syndrome is caused by hypertensive encephalopathy and the condition is treated, but poor when it is caused by spontaneous stroke. Patients with severe cognitive deficits in association with Anton's syndrome also have a poor prognosis (30).

Lacunar Stroke Syndromes

The term *lacune* means "little lake" and was coined to describe the pathological appearance of small cavities within brain parenchyma. These cavities are produced by small-branch occlusions of deep perforating vessels such as the lenticulostriate or thalamoperforant arteries. By definition, lacunar infarcts are 1.5 cm or less in the largest diameter, which corresponds to the tissue volume supplied by a deep perforating branch (located in subcortical structures such as the internal capsule, putamen, caudate, thalamus, cerebral white matter, and pons). Lacunar strokes are associated with hypertension and are caused by small-vessel occlusion from lipohylinosis of the vascular intima. Miller Fischer reintroduced the term "lacunar stroke" into clinical stroke neurology when he described the lacunar syndromes (31). Although as many as 100 lacunar syndromes have been described, 5 stand out as the most commonly seen in clinical practice.

One of the most common lacunar syndromes is the *pure sensory stroke,* with symptoms of numbness in the face, arm, and leg on one side of the body. There are no associated motor or cognitive deficits. The infarct is usually located in the thalamus. Patients with sensory strokes can develop late or chronic pain syndromes as a result of disruptions of normal sensory tracts. Lesions in other regions of the CNS along sensory pathways may also cause central poststroke pain syndrome (see Chapter 17).

Pure motor hemiparesis is also common and often results in some functional limitations that require rehabilitation. The patient has symptoms of motor loss in the face, arm, and leg, with or without spastic dystonia on one side of the body without associated sensory or cognitive changes. The stroke is located in the posterior limb of the internal capsule or cerebral peduncle, but may also occur in the base of the pons. Prognosis for functional recovery is good because patients lack other symptoms, such as language and visual deficits, and do not have apraxia. Spastic dystonia may complicate the rehabilitation process.

Dysarthria–clumsy hand syndrome, along with *ataxic hemiparesis,* are lacunar syndromes that most commonly occur from lesions in the base of the pons caused by occlusions of the paramedian pontine perforating vessels from the basilar artery. However, dysarthria–clumsy hand syndrome can also present following an infarct at the genu of the internal capsule in the somatotopic regions for face and hand, as well as in other areas of subcortical white matter. These patients have dysarthria and unilateral facial weakness without language deficits, and a mild hemiparesis of the upper limb on one side of the body. The prognosis for recovery is very good, and the patient will benefit from a course of speech therapy and motor retraining of the upper limb. Patients with ataxic hemiparesis often face a considerable challenge in regaining independent gait function because of problems with dynamic balance. But the prognosis is still very good, because the ataxic component often recovers more rapidly than the hemiparesis.

The lesion location for the *sensorimotor stroke* is most likely at the junction of the ventrolateral thalamus and the internal capsule, resulting in sensory loss and motor hemiparesis on one side of the body. Because the vascular supply to thalamus and internal capsule are distinct, the likely explanation is that edema from a thalamic stroke compresses adjacent fibers in the internal capsule, resulting in a mild hemiparesis. This has been described in one pathological case study (32).

RESEARCH FRONTIERS

Historically, our understanding of stroke syndromes came from the careful examination of pathological specimens. Today neuroimaging, especially with magnetic resonance imaging (MRI) and newer digital imaging software, has found a useful role in better defining the anatomical extent of cortical lesions caused by stroke. Techniques such as functional MRI (fMRI) (33) provide the opportunity to study the neuroanatomy following stroke and may further enhance

our understanding of the complex relations between clinical behavior, lesion location, and altered cortical activity in vivo (see Chapter 8).

Large digital-image databases are now being built, providing the opportunity to correlate neuroanatomy with genetic and phenotypic variations in normal adult humans (34). No such database currently exists for cases of cerebrovascular lesions, but such an image library would be invaluable. Several small studies have attempted to further characterize the neuroanatomy of language using fMRI and voxel-based lesion-symptom imaging techniques (35,36). The use of diffusion tensor tractography is helping to increase understanding of the association between white-matter tract lesions and stroke-related behavior (37–39). Such studies will certainly improve our understanding of stroke-related behavior and the corresponding neuroanatomical lesions. Even more important, however, are the prospects for better prediction of functional outcome and the targeting of candidates for rehabilitation interventions that can improve recovery.

CONCLUSION

Understanding the cerebrovascular and neurologic anatomy of stroke lesions can help the neurorehabilitation clinician perform an efficient neurologic examination and identify clinically meaningful impairments that will affect functional performance. Thus, a clear knowledge of common stroke syndromes becomes a valuable tool for assessing functional limitations and setting realistic rehabilitation goals for the patient with stroke. Future research with modern neuroimaging holds promise for better predicting functional recovery and for targeting rehabilitation interventions to achieve optimal outcomes.

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6

Stroke Syndromes: Infratentorial

Richard D. Zorowitz

The infratentorial region, comprising the brainstem and cerebellum, spans the diencephalon and the spinal cord. Despite its size, the brainstem has the potential to cause neurological devastation if damaged. It carries fibers that affect motor and sensory function, as well as arousal and survival; many of these fibers have important modulatory effects on both the cerebral cortex and the spinal cord. Although the cerebellum does not carry direct pathways from the cerebrum to the spinal cord, it too has the potential to cause neurological devastation because it also modulates movement and tone.

This chapter describes the development of the brainstem and cerebellum. Following this, the neuroanatomy of the brainstem and cerebellum and their organization into columns of afferent and efferent neurons is discussed. Understanding the organization of the brainstem and cerebellum is essential to understanding their functional correlates. It is these functional correlates that explain the syndromes discussed in the remainder of the chapter.

DEVELOPMENT OF THE BRAINSTEM

During development of the nervous system, the *neural tube* gives rise to all of the neurons and glial cells of the central nervous system. The caudal portion of the neural tube develops into the spinal cord, while the rostral portion becomes the brain. The rostral neural tube divides into three vesicles, called the *forebrain*, *midbrain*, and *hindbrain* (Figure 6.1). The forebrain, or *prosencephalon*, ultimately matures to form the *telencephalon* (cerebral hemispheres and lateral ventricles) and the *diencephalon* (thalamus and third ventricle).

Three layers form within the wall of the neural tube. The *neuroepithelial*, or *ventricular*, layer contains the innermost cells that ultimately will line the central canal of the spinal column and the ventricles of the brain. The *mantle*, or *intermediate*, layer consists of neurons and glial cells that will form the gray matter of the spinal cord. This layer contains the *alar plate*, which gives rise to sensory neuroblasts of the dorsal horn of the spinal cord; and the *basal plate*, which gives rise to motor neuroblasts of the ventral horn of the spinal cord.

The midbrain and hindbrain form the basis of the brainstem. The midbrain, or *mesencephalon*, does not divide, but evolves into the midbrain, cerebral aqueduct, and rostral cerebellum. The *alar plate sensory neuroblasts* form the cell layers of the superior colliculi and the nuclei of the inferior colliculi (1). The *basal plate motor neuroblasts* form the oculomotor (cranial nerve [CN] III) and trochlear (cranial nerve IV) nuclei, as well as the Edinger-Westphal (cranial nerve III) nucleus, which gives rise to preganglionic parasympathetic fibers. The red nucleus and substantia nigra also originate from the basal plate.

The hindbrain, or *rhombencephalon*, subdivides into two regions: the rostral *metencephalon* and caudal *myelencephalon*. The metencephalon matures into the caudal cerebellum, pons, and rostral fourth ventricle. In the pons, the alar plate sensory neuroblasts give rise to the spinal and principal sensory trigeminal (cranial nerve V) nuclei, and cochlear and vestibular (cranial nerve VIII) nuclei. They also form the solitary nucleus, which carries and receives visceral sensation and taste from the facial (cranial nerve VII), glossopharyngeal (cranial nerve IX), and vagus (cranial nerve X), and the cranial portion of the accessory (cranial nerve XI) nerves. This portion also relays information to the cerebellum through the pontine nuclei. The *basal plate motor neuroblasts* form the trigeminal (cranial nerve V), abducens (cranial nerve VI), facial (cranial nerve VII), and superior salivary (cranial nerve VII) nuclei.

The *myelencephalon* ultimately forms the medulla oblongata and caudal fourth ventricle. The alar plate sensory neuroblasts of the caudal portion of the medulla oblongata form the nuclei gracilis and cuneatus, inferior olivary (cerebellar relay) nuclei, solitary nucleus, spinal trigeminal (cranial nerve V) nucleus, and cochlear and vestibular (cranial nerve VIII) nuclei. The basal plate motor neuroblasts of the medulla oblongata give rise to the hypoglossal (cranial nerve XII) nuclei, nucleus ambiguus (cranial nerves IX, X, and XI), the dorsal motor nucleus of the vagus (cranial nerve X), and the inferior salivatory nucleus of the glossopharyngeal (cranial nerve IX) nerve.

DEVELOPMENT OF THE CEREBELLUM

As described earlier, the caudal portion of the cerebellum develops from the metencephalon, and the rostral portion arises from the caudal mesencephalon (2). It is formed by the thickened alar plates of the mantle layer of the neural tube known as *rhombic lips*. Four regions develop from the

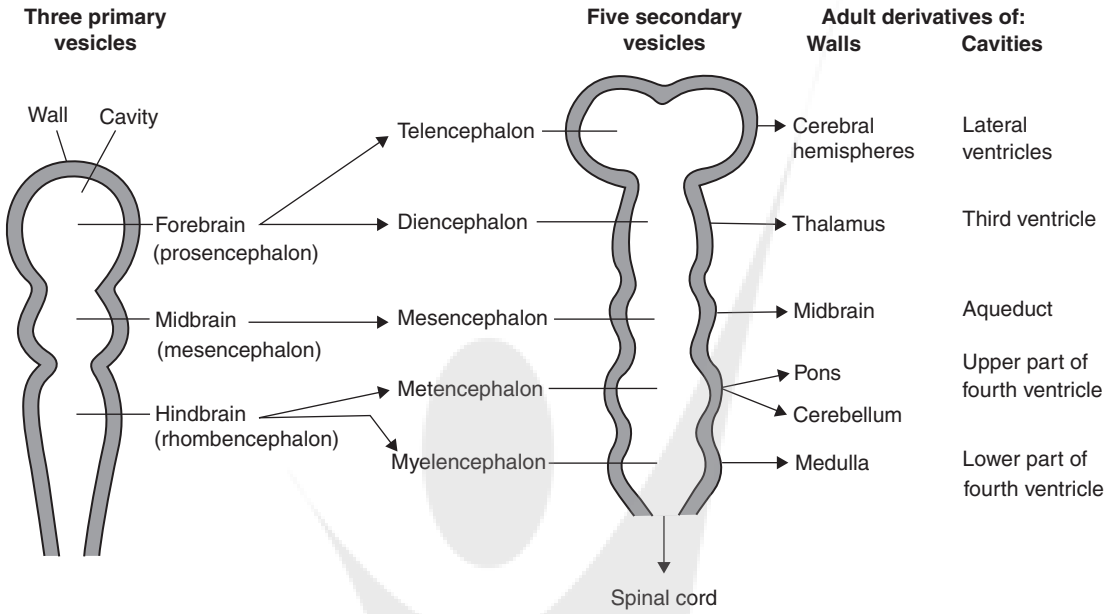

FIGURE 6.1 Development of the brain into forebrain, midbrain, and hindbrain.

Source: Reprinted with permission from Moore KL. *The Developing Human: Clinically Oriented Embryology*. 4th ed. Philadelphia, PA: W.B. Saunders; 1988:380.

cerebellar primordium. The *vermis* develops through midline growth. The *cerebellar hemispheres* develop by lateral growth. The *cerebellar cortex* migrates from the ventricles into the marginal zone, and forms three layers (molecular, Purkinje cell, and internal granular cell) and four pairs of cerebellar nuclei. The *external granular cell* layer is a germinal cell layer that exists on the surface of the cerebellum between the eighth week of development and the end of the second postnatal year. As the cerebellum grows, *folia* and *fissures* form.

ANATOMY OF THE BRAINSTEM (FIGURE 6.2)

The brainstem is the lower extension of the brain where it connects to the spinal cord. Neurological functions located in the brainstem include those necessary for survival (breathing, gastrointestinal function, heart rate, blood pressure) and for arousal and wakefulness. The brainstem also surrounds a narrow passage for the circulation of cerebrospinal fluid. The occlusion of this passage, the *aqueduct of Sylvius*, is often accompanied by the neurological complications of hydrocephalus.

To better understand how lesions of the brainstem cause specific neurological symptoms, it is important to understand the architecture of the brainstem. As the brainstem develops, neuroblasts develop columns that classify the functions of the body into discrete modalities. *General* fibers are found in most spinal nerves, whereas *special* fibers are found only in specific senses. *Somatic* fibers are found in organs of voluntary movement and sensation; *visceral* refers to internal organs. *Afferent* fibers travel from the periphery to the central nervous system, while *efferent* fibers travel from the central nervous system to the periphery. The modalities of nerve fibers are classified in Table 6.1. The functional divisions of the cranial nerves are listed by modality in Table 6.2.

As the brainstem develops, the alar plate becomes the sensory (afferent) nerves, and the basal plate becomes the motor (efferent) nerves. The motor nerves are positioned medially, and the sensory nerves are positioned laterally (Figure 6.3). By the time the brainstem is fully developed, the cranial nerve nuclei are organized into seven longitudinal columns (Figure 6.4). The cell columns run roughly parallel to the longitudinal axis of the brainstem, but are not always continuous. The organization of the cranial nerves into columns is significant for two reasons. First, neurons are organized with similar functions. For example, neurons mediating taste are located in the same position with respect to the midline. Second, different functions are affected when ischemia or hemorrhage damages areas of the brainstem, depending upon whether they are lateral or medial. As a result, one classification scheme of brainstem stroke syndromes is described by its lateral or medial location with respect to the midline.

Structures of the Brainstem

Midbrain (Figure 6.5)

The midbrain is a short, constricted structure that connects the pons and cerebellum with the thalamus and cerebral hemispheres. It consists of several portions: the *cerebral peduncles*, a pair of cylindrical bodies located ventrolaterally; the *corpora quadrigemina*, consisting of four rounded eminences; and the *cerebral aqueduct*, a passage representing

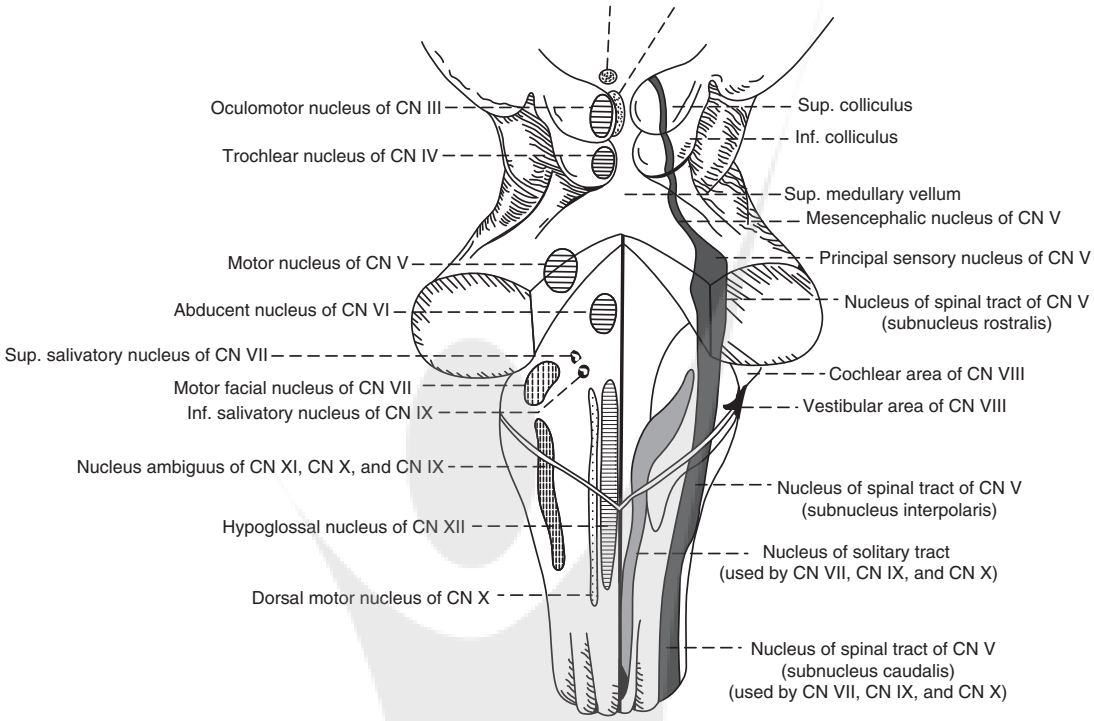

FIGURE 6.2 Neuroanatomy of the brainstem.

Source: Reprinted with permission from Fix JD. *Neuroanatomy*. 3rd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2001.

TABLE 6.1 Modalities of the Cranial Nerves

MODALITY	DEFINITION
General somatic afferent (GSA)	Arise from cells in spinal ganglia and conduct pain, touch, and temperature from the surface of the body and muscle/tendon/joint sense from deeper structures through posterior roots of the spinal cord
General visceral afferent (GVA)	Arise from viscera through the rami communicantes and posterior roots to spinal cord
General somatic efferent (GSE)	Arise from motor neuron cell bodies in ventral horns of spinal cord gray matter to skeletal muscle (i.e., alpha motor neurons, gamma motor neurons)
General visceral efferent (GVE)	Arise from cells in lateral column or base of the anterior column through anterior roots and white rami communicantes to sympathetic ganglia that conduct motor impulses to smooth muscles of the viscera and vessels and secretory impulses to the glands
Special somatic afferent (SSA)	Arise from nerves of special senses to the central nervous system (e.g., optic nerve, acoustic nerve)
Special visceral afferent (SVA)	Arise from nerves associated with gastrointestinal tract to the central nervous system (e.g., olfactory nerve, facial nerve, glossopharyngeal nerve, vagus nerve)
Special visceral efferent (SVE)	Arise from central nervous system to muscles of pharygeal arches (e.g., trigeminal nerve, facial nerve, glossopharyngeal nerve, vagus nerve, accessory nerve)

Source: Adapted from Gray H. Composition and central connections of the spinal nerves. In: Gray H. *Anatomy of the Human Body*. Philadelphia, PA: Lea & Febiger; 1918; Bartleby.com, 2000. www.bartleby.com/107/. Accessed on June 21, 2014.

TABLE 6.2 Functional Anatomy of the Brainstem

CRANIAL NERVE	MODALITY	STRUCTURE
Olfactory (I)	SVA	Projects directly to telecephalon
Optic (II)	SSA	Projects directly to diencephalon
Oculomotor (III)	GSE GVE	Oculomotor nucleus Edinger–Westphal nucleus
Trochlear (IV)	GSE	Trochlear nucleus
Trigeminal (V)	GSA GVE	Principal sensory and spinal nucleus of V Motor nucleus
Abducens (VI)	GSE	Abducens nerve
Facial (VII)	SVE GVE GVA SVA GSA	Facial nucleus Superior salivary nucleus Solitary nucleus Solitary nucleus Spinal nucleus of V
Vestibular (VIII)	SSA	Vestibular nucleus
Cochlear (VIII)	SSA	Cochlear nucleus
Glossopharyngeal (IX)	SVE GVE SVA GVA	Nucleus ambiguus Inferior salivary nucleus Solitary nucleus Spinal nucleus of V
Vagus (X)	SVE GVE SVA GVA GSA	Nucleus ambiguus Motor nucleus of X Solitary nucleus Solitary nucleus Spinal nucleus of V
Accessory (XI)	SVE	Nucleus ambiguus and accessory nucleus
Hypoglossal (XII)	GSE	Hypoglossal nucleus

Abbreviations: GSA, general somatic afferent; GSE, general somatic efferent; GVA, general visceral afferent; GVE, general visceral efferent; SSA, special somatic afferent; SVA, special visceral afferent; SVE, special visceral efferent.

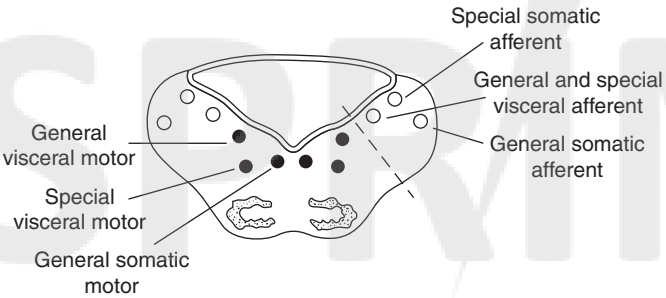

FIGURE 6.3 Positions of the motor and sensory nuclei in the developing brainstem. Sensory nuclei develop from the alar plate, while motor nuclei develop from the basal plate.

Source: Reprinted with permission from Kandel ER, Schwartz JH, Jessell TM. *Principles of Neural Science*. 3rd ed. New York, NY: McGraw Hill Professional Neurosciences; 1995:686.

the original cavity of the midbrain that connects the third and fourth ventricles. Each cerebral peduncle is divided into a dorsal and ventral part, separated by the *substantia nigra*. The dorsal part is known as the *tegmentum*, and the ventral part is known as the *base* or *crusta*. The major gray-matter structures of the tegmentum are the *red nucleus* and the *interpeduncular ganglion*. The major tracts include the *superior cerebellar peduncle*, the *medial longitudinal fasciculus* (MLF), and the *medial lemniscus*.

The *red nucleus* is located in the anterior aspect of the tegmentum and the posterior aspect of the subthalamic region. It appears circular in shape, and receives fibers from the superior cerebellar peduncle and medial lemniscus. Axons cross the midline and project into the lateral funiculus of the

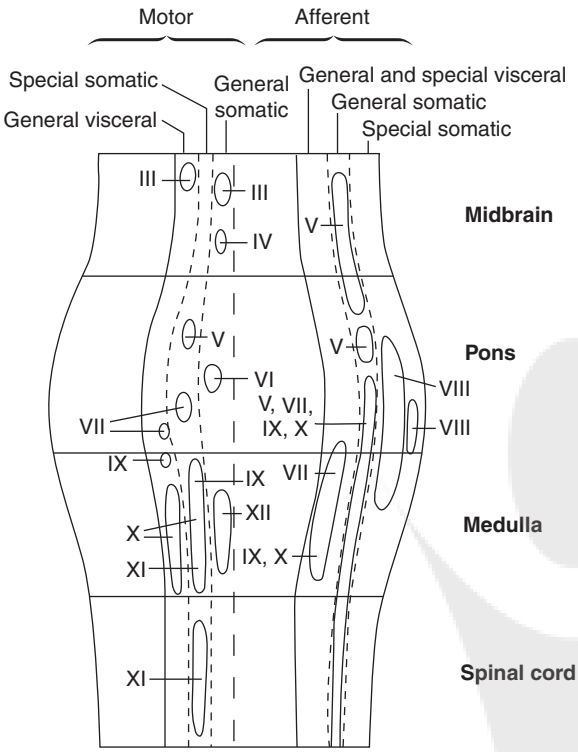

FIGURE 6.4 Columnar organization of the motor and sensory nuclei in the brainstem.

Source: Reprinted with permission from Kandel ER, Schwartz JH, Jessell TM. *Principles of Neural Science*. 3rd ed. New York, NY: McGraw Hill Professional Neurosciences; 1995:688.

spinal cord as the *rubrospinal tract*, an important part of the pathway from the cerebellum to the lower motor centers.

The *superior cerebellar peduncles* (*brachia conjunctiva*) are two axonal tracts that arise from the dentate nucleus of the cerebellum. The fiber bundles pass rostrally through the dorsal pons to the level of the inferior colliculus. At this point, the fibers decussate, ascend further, and terminate either in the red nucleus or within the motor, ventral lateral, or ventral anterior nuclei of the thalamus. The majority of fibers that convey signals out of the cerebellum to the brainstem are located in these tracts.

The MLF carries information about the direction that the eyes should move as well as head movement (from cranial nerve VIII). The MLF arises from the vestibular nucleus and is thought to mediate the maintenance of gaze. This is achieved by inputs from several structures: the acoustic (cranial nerve VIII) nerve that mediates head movements; the flocculus of the cerebellum that adjusts gain; and head and neck propioceptors and foot and ankle muscle spindles, through the fastigial nucleus. It mediates conjugate gaze by carrying electrical signals from the abducens (cranial nerve VI) nuclei, across the midline, then ascending to the oculomotor (cranial nerve III) and trochlear (cranial nerve IV) nuclei. The MLF also descends into the cervical spinal cord, where it innervates some muscles of the neck.

The vertical gaze center is located in the rostral interstitial nucleus of the MLF that lies just posterior to the red nucleus. From each vertical gaze center, signals are conducted to the subnuclei of the ocular muscles that control vertical gaze in both eyes. Cells mediating downward eye movements are intermingled in the vertical gaze center, but ischemia of this region may result in selective paralysis of upgaze.

The *medial lemniscus* originates in the nucleus gracilis and cuneatus of the medulla oblongata, and crosses to the opposite side in the sensory decussation. It then ascends through the medulla oblongata into the pons and lower portion of the midbrain, where it receives fibers from sensory nuclei of the contralateral cranial nerves. The majority of the fibers, however, enter the ventral lateral nucleus of the thalamus, give off collaterals, and then terminate in the principal sensory nucleus of the thalamus.

The *corpora quadrigemina* are four rounded structures that form the dorsal aspect of the midbrain. The corpora quadrigemina are arranged in pairs, as the *superior* and *inferior colliculi*. The superior colliculi are associated with the sense of sight, the inferior with that of hearing.

The afferent fibers of the superior colliculi largely originate in the retina and are conveyed to it through the superior brachium and lateral geniculate body. Some of the efferent fibers cross the midline to the opposite colliculus, while many ascend through the superior brachium and terminate in the cortex of the occipital lobe.

Pons (Figure 6.6)

The pons is a bridge-like structure that links different parts of the brain and relays information from the medulla oblongata to the higher cortical structures of the cerebrum. It contains the ventilatory and horizontal gaze centers. The pons sits in front of the cerebellum, and is connected to the cerebellum through the *middle cerebellar peduncle*. The pons consists of two aspects: the ventral surface (pars basilaris pontis), and the dorsal surface (pars dorsalis pontis). The ventral surface of the pons consists of superficial and deep transverse fibers, longitudinal fasciculi, and some small nuclei of gray substance (termed *nuclei pontis*) that give rise to transverse fibers. It is in the nuclei pontis that the cortical axons that travel through the internal capsule and cerebral peduncle form synapses with transverse fibers that decussate and pass through the middle peduncle into the cerebellum. The dorsal surface of the pons consists largely of ascending projections of the reticular formation and gray substance from the medulla oblongata. Other significant structures in the pons include the *superior olivary nucleus* and the *paramedian pontine reticular formation* (PPRF).

The PPRF is located anterolateral to the MLF. It receives input from the superior colliculus and from the frontal eye fields. The rostral aspect of the PPRF (rostral interstitial nucleus of the MLF) probably coordinates vertical saccades, while the caudal aspect of the PPRF may generate horizontal saccades. In particular, excitatory burst neurons (EBNs) in the PPRF generate "pulse" movements that initiate a saccade. With respect to horizontal saccades, the "pulse"

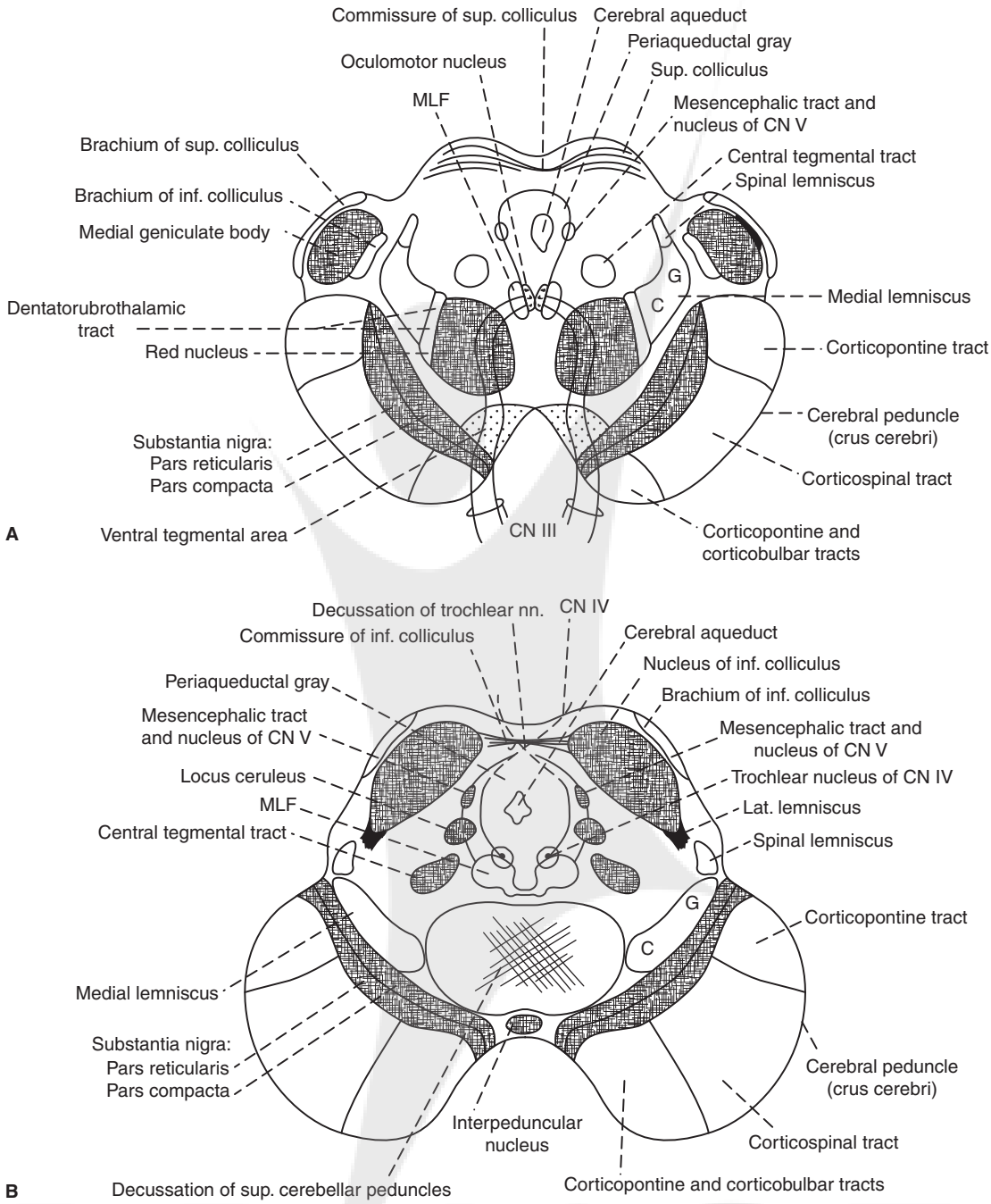

FIGURE 6.5 Clinical neuroanatomy of the midbrain. (A) Midbrain at the level of the superior colliculus. (B) Midbrain at the level of the inferior colliculus.

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information is conveyed via axonal fibers to the abducens (cranial nerve VI) nucleus, subsequently initiating horizontal eye movements. Two types of neurons in the abducens nucleus complete horizontal movement: a lower motor neuron that innervates the ipsilateral lateral rectus muscle and an internuclear neuron that sends axons across the midline, up the MLF, and into lower motor neurons of the contralateral oculomotor nucleus that innervate the medial rectus muscle.

Medulla Oblongata (Figure 6.7)

The medulla oblongata extends from the inferior border of the pons to a plane passing transversely between the pyramidal decussation and the first pair of cervical nerves. This plane corresponds with the upper border of the atlas and basilar part of the occipital bone behind, and the middle of the odontoid process of the axis in front. The medulla oblongata functions primarily as a relay station for the crossing of

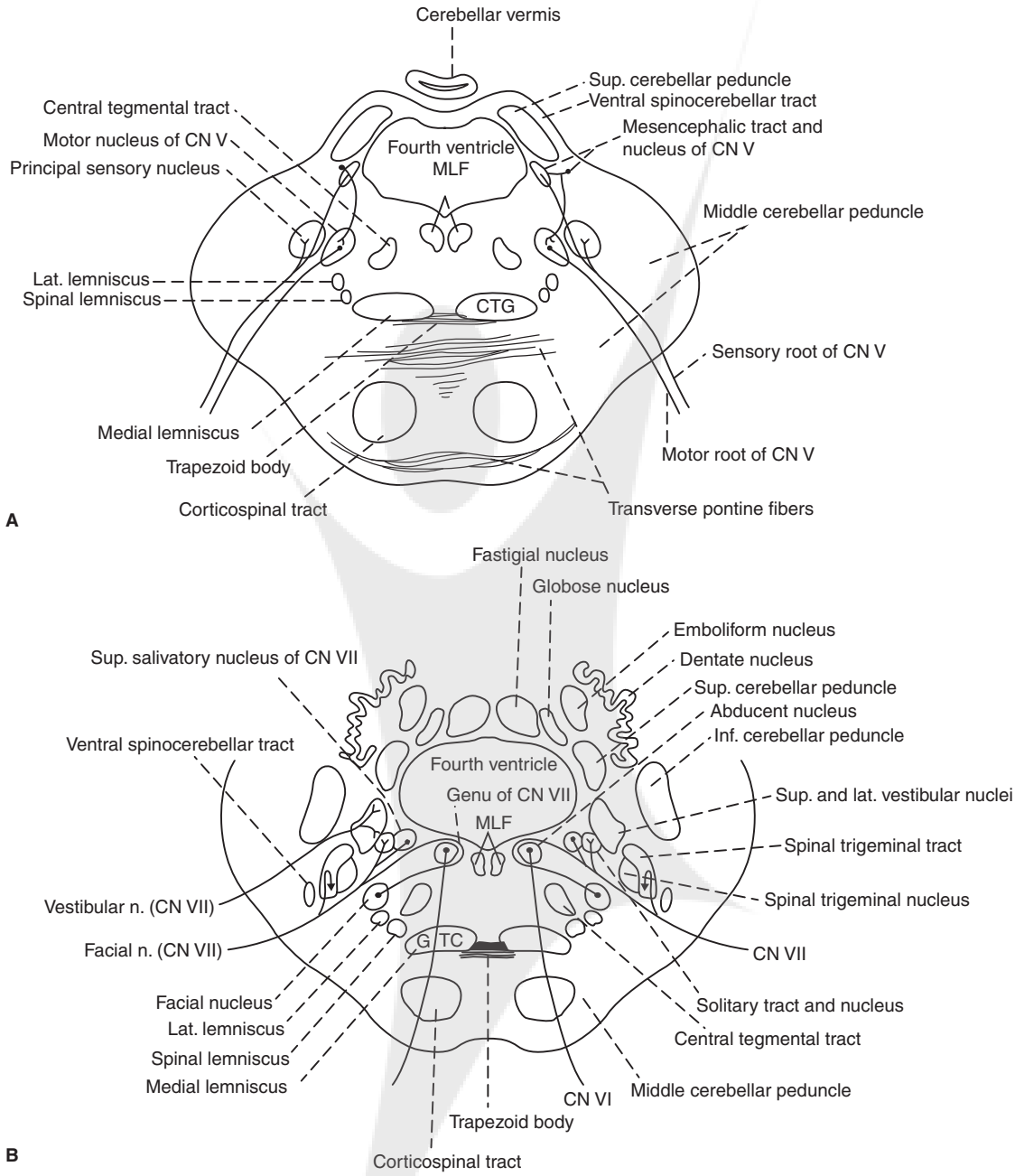

FIGURE 6.6 Clinical neuroanatomy of the pons. (A) Midpontine region. (B) Caudal aspect of the pons.

Source: Reprinted with permission from Fix JD. *Neuroanatomy*. 3rd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2001.

motor tracts between the spinal cord and the brain. It also contains the respiratory, vasomotor, and cardiac centers, as well as many mechanisms for controlling some involuntary actions such as coughing, gagging, swallowing, and vomiting. Significant structures in the medulla oblongata include the *olive* and the *inferior cerebellar peduncle*. The *olive* is located lateral to the pyramidal tracts.

The *inferior cerebellar peduncle* is located in the superoposterior portion of the medulla oblongata. It is a thick rope-like strand that sits between the inferior portion of the fourth ventricle and the glossopharyngeal (cranial nerve IX) and vagus (cranial nerve X) nerve roots.

The inferior cerebellar peduncles connect the spinal cord and medulla oblongata with the cerebellum. The inferior cerebellar peduncle carries many types of input and output fibers that mainly integrate proprioceptive sensory input with motor vestibular functions, such as balance and posture maintenance. Proprioceptive information from the

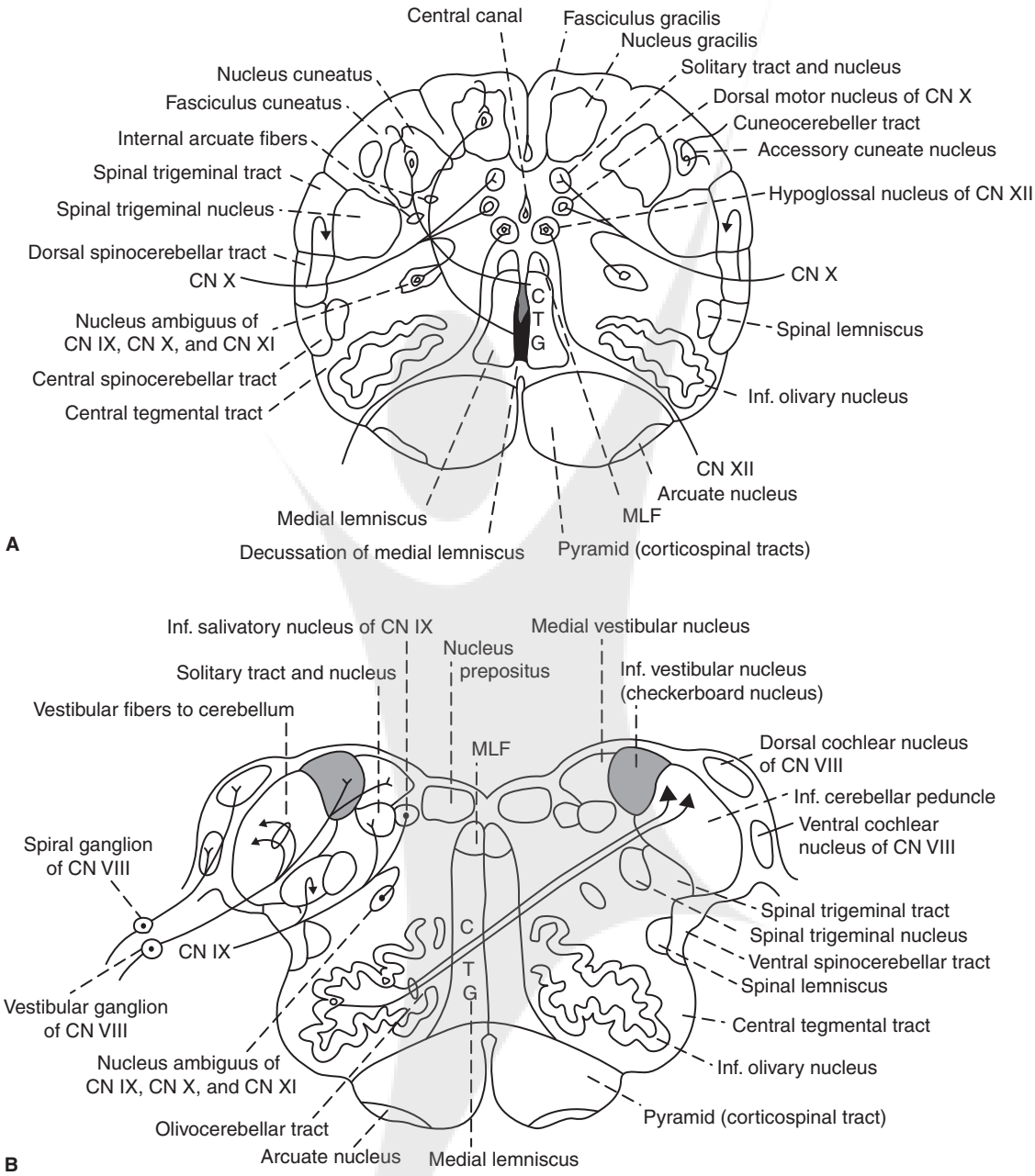

FIGURE 6.7 Clinical neuroanatomy of the medulla oblongata. (A) Rostral aspect of the medulla oblongata. (B) Caudal aspect of the medulla oblongata.

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body is conveyed to the cerebellum through the posterior spinocerebellar tract. The inferior cerebellar peduncle also carries information directly from Purkinje cells to the vestibular (cranial nerve VIII) nuclei at the junction of the pons and medulla oblongata.

Nuclei

A cranial nerve nucleus is a collection of neurons (gray matter) in the brainstem associated with one or more cranial nerves. Axons carrying information to and from the cranial nerves synapse at these nuclei. Ischemic or hemorrhagic lesions of these nuclei usually lead to neurological deficits resembling those seen when the nerves with which they are associated are severed. All cranial nerve nuclei, except for the trochlear (cranial nerve IV) nerve, supply nerves of the same side of the body.

The *olfactory nerve* (cranial nerve I) arises from spindle-shaped bipolar cells in the surface epithelium of the olfactory region of the nasal cavity. The nonmyelinated axons ascend through the cribriform plate to the olfactory bulb. At this point, several fibers, each ending in a tuft of terminal filaments, come into contact with the brush-like

end of a single dendrite from a mitral cell, giving rise to the olfactory glomeruli of the bulb. The termination of a number of olfactory fibers in a single glomerulus accounts (in part at least) for the detection by the olfactory organs of very dilute solutions. The olfactory fibers form synapses with dendrites of one or two mitral cells, providing for the summation of stimuli in the mitral cells. The majority of the axons that arise from the mitral cells of the olfactory bulb and course in the olfactory tract travel through the lateral olfactory stria to the uncus and hippocampal gyrus, and terminate in the cortex. Other fibers may pass to the uncus and hippocampal gyrus from the primary olfactory centers in the trigonum and anterior perforated substance. The branches and axons that pass backward terminate partly in the dentate gyrus and hippocampal gyrus. Shorter association fibers connect various sections of the gyrus fornicatus (cingulate gyrus, isthmus, and hippocampal gyrus) and these with other regions of the cortex. These gyri constitute the cortical center for smell.

The *optic nerve* (cranial nerve II) consists chiefly of coarse fibers that arise from the ganglionic layer of the retina. They constitute the third neuron in the series composing the visual path and are supposed to convey only visual impressions. A number of fine fibers also pass in the optic nerve from the retina to the primary centers and are supposed to be concerned with pupillary reflexes. In addition, there are a few fibers that pass from the brain to the retina. They reportedly control chemical changes in the retina and the movements of the pigment cells and cones.

In the optic chiasm, the nerves from the medial half of each retina cross to the opposite optic tract, and the nerves from the lateral half of each retina continue in the optic tract of the same side. The crossed fibers occupy the medial side of each optic nerve, but are more intermingled in the chiasm and in the optic tract. Most of the fibers of the optic tract terminate in the lateral geniculate body, but some may pass through the superior brachium to the superior colliculus, or through the lateral geniculate body to the pulvinar of the thalamus. The superior colliculus receives fibers from the visual sensory cortex in the occipital lobe that pass through the optic radiations.

The *oculomotor nerve* (cranial nerve III) contains somatic motor fibers to the inferior oblique, inferior rectus, superior rectus, levator palpebræ superioris, and medial rectus muscles. In addition, preganglionic sympathetic efferent fibers are carried to the ciliary ganglion. The postganglionic fibers from the ciliary ganglion supply the ciliary muscle and the sphincter of the iris. The axons arise from the nucleus of the oculomotor nerve, and traverse the posterior longitudinal bundle, tegmentum, red nucleus, and the medial margin of the substantia nigra to emerge from the oculomotor sulcus on the medial side of the cerebral peduncle.

The nucleus of the oculomotor nerve contains several distinct groups of cells that vary in size and appearance from each other and terminates its axons at separate muscles. It is uncertain which group supplies which muscle. There are seven of these nuclei on either side of the midline and one medial nucleus. The cells of the anterior nuclei are smaller and may give off sympathetic efferent axons. The majority of fibers arise from the nucleus of the same side. However, some may cross to the opposite side and supply the contralateral medial rectus muscle. Because the oculomotor and abducens nuclei are connected by the MLF, this decussation of fibers to the medial rectus may facilitate the conjugate movements of the eyes in which the medial and lateral recti muscles are involved.

The *trochlear nerve* (cranial nerve IV) contains only somatic motor fibers. It supplies the superior oblique muscle of the eye. Its nucleus is a small, oval mass located in the ventral part of the central gray matter of the cerebral aqueduct at the level of the superior aspect of the inferior colliculus. The axons from the nucleus descend in the tegmentum toward the pons, but abruptly turn dorsally before reaching it, cross horizontally, and decussate with the nerve of the opposite side. The nerve emerges immediately behind the inferior colliculus. There are no branches from the fibers of the pyramidal tracts to these nuclei. It is thought that the volitional pathway must be an indirect one.

The *trigeminal nerve* (cranial nerve V) contains somatic motor and sensory fibers. The motor fibers arise in the trigeminal motor nucleus, and travel ventrolaterally through the pons to supply the muscles of mastication. The sensory fibers arise from the semilunar ganglion, and are distributed to the face and anterior two-thirds of the head. The central fibers pass into the pons with the motor root, and bifurcate into ascending and descending branches that terminate in the sensory nuclei of the trigeminal.

The sensory nucleus consists of an enlarged upper end, the main sensory nucleus, and a long, more slender portion that descends through the pons and medulla oblongata to become continuous with the dorsal part of the posterior column of the gray matter of the spinal cord. This descending portion consists mainly of substantia gelatinosa and is called the *nucleus of the spinal tract of the trigeminal nerve*. Most of the fibers cross to the trigeminothalamic tract of the opposite side, ascend dorsal to the medial lemniscus, and terminate in a distinct part of the thalamus. The somatic sensory fibers of the vagus, glossopharyngeal, and facial nerves probably end in the nucleus of the descending tract of the trigeminal nerve. Their cortical impulses are probably carried up in the central sensory path of the trigeminal nerve.

The *abducens nerve* (cranial nerve VI) contains only somatic motor fibers that supply the lateral rectus muscle of the eye. The fibers arise from the abducens nucleus, pass ventrally through the pons, and exit from the transverse groove between the caudal edge of the pons and the pyramid. These fibers probably terminate in relation with the MLF, which controls conjugate gaze. The fibers of the MLF originate in the terminal nuclei of the vestibular nerve, and give off collateral and terminal neurons to the abducens, trochlear, and oculomotor nuclei. The abducens nucleus also receives collateral and terminal neurons from the tectospinal fasciculus, the reflex auditory center in the inferior colliculus, and other sensory nuclei of the brainstem.

The *facial nerve* (cranial nerve VII) consists of somatic and visceral afferent and efferent fibers. The afferent fibers arise from cells in the geniculate ganglion, and pass through what is often known as the *nervus intermedius*. There are few somatic afferent fibers. Their purpose is to convey impulses from the middle ear, but their existence and central termination have not been confirmed fully. There also are few visceral afferent fibers, and their terminations are likewise unknown. Taste fibers carry impulses from the anterior two-thirds of the tongue via the *chorda tympani* to the solitary tract and nucleus.

Somatic efferent fibers supply muscles derived from the hyoid arch, and originate from the facial nucleus. The facial nucleus consists of a dorsal and a ventral region. The dorsal region innervates muscles of the upper face, and the ventral region innervates muscles of the lower face. Impulses are carried from the cerebral cortex through the corticobulbar tract. Interestingly, the dorsal region of the facial nucleus receives bilateral cortical input, while the ventral region receives only contralateral input. The facial nucleus also receives fibers from the superior colliculus and ventral longitudinal bundle for optic reflexes; the inferior colliculus through the auditory reflex path; and indirectly from sensory nuclei of the brainstem.

Visceral efferent fibers arise from either the small cells of the facial nucleus or cells in the reticular formation, located dorsomedial to the facial nucleus, known as the *superior salivary nucleus*. These preganglionic fibers synapse at the submaxillary ganglion with postganglionic fibers that innervate the submaxillary and sublingual glands. Other preganglionic fibers travel by way of the great superficial petrosal nerve to the sphenopalatine ganglion.

The *acoustic nerve* (cranial nerve VIII) consists of the *cochlear nerve* and the *vestibular nerve*. The cochlear nerve, the nerve of hearing, terminates at the *cochlear nucleus*. The cochlear nucleus consists of a larger dorsal nucleus on the dorsolateral aspect of the inferior peduncle, and a ventral nucleus more ventral to the inferior peduncle and medial geniculate body. Most of the axons continue to ascend beneath the optic tract into the corona radiata and subsequently to the cortex of the superior temporal gyrus.

The *vestibular nerve* mediates the maintenance of bodily equilibrium. Once within the medulla oblongata, it bifurcates into ascending and descending branches. The descending branch terminates in the medial vestibular nucleus, the principal nucleus of the vestibular nerve. The ascending branch passes through the inferior cerebellar peduncle to the contralateral nucleus tecti.

The *glossopharyngeal nerve* (cranial nerve IX) contains somatic and sympathetic afferent, taste, somatic motor, and sympathetic efferent fibers. The afferent fibers arise from the superior ganglion and in the petrosal ganglion. There are few somatic afferent fibers that carry sensory impulses from the external ear, pharynx, and faucial arches. The visceral afferent fibers from the pharynx and middle ear assist in chewing and swallowing. Taste fibers from the tongue combine with fibers from the *nervus intermedius* and terminate in the solitary nucleus. Somatic efferent fibers originate in the nucleus ambiguus and innervate the stylopharyngeus muscle. Visceral efferent fibers originate in the nucleus dorsalis or the inferior salivary nucleus, and synapse through the otic ganglion to their termination in the parotid gland.

The *vagus nerve* (cranial nerve X) contains somatic and visceral afferent and efferent fibers, as well as taste fibers. There are few somatic afferent fibers that carry impulses from a small area of the skin on the back of the ear and posterior part of the external auditory meatus. The visceral afferent fibers carry impulses from the heart and pancreas, and probably the stomach, esophagus, and respiratory tract, to the *dorsal nucleus of the vagus* and glossopharyngeal nerves. The dorsal nucleus comes into relation with neurons that may carry impulses to the muscles of ventilation, such as the phrenic nerve and the nerves to the intercostal and levatores costarum muscles. Taste fibers conduct impulses from the epiglottis and larynx through the vagus nerve and join the *solitary tract*, subsequently terminating in the *solitary nucleus*. The solitary nucleus connects with motor centers of the pons, medulla oblongata, and spinal cord to mediate mastication and swallowing. Somatic efferent fibers from the *nucleus ambiguus* innervate voluntary muscles of the pharynx and larynx, and receive impulses from the opposite pyramidal tract. Visceral efferent fibers arise from the dorsal nucleus and synapse through sympathetic ganglia to fibers that facilitate the function of the esophagus, stomach, small intestine, gallbladder, and lungs; inhibit the function of the heart; and cause secretion within the stomach and pancreas.

The *accessory nerve* (cranial nerve XI) contains only somatic efferent fibers, and consists of spinal and cranial portions. The spinal portion arises from lateral cells in the anterior column of the upper five or six segments of the cervical spinal cord, and innervates the trapezius and sternocleidomastoid muscles. The cranial portion originates in the nucleus ambiguus. The fibers travel through the vagus nerve to the laryngeal nerves, and supply the muscles of the larynx. The spinal portion receives impulses from the ipsilateral pyramidal tracts, while the cranial portion receives impulses from the opposite pyramidal tract and forms the terminal sensory nuclei of the cranial nerves.

The *hypoglossal nerve* (cranial nerve XII) contains only somatic efferent fibers and innervates the muscles of the tongue. Its axons originate in the hypoglossal nucleus and exit the medulla oblongata at the anterolateral sulcus. The hypoglossal nuclei are connected by commissural fibers and dendrites of motor cells that connect the two nuclei. The hypoglossal nucleus receives impulses from the contralateral pyramidal tract.

Tracts (Figure 6.8)

The brainstem is the "superhighway" among the cerebrum, cerebellum, and spinal cord. Motor impulses travel from the cerebral cortex to the extremities, while sensory impulses travel in the opposite direction. Motor and sensory signals also are relayed to and from cranial structures through

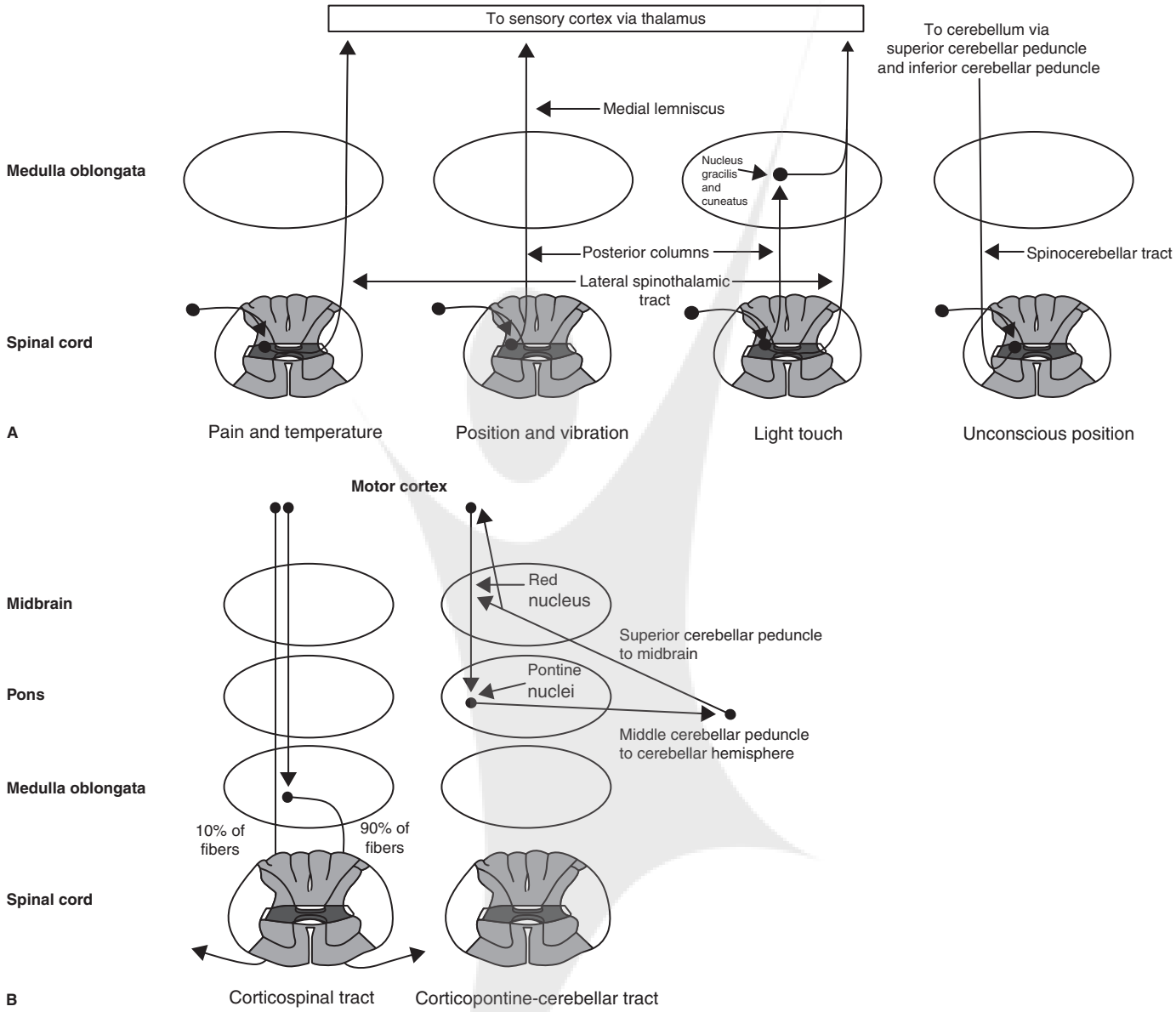

FIGURE 6.8 Schematic diagrams of the brainstem tracts. (A) Brainstem sensory tracts. (B) Brainstem motor tracts.

bulbar pathways. Signals to the cerebellum modulate movement and tone. Impulses to and from the autonomic nervous system mediate the function of visceral structures. Overall, three major types of tracts provide the connections among all of these structures: motor, sensory, and extrapyramidal.

Corticospinal (pyramidal) tract. The *corticospinal* tract is also called the *pyramidal* tract because the bundle of corticospinal axons looks like two column-like structures ("pyramids") on the ventral surface of the medulla oblongata. The corticospinal tract contains a massive number of motor axons that travel between the cerebral cortex of the brain and the spinal cord. The axons originate in the motor cortex and move closer together as they travel caudally through the cerebral white matter and form part of the posterior limb of the internal capsule. The fibers continue into the brainstem, and remain uncrossed until they reach the spinomedullary junction.

At this point, approximately 90% of the corticospinal fibers cross over to the contralateral side in the medulla oblongata (pyramidal decussation), forming the *lateral corticospinal tract* of the spinal cord. The remaining 10% of fibers remain ipsilateral, forming the *anterior corticospinal tract*. These fibers cross at the level where they exit the spinal cord, thereby combining with the lateral corticospinal tract axons at the ventral horn of a given spinal cord level to synapse with the second-order neuron. It is not difficult to understand why one side of the brain controls the opposite side of the body.

The *corticobulbar tract* is considered to be a pyramidal tract. The corticobulbar tract carries signals that control motor neurons located in the cranial nerve brain nuclei. The neurons in the motor cortex send axons contralateral to the cranial nuclei of the midbrain (cortico-mesencephalic tract), pons (cortico-pontine tract), and medulla oblongata (cortico-bulbar tract), and decussate when they reach each cranial nucleus.

Spinothalamic tract. The *spinothalamic tract* is a sensory pathway originating in the spinal cord. It consists of two parts: the *lateral spinothalamic tract*, which transmits information about pain and temperature; and the *anterior spinothalamic tract*, which transmits information about pressure and crude touch. The pathway decussates through the anterior white commissure one to two spinal nerve segments above the point of entry, and travels up the spinal cord into the rostral ventromedial medulla. The neurons ultimately synapse with third-order neurons in the medial dorsal, ventral posterior lateral, and ventral medial posterior nuclei of the thalamus. The cell bodies of neurons that comprise the spinothalamic tract originate primarily in the dorsal horn of the spinal cord. The axons of cells that mediate pain and temperature decussate through the anterior white commissure just above their level of entrance to the spinal cord and travel rostrally in the contralateral spinothalamic tract. The axons of cells that mediate proprioception and vibration travel in the ipsilateral dorsal columns to the nucleus gracilis and nucleus cuneatus within the medulla oblongata, at which time they decussate to the contralateral medial lemniscus. After they enter the brainstem, the sensory axons are positioned more dorsally, and ultimately synapse with third-order neurons in the medial dorsal, ventral posterior lateral, and ventral medial posterior nuclei of the thalamus.

Cerebellar tracts. (See also "Internal Structures of the Cerebellum" subsection in the "Structures of the Cerebellum" section later in this chapter). The cerebellum is connected to the brainstem through three pathways known as *cerebellar peduncles*. The *superior cerebellar peduncle* connects the cerebellum to the pons and midbrain, and contains the *dentorubrothalamic* and *ventral spinocerebellar* tracts. The *middle cerebellar peduncle* contains contralateral pontocerebellar fibers. The *inferior cerebellar peduncle* connects the medulla oblongata to the cerebellum, and contains the ipsilateral *dorsal spinocerebellar* tract.

The cerebellum receives significant input from and gives feedback to the cerebral hemispheres through the *corticopontocerebellar* and *cerebellothalamocortical* tracts. The corticopontocerebellar tracts arise from all lobes of the cerebral hemispheres, most notably the prefrontal area, sensorimotor cortex, and occipital lobes. First-order neurons travel caudally to the ipsilateral pons and synapse with second-order neurons that cross to the contralateral cerebellar hemisphere via the middle cerebellar peduncle. The *cerebellothalamocortical* tract originates largely from the contralateral dentate nucleus and nucleus interpositus of the cerebellum. The fibers travel through the superior cerebellar peduncle into the contralateral ventral lateral nucleus of the thalamus. They synapse with fibers that ultimately terminate in the contralateral premotor and primary motor cortices (although some fibers may terminate ipsilaterally as well).

Vasculature of the Brainstem (Figure 6.9)

Vertebral Artery

The main blood supply of the brainstem comes from the vertebral arteries, the first branch of each subclavian artery. The vertebral artery ascends through the foramina in the transverse processes of the upper six cervical vertebrae, winds behind the superior articular process of the atlas, enters the skull through the foramen magnum, and unites at the inferior aspect of the pons with the opposite vertebral artery to form the basilar artery. Dissection of the vertebral artery may occur when sudden torque forces are applied to the vertebrae.

The branches of the vertebral artery are classified by those given off in the neck, and those given off within the cranium. Spinal branches enter the vertebral canal through the intervertebral foramina, and each divides into two branches: one supplies the spinal cord and its membranes; the other divides into an ascending and a descending branch, which forms an anastomotic chain with arteries from above and below to supply the periosteum and bodies of the vertebrae. Muscular branches supply the deep muscles of the neck along with the occipital and deep cervical arteries. The meningeal branch originates opposite the foramen magnum, and supplies the falx cerebelli. Medullary branches, known as *bulbar arteries*, are minute vessels that supply blood to the medulla oblongata.

The *posterior spinal arteries* arise at the level of the medulla oblongata, and enter the vertebral canal through the intervertebral foramina. Branches from the posterior spinal arteries anastomose around the posterior roots of the spinal nerves and communicate with vessels from the opposite side. An ascending branch near the origin of each posterior spinal artery ends at the side of the fourth ventricle.

The *anterior spinal artery* arises near the union of the vertebral arteries, descends anteriorly to the medulla oblongata, and unites with the opposite artery at the level of the foramen magnum. The single trunk descends anterior to the spinal cord, and is reinforced by many small branches which enter through intervertebral foramina throughout the vertebral canal.

The *posterior inferior cerebellar artery* (PICA) is the largest branch of the vertebral artery. In the brainstem, it supplies the medial and inferior vestibular nuclei, inferior cerebellar penduncle, nucleus ambiguus, intra-axial fibers of the glossopharyngeal and vagus nerves, and portions of the spinothalamic tract and spinal trigeminal nucleus and tract. Disruption of the PICA may cause Horner's syndrome because it also supplies a portion of the hypothalamospinal tract (descending sympathetic tract) to the ciliospinal center of Budge at T1–T2.

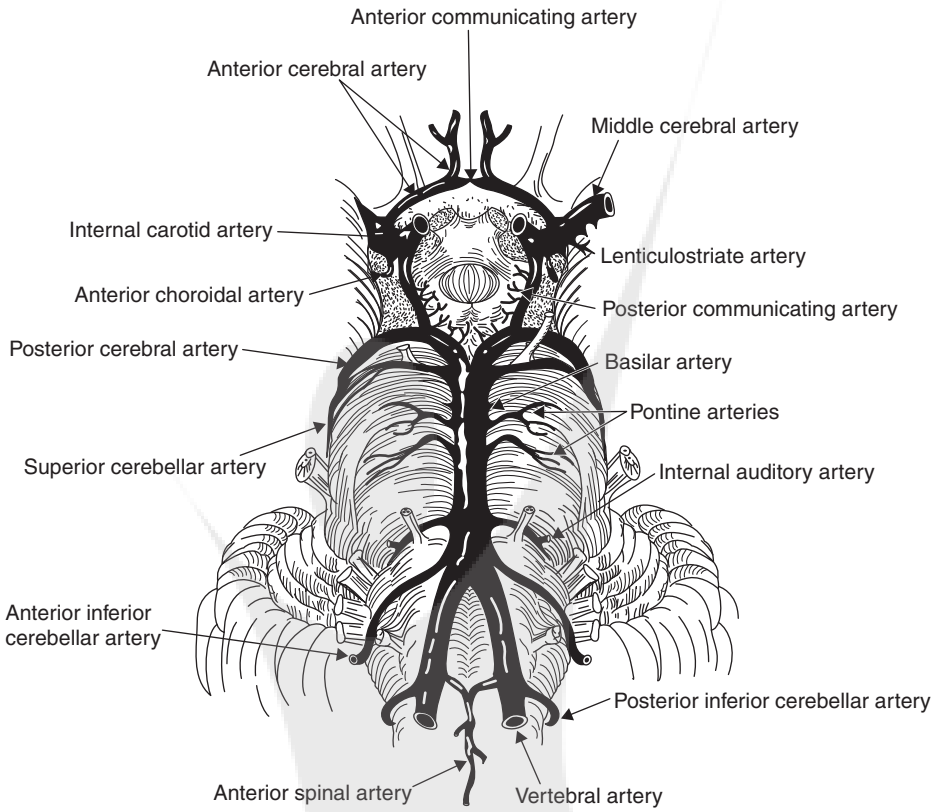

FIGURE 6.9 Vasculature of the brainstem and cerebellum.

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Basilar Artery

The basilar artery is named because of its position at the base of the skull. It ascends from its union of the vertebral arteries in the inferior aspect of the pons to the superior border of the pons. At this level, it divides into the two posterior cerebral arteries.

The *pontine branches* come off at right angles from both sides of the basilar artery and supply the pons and adjacent parts of the brain.

The *internal auditory artery* arises near the middle of the artery, and accompanies the acoustic nerve through the internal acoustic meatus, where it supplies blood to the internal ear.

The *anterior inferior cerebellar artery* (AICA) supplies the facial nucleus and intra-axial fibers, the spinal trigeminal nucleus and tract, vestibular nuclei, cochlear nuclei, intra-axial fibers of the acoustic nerve, spinothalamic tract, and inferior and middle cerebellar peduncles. In most people, the AICA gives rise to the labyrinthine artery. Disruption of the AICA may also cause Horner's syndrome because it supplies a portion of the hypothalamospinal tract.

The *superior cerebellar artery* (SCA) originates just below the division of the basilar artery, and passes laterally below cranial nerve III. It supplies the rostral and lateral pons, as well as the superior cerebellar peduncle and spinothalamic tract. Pressure from the artery on the trigeminal nerve is the usual cause of trigeminal neuralgia.

ANATOMY OF THE CEREBELLUM (FIGURE 6.10)

The cerebellum comprises the largest part of the hindbrain. It is positioned posterior to the pons and medulla oblongata. The cerebellum is characterized by a laminar appearance, with deep, curved fissures that divide it into a number of layers or leaves. Between the central portion of the cerebellum and the brainstem is the cavity of the fourth ventricle. It is not convoluted like the cerebrum, but contains many sulci that vary in depth. The proportional size of the cerebellum to the cerebrum increases from approximately 1:20 in the infant to 1:8 in the adult.

The function of the cerebellum is the coordination of movement necessary in equilibration, locomotion, and prehension. The cerebellum processes impulses that mediate muscle and tendon sense, joint sense, and equilibratory disturbances. The exact functions of its different parts are still not well understood.

Structures of the Cerebellum

Lobes of the Cerebellum

The cerebellum has three sections, a median and two lateral, that are contiguous and similar in structure. The median section is the *vermis*, named for its ringlike bands that form ridges and furrows. The lateral sections are the *hemispheres*.

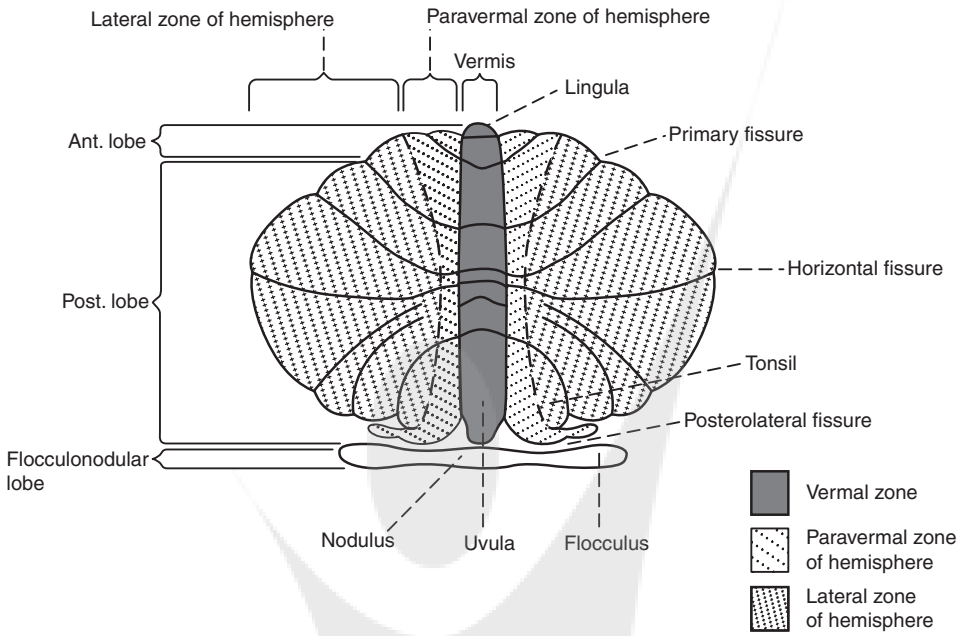

FIGURE 6.10 Schematic neuroanatomy of the cerebellum.

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The superior aspect of the vermis is subdivided from anterior to posterior into the *lingula*, the *lobulus centralis*, the *monticulus*, and the *folium vermis*. With the exception of the lingula, each division is contiguous with the corresponding portion of the hemispheres: the *alae*, the *quadrangular lobules*, and the *superior semilunar lobules*.

The inferior aspect of the cerebellum also is divided into the midline *inferior vermis*, and the *hemispheres* on either side. The inferior vermis is subdivided from anterior to posterior into the *nodule*, the *uvula*, the *pyramid*, and the *tuber vermis*. The corresponding subdivisions of the hemispheres consist of the *flocculus*, the *tonsilla cerebelli*, the *biventral lobule*, and the *inferior semilunar lobule*.

Internal Structure of the Cerebellum

The cerebellum consists of white and gray matter. In the sagittal plane, the interior consists of a gray mass, the *dentate nucleus*, which sits in the middle of a central stem of white matter. The white matter contains two sets of nerve fibers: the *projection fibers* and the *fibrae propriae*. The projection fibers consist of the three cerebellar peduncles (Figure 6.11; see also the "Cerebellar Tracts" subsection of the "Structures of the Brainstem" section).

The *dentate nucleus* lies slightly medial to the center of the stem of white matter of the hemisphere. It consists of an irregularly folded grayish-yellow lamina that contains white matter. Most of the fibers of the superior peduncle emerge from the anteromedial aspect of the dentate nucleus, where an opening, the *hilus*, is found. The superior peduncle is responsible for the planning, initiation, and control of volitional movement.

The *superior cerebellar peduncles* are largely derived from cells of the dentate nucleus of the cerebellum. They travel rostrally beneath the corpora quadrigemina, decussate ventral to the Sylvian aqueduct, and divide into ascending and descending tracts. The ascending tract terminates in the red nucleus, thalamus, and oculomotor nucleus, while the descending tract appears to terminate in the dorsal aspect of the pons.

The *middle cerebellar peduncles* are comprised entirely of cells that originate in the contralateral pontine nuclei and terminate in the cerebellar cortex. The tracts have three fasciculi. The superior fasciculus distributes nerve fibers to the inferior lobules of the cerebellar hemisphere and to posterolateral margins of the superior surface. The inferior fasciculus distributes nerve fibers to the folia close to the inferior vermis. The deep fasciculus distributes nerve fibers to the upper anterior cerebellar folia and inferior cerebellar peduncles.

The *inferior cerebellar peduncles* consist of a variety of nerve fibers: the *dorsal spinocerebellar tract* that terminates in the superior vermis; the ipsilateral and contralateral nucleus gracilis and nucleus cuneatus; the contralateral olivary nuclei; the ipsilateral and contralateral medullary reticular formation; the vestibular nucleus and tract that terminate partly in the contralateral roof nucleus; the contralateral cerebellobulbar tracts from the contralateral roof nucleus and dentate nucleus; and some nerve fibers from the ventral spinocerebellar tract that combine with dorsal spinocerebellar tract.

The *fibrae propriae* of the cerebellum are of two kinds: (a) *commissural* fibers, which connect the two halves of the

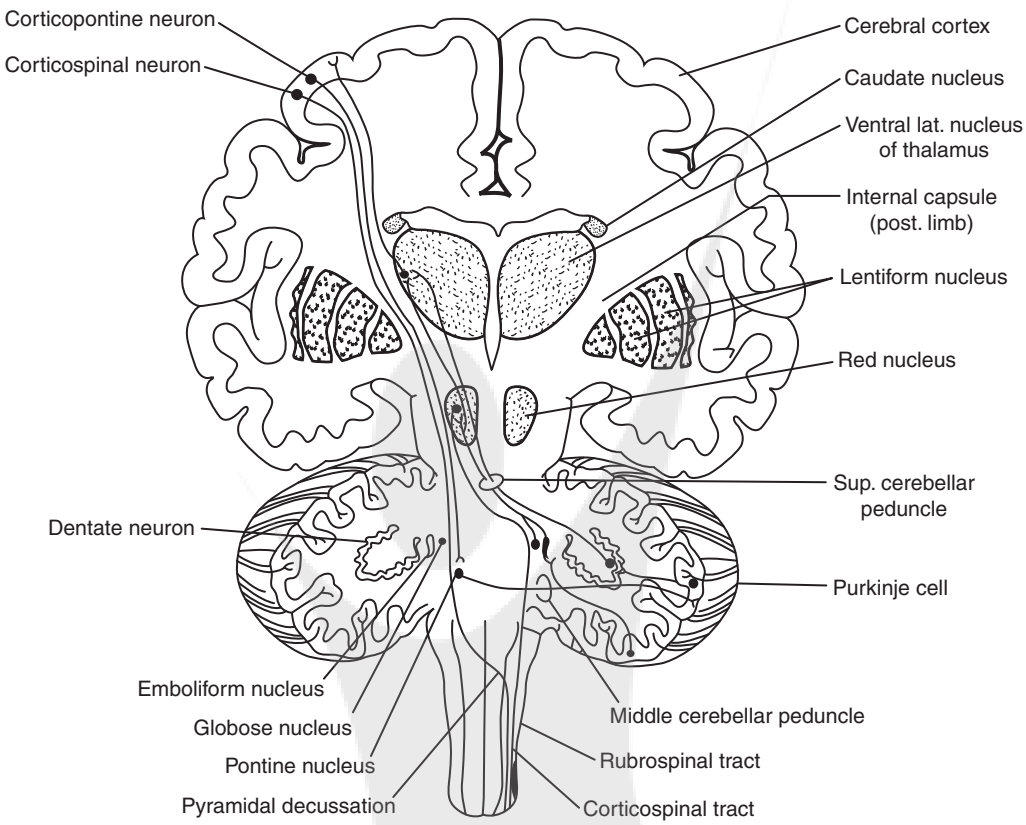

FIGURE 6.11 Connections to the cerebellum.

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cerebellum by a decussation at the anterior and posterior aspects of the vermis; and (b) *arcuate* or *association* fibers, which connect adjacent laminae.

Vasculature of the Cerebellum (see Figure 6.9)

The cerebellum receives its vascular supply from branches of the vertebral and basilar arteries. When any of the arteries is disrupted, there is potential for collateral flow from the other cerebellar arteries. In patients with acute basilar artery thrombosis, neurologic outcome improves after intra-arterial thrombolysis if the basilar artery demonstrated collateral filling and thrombosis of the basilar artery was not proximal (3). Patients with collateral filling of the basilar artery also tolerated their symptoms longer.

The PICA traverses the superior portion of the medulla oblongata over the inferior peduncle to the undersurface of the cerebellum. Here it divides into two branches: medial and lateral. The medial branch continues posteriorly to the notch between the two hemispheres of the cerebellum. The lateral branch supplies the undersurface of the cerebellum to its lateral border, where it anastomoses with the anterior inferior cerebellar and superior cerebellar arteries.

The AICA travels posteriorly to the anterior portion of the undersurface of the cerebellum. It anastomoses with the PICA.

The SCA travels laterally around the cerebral peduncle to the upper surface of the cerebellum and dentate nucleus. It then divides into branches that supply the pia mater and anastomose with the anterior and posterior inferior cerebellar arteries.

MIDBRAIN SYNDROMES (TABLE 6.3)

The clinical anatomy of the midbrain is not as complicated as that of the pons or medulla oblongata. However, symptoms of midbrain lesions may be quite varied due to the multiplicity of functions for which the midbrain is responsible (Figure 6.12). In addition to facial and limb sensory-motor deficits, cranial nerve III and IV lesions may cause oculomotor deficits and Horner's syndrome. Infarcts of the tegmentum may result in upgaze paralysis. Classic lacunar infarcts, such as pure motor stroke and ataxic hemiparesis, can be related to infarcts of the dorsolateral midbrain. Subthalamic infarcts may be associated with unilateral or bilateral ballismus or asterixis. Involvement of the red nucleus causes the typical resting tremor that worsens with movement. Coma or changes in consciousness may occur with bilateral midbrain infarcts, but neuropsychological changes should be suspected due to involvement of the posterior cerebral arteries downstream of the midbrain lesions (4).

TABLE 6.3 Midbrain Syndromes

SYNDROME	STRUCTURE	SYMPTOM(S)
Weber	III	Ipsilateral ptosis, external strabismus, dilated pupil
	Corticospinal/corticobulbar tracts	Contralateral paresis of lower face, tongue, arm, leg
Benedikt	III	Ipsilateral ptosis, external strabismus, dilated pupil
	Red nucleus	Contralateral coordination deficit (ataxia, dysmetria, dysdiadochokinesia, rubral tremor [coarse resting tremor that increases with movement]), psuedo-Parkinson tremor
	Corticospinal tract Medial lemniscus (sometimes) Spinothalamic tract (sometimes)	Contralateral paresis of lower face, tongue, arm, leg Contralateral touch, proprioception (contralateral pain, temperature)
Claude	III	Ipsilateral ptosis, external strabismus, dilated pupil
	Red nucleus	Contralateral coordination deficit (ataxia, dysmetria, dysdiadochokinesia, rubral tremor [coarse resting tremor that increases with movement]), psuedo-Parkinson tremor
Parinaud (dorsal rostral midbrain)	Pretectal nuclei (high midbrain tegmentum ventral to superior colliculus)	Bilateral upward gaze paralysis
	Corticotectal fibers (supranuclear fibers to III)	Convergence paralysis, pupillary areflexia
Koerber–Salus–Elschnig (Sylvian aqueduct)	III	Ipsilateral ptosis, external strabismus, dilated pupil Altered mental status Abnormal respiration
Chiray–Foix–Nicolesco (midbrain tegmentum)	Upper red nucleus	Contralateral coordination deficit (ataxia, dysmetria, dysdiadochokinesia, rubral tremor [coarse resting tremor that increases with movement]), psuedo-Parkinson tremor
	Corticospinal/corticobulbar tracts	Contralateral paresis of lower face, tongue, arm, leg
	Spinothalamic tract	Contralateral hemisensory deficit
Nothnagel (dorsal midbrain)	III	Ipsilateral ptosis, external strabismus, dilated pupil
	Brachium conjunctivum	Vertical gaze paralysis
	Medial longitudinal fasciculus (MLF)	Ipsilateral adduction paresis on attempted horizontal gaze, contralateral monocular nystagmus of abducting eye on attempted horizontal gaze
Akinetic mutism (upper segment of basilar artery)	Reticular activating system	Absolute mutism tetraplegia with bulbar paralysis except for eyes

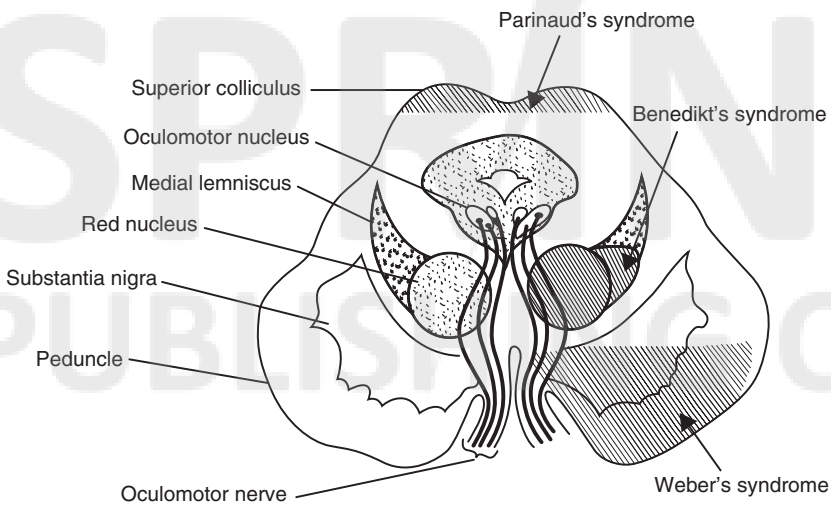

FIGURE 6.12 Midbrain syndromes.

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Weber Syndrome

Marotte (1853) (5) first described a patient who presented with a cranial nerve III palsy and contralateral hemiplegia. However, Weber (1863) (6) provided the first detailed clinical description of this syndrome. He also attempted to relate the clinical signs and symptoms of the syndrome with vivisection of the human brain in order to answer the question of localization of the lesion. Notably, Weber described clonus of the ankle and flexor spasms of the leg, but did not recognize their significance in cerebral infarction. In this article, he also accurately described the clinical findings of the Babinski sign nearly 30 years before Babinski reported them.

Benedikt Syndrome

The lesion of Benedikt syndrome causes ipsilateral oculomotor paralysis with contralateral tremor and hemiparesis. Patients with this syndrome often have ipsilateral sensory loss. Because the major outflow of the cerebellum traverses the superior cerebellar peduncle (brachium conjunctivum) and red nucleus on its way to the ventral lateral nucleus of the thalamus, patients have a "rubral" tremor, present at rest but amplified with movement. Benedikt (1889) (7) first described the syndrome in a cursory manner in 1874, but spoke of it in more detail during a lecture in Paris. He developed the concept of a primary motor system, and coined the term "parallel motor system" for the afferent and efferent pathways of the cerebellum.

Parinaud Syndrome

The lesion of Parinaud syndrome causes paralysis of conjugate upward gaze and convergence. It is often accompanied by paralysis of the conjugate downward gaze and pupillary areflexia. Parinaud (1883) (8) concluded that the lesion should be located in the tegmentum of the midbrain. It was many years after his death in 1905 that the actual structure—the superior colliculi—and its connections were identified.

Koerber–Salus–Elschnig Syndrome

This lesion of the periaqueductal gray of the midbrain causes rhythmic retraction of the eyes into the orbit, independent of eye movement. Voluntary eye movements usually amplify the abnormality. Salus (1910) (9) found a cysticercus cyst that localized the lesion very specifically to this region. While Koerber (1903) (10) and Elschnig (1913) (11) share the name of the syndrome, Koerber did not identify any brain tissue for neuroanatomic correlation, but termed the syndrome "nystagmus retractorius." Elschnig, who was Salus's teacher, encouraged him to write the case study and found another case of the syndrome the following year.

PONTINE SYNDROMES (TABLES 6.4 AND 6.5)

The pons is supplied by three groups of arteries (12). Branches from the basilar artery form the anteromedial and anterolateral groups. Branches from the AICA form the lateral group. Branches from the SCA form the posterior group.

Infarcts of the pons may result in a range of symptoms (Figure 6.13). Cranial nerve VI and MLF lesions may cause oculomotor deficits. Infarcts of the PPRF may result in conjugate horizontal gaze paralysis. Classic lacunar infarcts, such as pure motor stroke and ataxic hemiparesis, can be related to infarcts of the basis pontis. Involuntary limb spasm also has been described (13).

Pontine syndromes are classified into two types. Table 6.4 uses an anatomic scheme, categorizing lesions as superior, midpontine, and inferior; and as medial or lateral. Medial pontine lesions usually affect the corticospinal tract and medial lemniscus, resulting in contralateral hemiparesis and reduced proprioception and vibration sensation. Lateral pontine lesions usually affect the trigeminal sensory nucleus or tract, autonomic fibers, and spinothalamic tract, resulting in ipsilateral loss of facial sensation, ipsilateral Horner's syndrome, and contralateral loss of pain and temperature. Table 6.5 lists pontine syndromes by eponym.

Millard–Gubler Syndrome

Millard–Gubler syndrome affects cranial nerve VII and the corticospinal tract, resulting in ipsilateral facial weakness and contralateral hemiparesis. Gubler (1856) (14) described the lesion as invading the medial pons, but missing cranial nerve VI because of its slightly anterior course within the pons. He also demonstrated the clinical evidence of the decussation of the facial nerve, thereby differentiating between the "central" lower facial droop and the "peripheral" total facial weakness. In contrast, Millard (1856) (15) made no attempt to localize the anatomy of the lesion. His name is attached to Gubler's probably because the manuscripts were published one after the other.

Foville Syndrome

Foville syndrome consists of conjugate horizontal gaze paralysis in the ipsilateral direction. Cranial nerve VII paralysis results in ipsilateral facial weakness, but hemiparesis is contralateral. Foville (1858) (16) was the first to document the presence of a lateral gaze center in the pons. Although the hemiparesis usually resolves, the gaze paralysis and facial weakness persist indefinitely.

Raymond Syndrome

Raymond syndrome consists of ipsilateral cranial nerve VI paralysis with contralateral hemiparesis. Raymond (1896) (17) described a patient with right hemiplegia, but with aphasia and difficulty recognizing her husband's face

TABLE 6.4 Pontine Syndromes by Location

SYNDROME	STRUCTURE	SYMPTOM(S)
Medial inferior	VI	Ipsilateral horizontal diplopia with nystagmus
	Corticospinal tract	Contralateral face/arm/leg hemiplegia
	Medial lemniscus	Contralateral touch/proprioception hemideficit
	Paramedian pontine reticular formation (PPRF)	Ipsilateral conjugate gaze paralysis
Lateral inferior	Vestibular nuclei (VIII)	Ipsilateral horizontal/vertical nystagmus, vertigo, nausea, vomiting, oscillopsia
	VII	Ipsilateral peripheral facial palsy
	PPRF	Ipsilateral conjugate gaze paralysis
	VIII	Tinnitus, deafness
	Middle cerebellar peduncle	Ataxia
	V sensory	Ipsilateral impaired facial sensation
	Spinothalamic tract	Contralateral arm/leg pain/temperature deficit
Medial midpontine	Middle cerebellar peduncle	Ipsilateral ataxia arm/leg and gait
	Corticospinal/corticobulbar tracts	Contralateral face/arm/leg hemiplegia, eye deviation
	Variable medial meniscus	Contralateral touch/proprioception deficit
Lateral midpontine	Middle cerebral peduncle	Ipsilateral limb ataxia
	V motor	Ipsilateral mastication muscle paralysis
	V sensory	Ipsilateral hemisensory deficit (including corneal reflex)
Medial superior	Superior/middle cerebellar peduncle	Ipsilateral cerebellar ataxia
	MLF	Internuclear ophthalmoplegia
	Central tegmental bundle	Palate/pharynx/vocal cord/ventilatory apparatus/face/oculomotor apparatus myoclonus
	Corticospinal/corticobulbar tracts	Contralateral face/arm/leg hemiplegia
	Rare medial lemniscus	Contralateral touch/proprioception face/arm/leg hemideficit
Lateral superior	Superior/middle cerebellar peduncle	Ipsilateral arm/leg/gait ataxia
	Vestibular nuclei (VIII)	Dizziness, nausea, vomiting, horizontal nystagmus
	Spinothalamic tract	Contralateral face/arm/leg pain/temperature loss
	Lateral medial lemniscus	Touch/proprioception leg > arm hemideficit
	Unknown	Conjugate gaze paresis to side of lesion, loss of optokinetic nystagmus, skew deviation, Horner syndrome

(prosopagnosia). The cranial nerve VI paralysis did not occur for another three months. Raymond described this condition as a "special hemiplegia" that was treated with "mercurial packs and high doses of potassium iodide" for "intensive antisyphilitic treatment." With this treatment, the visual disturbances and cognitive impairments resolved, but the hemiplegia resolved only partially.

Locked-In Syndrome

Locked-in syndrome occurs when an occlusion of the basilar artery causes an infarction of the basis pontis bilaterally. The corticospinal and corticobulbar tracts are interrupted, resulting in tetraplegia and paralysis of all cranial nerve muscles except for those controlling eye movements. It is not unusual for the PPRF to be affected, such that horizontal eye movements are affected and only vertical eye movements are preserved. Because the reticular formation above the caudal pons is spared, patients remain awake and aware. Their only means of communication is systematic eye movements that can be utilized manually to respond to questions, or with augmentative communication devices.

MEDULLARY SYNDROMES (TABLE 6.6)

The medulla oblongata receives its blood supply from a number of penetrating arteries located in the distal vertebral artery. There may also be variable blood supplies from small branches of the PICA, AICA, or the basilar artery. Typically, a lateral medullary infarct occurs because of occlusion of one or more of these penetrating arteries, or more often by occlusion of the vertebral artery (18). The dorsal medulla oblongata receives its blood supply exclusively from the PICA, and is usually accompanied by cerebellar infarction (19). The medial medulla oblongata receives its blood supply caudally from penetrating arteries of the anterior spinal artery, and rostrally from branches of the vertebral artery (20). Medial infarcts usually affect the corticospinal tracts,

TABLE 6.5 Pontine Syndromes by Eponym

SYNDROME	STRUCTURE	SYMPTOM(S)
Millard–Gubler	VII tract	Ipsilateral facial palsy
	Corticospinal tract	Contralateral arm/leg hemiparesis
Foville	PPRF	Ipsilateral horizontal gaze palsy
	VII	Ipsilateral facial palsy
	Corticospinal tract	Contralateral arm/leg hemiparesis
Raymond	VI tract	Ipsilateral lateral rectus paresis
	Corticospinal tract	Contralateral arm/leg hemiparesis
Pontocerebellar Angle	VIII	Early ipsilateral tinnitus, deafness, head tilt/rotation; late hyperacusis
	Inferior/middle cerebellar peduncles	Ipsilatreal intention tremor, dysmetria, ataxic gait, adiadochokinesis
	V spinal tract	Ipsilateral facial pain/temperature hemisensory deficit
	VII	Ipsilateral facial palsy, taste loss anterior 2/3 tongue
	Spinothalamic tract	Contralateral arm/leg pain/temperature hemisensory deficit
	Occasional XI, XII	Ipsilateral trapezius, tongue
Brissaud	VII	Ipsilateral facial spasm
	Corticospinal tract	Contralateral arm/leg hemiparesis
One-and-a-Half	PPRF	Ipsilateral horizontal gaze palsy
	MLF	Contralateral internuclear ophthalmoplegia
Locked-In	Bilateral corticospinal/corticobulbar tract	Tetraplegia with facial palsy (except blinking eyes)
	Bilateral paramedian pontine reticular formation	Bilateral horizontal gaze palsy

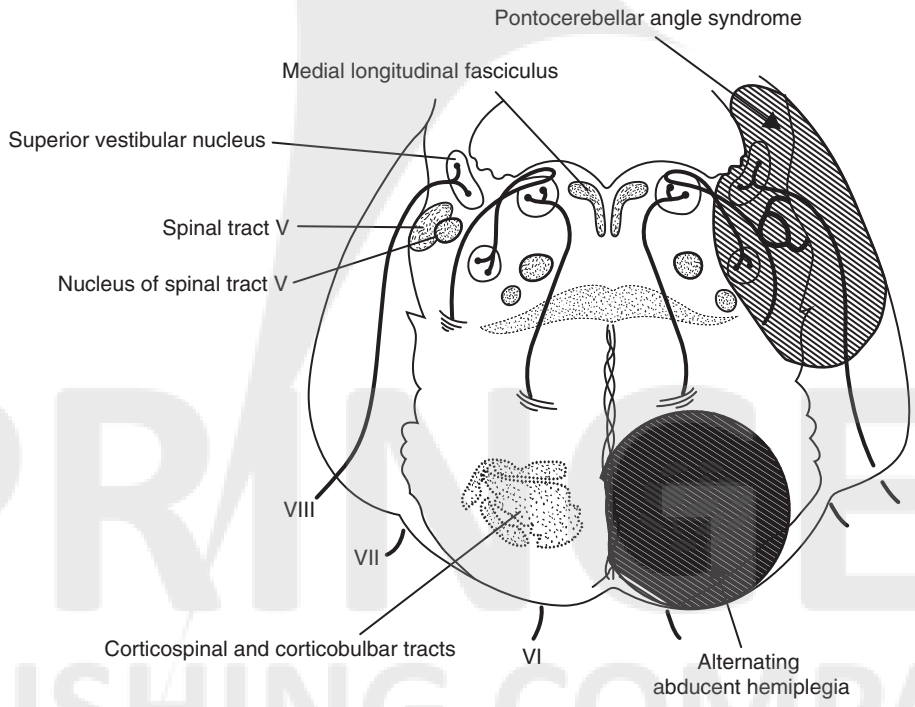

FIGURE 6.13 Pontine syndromes.

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TABLE 6.6 Medullary Syndromes

SYNDROME	STRUCTURE	SYMPTOM(S)
Paramedian Bulbar ("Hypoglossal Hemiplegia Alternans")	XII	Ipsilateral paralysis of tongue, contralateral hemiplegia (arm > leg)
	Corticospinal tract	
	Medial lemniscus	Contralateral touch/proprioception arm/leg hemideficit
Lateral Bulbar (Wallenberg)	Lower vestibular nuclei	Vertigo, dizziness, nausea, vomiting
	Nucleus ambiguus (IX, X motor)	Dysphagia, hiccups, dysphonia, uvula deviates to normal side
	V spinal tract	Ipsilateral face pain/temperature hemideficit
	Spinothalamic tract	Contralateral arm/leg pain/temperature hemideficit
	Spinocerebellar/olivocerebellar tracts	Ipsilateral hypotonia, ataxia of limbs (UE > LE)
	Pupillodilator (sympathetic) fibers	Ipsilateral Horner's sign (ptosis, miosis, anhydrosis)
Avellis	Nucleus ambiguus (X, bulbar XI)	Ipsilateral soft palate, pharynx, larynx paralysis; dysarthria; dysphagia
	Solitary tract (sensory X)	Ipsilateral pharynx, larynx hemisensory deficit
	Spinothalamic tract	Contralateral UE/LE pain/temperature hemisensory deficit
Schmidt	X	Ipsilateral soft palate, pharynx, larynx paralysis; dysarthria; dysphagia
	Spinal XI	Ipsilateral sternocleidomastoid paralysis, sometimes trapezius paralysis
Jackson	X	Ipsilateral soft palate, pharynx, larynx paralysis
	XI	Ipsilateral sternocleidomastoid, trapezius paralysis
	XII	Ipsilateral tongue paralysis, atrophy
Tapia	X	Ipsilateral soft palate, pharynx, larynx paralysis
	XII	Ipsilateral tongue paralysis, atrophy
Bonnier	VIII	Paroxysmal vertigo
	IX	Loss of taste on posterior third of tongue
	X	Ipsilateral soft palate, pharynx, larynx paralysis
	Corticospinal tract	Contralateral hemiplegia (arm > leg)
	Other	Somnolence at times Apprehension, tachycardia
Babinski-Nageotte bulbar (similar to Wallenberg syndrome with addition of hemiplegia)	IX	Loss of taste on posterior third of tongue
	X/bulbar XI	Ipsilateral soft palate, pharynx, larynx paralysis
	XII	Ipsilateral tongue paralysis, atrophy
	V spinal tract	Ipsilateral face pain/temperature hemideficit
	Spinocerebellar tract	Ipsilateral hypotonia, ataxia of limbs (UE > LE)
	Corticospinal tract	contralateral hemiplegia (arm > leg)
	Spinothalamic tract	Contralateral arm/leg pain/temperature hemideficit
	Pupillodilator (sympathetic) fibers	Ipsilateral Horner's sign (ptosis, miosis, anhydrosis)

causing contralateral hemiparesis. Lateral infarcts usually involve the spinothalamic tracts, resulting in contralateral loss of pain and temperature sensation. Other infarcts may occur as well, but are less common (Figure 6.14).

Wallenberg (Lateral Medullary) Syndrome

Wallenberg syndrome is probably one of the best-known brainstem syndromes, comprising approximately 2% of all admissions for acute stroke (21). Wallenberg (1895) (22) described this "acute disease of the medulla" with the onset of intense vertigo associated with vomiting. He also listed the presence of dysphonia and dyphagia; ipsilateral facial hemisensory deficit, limb ataxia, and palate and vocal cord paralysis; and contralateral arm and leg hemisensory deficit. Although an ipsilateral Horner's syndrome is present, Wallenberg did not document its presence because his patient had a congenital disease of the eyes. Because of its lateral location, the syndrome does not cause paralysis, as the corticospinal tract is a medial structure.

Jackson Syndrome

Jackson syndrome consists of cranial nerve X, spinal XI, and XII paralysis resulting in ipsilateral weakness of the trapezius, sternocleidomastoid, soft palate, and tongue, as well as dysphagia and dysphonia. Jackson (1865) (23) described this syndrome in a patient with tuberculosis throughout

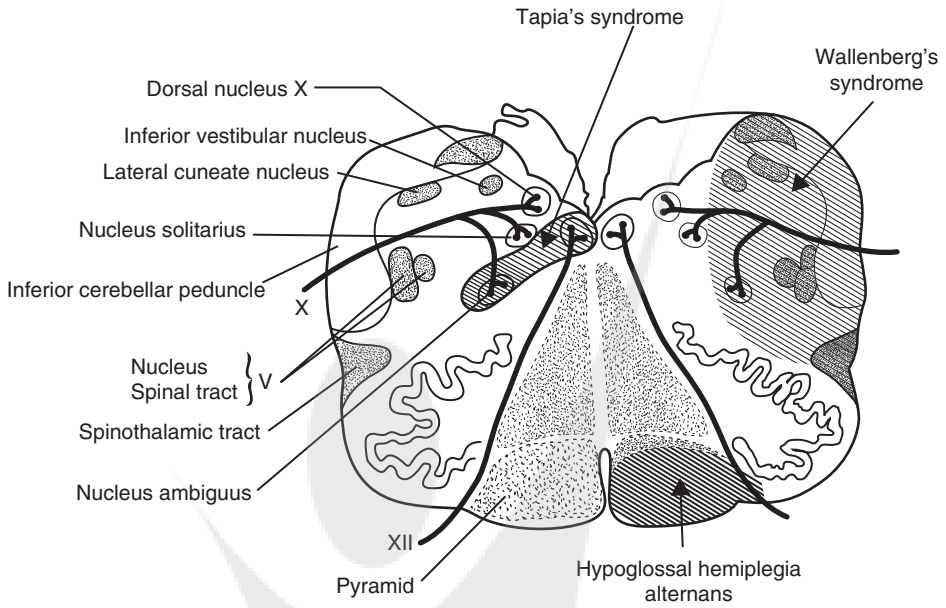

FIGURE 6.14 Medullary syndromes.

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the brainstem. The correlative neuroanatomy is not well described, but the eponym remains attributed to him.

CEREBELLAR SYNDROMES (TABLE 6.7)

Cerebellar infarcts typically present with the cardinal signs of vertigo, headache, emesis, and gait ataxia (24). However, it was not until the advent of MRI that clinicians could accurately diagnose cerebellar infarcts and correlate them with vascular territories. There is now a better understanding of how to characterize cerebellar infarcts based upon the vascular territories they supply. Table 6.7 reflects one of these classification schema (25).

RESEARCH FRONTIERS

As the preceding descriptions of the syndromes demonstrate, the understanding of brainstem and cerebellar syndromes largely came from the vivisection of autopsy specimens. With the advent of MRI, the neuroanatomy of these lesions could be defined better and earlier (26). Techniques such as functional MRI have provided vital information for better understanding the functional anatomy of the auditory system (27), visual system, (28), and the cerebellum (29). Diffusion-weighted images (DWI) with direction-selective gradients have been used to identify both nuclei and white-matter tracts within the brainstem (30). An evaluation

TABLE 6.7 Cerebellar Syndromes

SYNDROME	STRUCTURE	SYMPTOM(S)
Rostral (superior cerebellar)	Subthalamic area, thalamus, Occipitotemporal lobes	Coma ± tetraplegia Ipsilateral dysmetria, Horner's syndrome; contralateral pain/temperature hemisensory deficit, IV palsy
	Laterotegmental area of upper pons	Dysarthria; headache; dizziness; emesis; delayed coma (pseudotumor form)
Medial (anterior inferior cerebellar)	Lateral area of lower pons	Ipsilateral V, VII, VIII, Horner's syndrome, dysmetria Contralateral pain/temperature Hemisensory deficit
Caudal (posterior inferior cerebellar)	Dorsolateromedullary area	Vertigo, headache, emesis, ataxia, delayed coma (pseudotumor form)
Caudal and medial	Lateral area lower pons and/or lateromedullary area	Vertigo, headache, emesis, ataxia, delayed coma (pseudotumor form)
Rostrocaudal	Brainstem, thalamus, occipitotemporal lobe	Coma ± tetraplegia

of 22 regions of the brainstem has led to the development of a lesion score that potentially may be an independent marker of outcome in basilar artery occlusion (31). Newer high-resolution MRI technology may lead to spatially unbiased localization of lesions, that is, the location of structures on an MRI image equals the expected anatomic location of that structure (32). Three-dimensional MRI velocity mapping may identify substantial diastolic retrograde flow originating from complex plaques in the descending aorta that results in infarcts of the brainstem and cerebellum (33).

Diffusion tensor imaging (DTI) currently is used noninvasively to study the three-dimensional structure of white-matter tracts of the brainstem (34) and cerebellum (35). Specific imaging studies include those of the medial lemniscus (36). Wallerian degeneration in the corticospinal tract imaged by DTI correlates with motor deficit at 7 days (37), 30 days (38), and more than 6 months (39) after a middle cerebral artery infarct; thus, it could potentially be used as a surrogate marker in clinical trials.

In better understanding the neuroanatomical correlates of behavior and activity, clinicians can predict more accurately the types of deficits that occur with brainstem and cerebellar strokes. Using this information, more research is needed to explore physical and pharmacological interventions that can improve recovery from stroke. Ultimately, clinicians can gain a better understanding of functional outcomes when specific infarcts or hemorrhages occur in these regions.

CONCLUSION

Recognition of signs and symptoms of infratentorial stroke syndromes is essential in the diagnosis and treatment of stroke. Infratentorial strokes affect a wide variety of body systems, and knowledge of the combinations of neurological signs is vital if one is to suspect the presence of a brainstem or cerebellar infarct or hemorrhage. Although imaging modalities have vastly improved to visualize previously unvisualizable lesions, the diagnosis of a stroke still begins with a detailed physical examination and knowledge of neuroanatomic correlates. However, more research is needed to better understand the interactions between nuclei and tracts that form the foundation of activity and behavior. With a more detailed knowledge base, clinicians may be able to more effectively diagnose and treat infratentorial strokes with appropriate physical and pharmacological modalities. With more effective and varied treatments, clinicians may be able to improve functional outcomes and quality of life in the future.

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II

NEUROPHYSIOLOGY OF STROKE RECOVERY

7

The Mechanisms and Neurophysiology of Recovery From Stroke

Randolph J. Nudo and Scott Barbay

More than three decades have passed since the groundbreaking studies of Michael Merzenich, Jon Kaas, and others, who demonstrated that the neural representations of the hand in the somatosensory cortex are altered by peripheral injury. A once-tenuous notion that functions of the cerebral cortex are alterable in adult mammals has developed into a neuroscientific tenet. The phenomenology of cortical plasticity and the study of its underlying mechanisms have rapidly migrated from the laboratory to the clinic, as new interventional strategies are now conceptualized in relation to their ability to encourage adaptive plasticity.

After injury to the cerebral cortex, as often occurs in stroke, a large portion of the sensory–motor apparatus in the frontal and parietal cortex is often damaged, resulting in deficits in motor function in the contralateral musculature. However, substantial spontaneous recovery occurs in the weeks to months following injury. Understanding how the remaining sensory–motor apparatus can support the recovery of such functions has been a primary goal of much of the recent research in this area. Thus, this chapter will review the basic organization of the sensorimotor cortex, the current theoretical models for functional recovery, and our understanding of the ability of spared tissue to be functionally and structurally altered. This review relies most heavily on recent neurophysiological and neuroanatomical data from nonhuman primate and rodent models and neuroimaging studies in humans.

ORGANIZATION OF MOTOR CORTEX IN PRIMATES

Since middle cerebral artery strokes often affect the motor cortex, we provide a brief review of the structure and function of cortical areas involved in the motor control of skeletal musculature. The motor cortex, defined as the part of the cerebral cortex that requires the least amount of electrical stimulation to evoke movement, is subdivided into several distinct areas (Figure 7.1).

Though each area has been reported to play a somewhat different role in the control of movement, there is considerable overlap in function (1,2). Further, it is now clear that the motor cortex does not execute motor tasks in isolation. A broad network minimally involving the primary and secondary motor areas, the dorsolateral prefrontal cortex, the parietal cortex, the striatum, and the cerebellum is involved in motor skill acquisition, planning, and execution. Thus, motor behavior is controlled by a distributed network, and it may be overly simplistic to think in terms of compartmentalized units that have mutually exclusive functions (3).

Primary Motor Cortex

The primary motor cortex (M1) is thought to mediate skilled voluntary movements, especially of the distal musculature, since M1 lesions result in disruption of skilled limb use in the contralateral musculature (4–7). The global topography of motor representations in M1 follows an orderly progression from hindlimb medially to forelimb and face laterally (Figure 7.1). M1 is subdivided into a caudal component (M1c), receiving predominantly cutaneous somatosensory information, and a rostral component (M1r), receiving predominantly proprioceptive input (8,9). Consistent with this parcellation, in nonhuman primates, differential motor deficits result from small lesions in either M1r or M1c (10). Cortical areas that are reciprocally connected with M1 include primary somatosensory areas 3a, 1, 2, the second somatosensory area (S2), the ventral premotor cortex (PMv), the dorsal premotor cortex (PMd), the supplementary motor area (SMA), cingulate motor areas (CMA), and, to a lesser extent, primary somatosensory area 3b, posterior parietal cortex (PP), and the parietal ventral area PV (11–14).

The corticospinal (CS) neurons provide the cerebral cortex with direct access to the spinal cord motoneurons and have been the subject of intense investigation since the mid-1800s. CS neurons can be found throughout much of the frontal and parietal cortex, although the concentration is greatest in M1 (15). A subset of CS neurons, found predominantly in M1, project monosynaptically to motoneurons of the spinal cord and are thus called corticomotoneuronal (CM) cells. Spike-triggered averaging techniques in awake nonhuman primates reveal that individual CM cells can facilitate up to four or five motoneuron pools (16). This provides further evidence for the divergence in the anatomical projections from cortex to spinal cord and challenges the notion that functional organization in the motor cortex is

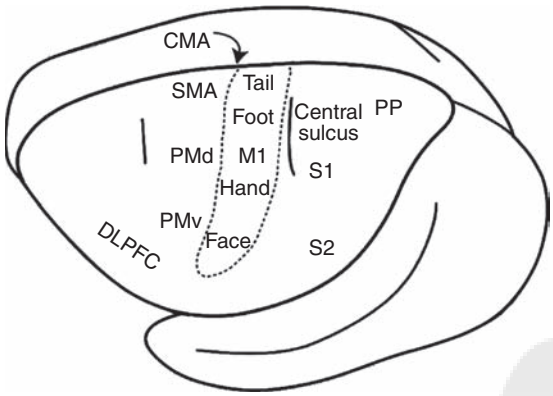

FIGURE 7.1 Motor areas in the frontal cortex of a nonhuman primate (squirrel monkey). At least five separate motor areas can be identified. These include M1, SMA, PMd, PMv, and CMA. This basic arrangement is similar in all primates, though these areas have been divided further in some species. Also, in some primates, the sulci are much deeper (e.g., humans, macaques), and thus, these motor areas are not as accessible. Each motor area contains a separate representation of the forelimb, and some areas contain a complete representation of the skeletal motor apparatus. It has been suggested that each of these motor areas plays a somewhat different role in motor control; though considerable overlap exists. Thus, it is more accurate to consider the cortical motor apparatus as part of a distributed network for control of movement.

Abbreviations: CMA, cingulate motor areas; DLPFC, dorsolateral prefrontal cortex; M1, primary motor cortex; PMd, dorsal premotor cortex; PMv, ventral premotor cortex; PP, posterior parietal cortex; S1, primary somatosensory cortex; S2, second somatosensory area; SMA, supplementary motor area.

based on muscle-specific domains. Direct evidence refuting muscle-specific domains in the motor cortex has been provided from neuronanatomical studies. Rabies viruses can be used as transneuronal retrograde markers. Injecting the virus into a single muscle results in retrograde transport of the virus to the cell bodies in the spinal cord motoneuron pool. There, the virus replicates and is picked up by terminal arbors that innervate the motoneurons. In turn, the virus is retrogradely transported back to second-order neurons in the cerebral cortex, red nucleus, and other locations. At the appropriate survival time, post-mortem analysis reveals the location of CS neurons that contain the virus. Thus, these neurons represent CM cells that project to the specific motoneuron pool of interest. Combining results of injections into various forelimb muscles of different animals reveals that the cortical neurons that influence the various forelimb muscles are completely interspersed and overlapping (17). Thus, the motor cortex can be viewed as containing a shared neural substrate for motor control of the hand. The highly overlapping and divergent architecture provides an ideal substrate for flexibility in outputs to the spinal cord that can be rearranged based on behavioral demands.

One of the more common methods for demonstrating the functional spatial topography of M1 is via electrical or magnetic stimulation and the observation of evoked movements or electromyographic activity. Current thresholds for evoking movement via either invasive or noninvasive stimulation methods are lowest in M1, coinciding with the location of large numbers of CM cells. Owing to these neuroanatomical and neurophysiological differences, M1 is thought to be the cortical motor area most related to movement execution. However, discrete movements of specific joints can also be evoked by stimulation of other motor areas of the frontal cortex, though at somewhat higher current levels. At least seven nonprimary motor areas involved in controlling arm movements have been identified in the frontal cortex of primates (18). Many of these premotor areas have also been identified in humans based on functional neuroimaging data, though homologies are in some instances not completely clear (14,15,19–21).

Dorsal Premotor Cortex

The premotor areas are located anterior to the M1 motor strip in Brodmann's area 6. Based on separate hand representations, different anatomical connectivity, and somewhat different functional attributes, the premotor cortex has been subdivided into a dorsal portion or PMd and a ventral portion or PMv. PMd is located immediately anterior to the M1 representation. The histologically defined boundary between M1 and PMd is not well defined. For example, using the density of large CS neurons as a guide to the identification of the M1-PMd border yields a gradient, rather than a sharp boundary, with more large CS neurons located in M1. PMd contains separate representations of the forelimb, hindlimb, and trunk, and is thought to be involved in visually guided tasks since PMd neurons are active during a preparatory motor-set (22) and in relation to visuomotor-association tasks (23). Compared with M1, the activity of PMd neurons (and PMv, SMA neurons) is less related to the kinematics of the movement but more related to aspects of the goal (24) and to movement selection (25). PMd inactivation affects the ability of macaque monkeys to select movements without affecting the spatial organization of the movements selected (26). Neuroimaging studies in humans confirm the role of PMd in visually guided motor tasks (27). PMd has topographically organized, intracortical connections with other frontal motor regions (11,28,29) and with the posterior parietal cortex (PP).

Ventral Premotor Cortex

In nonhuman primates, the PMv is located anterior and lateral to the M1 hand representation. In primate species with lissencephalic brains (e.g., prosimian primates, squirrel monkeys, marmoset monkeys) PMv is exposed on a flat sector of cortex, whereas in other primate species (e.g., macaque monkeys, Cebus monkeys) PMv is largely buried in the arcuate sulcus. In general, PMv is thought to be involved in visual–motor and somatosensory–motor integration for motor control of the upper extremity (30–37). PMv provides prominent inputs to M1, exerting a powerful facilitatory effect, especially during visually guided movements of the hand (38,39).

PMv also has reciprocal, topographically organized connections with other motor areas of the frontal cortex (M1, SMA, PMd, CMA) (11,19,28,29) and with the parietal cortex, much like PMd. However, there are substantial differences between PMd and PMv in their connections with the parietal cortex. PMd is not strongly connected with the somatosensory areas of the anterior parietal lobe but, rather, with medial parietal areas that are more related to visual and visuomotor function (29,30,40–42). Most of the parietal inputs to PMv (15% of all inputs) (11) arise from more lateral areas, such as the second somatosensory area (S2) and the parietal ventral area (PV). Relatively few inputs (1.5%) arise from the more medial PP areas that are thought to be most involved in visually guided motor behaviors (11,43). Human neuroimaging studies have shown somatotopic maps of face and fingers in PMv (44). In addition, activation is increased in PMv of humans during a working memory task requiring a vibrotactile discrimination (45). Thus, although PMv appears to receive polymodal information, its primary inputs are from parietal somatosensory areas. Inactivation of PMv in macaque monkeys has little effect on the ability to reach out and grasp food morsels (37), in contrast to M1 inactivation (6).

Supplementary Motor Area

The SMA, sometimes called M2, is located in the medial aspect of Brodmann's area 6, largely extending onto the medial wall. Evidence from neuroanatomical and neurophysiological studies in monkeys and from neuroimaging studies in humans suggest a direct (though not exclusive) involvement of SMA in motor planning, especially in motor sequences and in bimanual motor control (46–48). Like other cortical motor areas, movements of the skeletal musculature can be evoked by stimulation of SMA (49–51) and constituent neurons project directly to the spinal cord (15,51–53). Several human neuroimaging studies and monkey neurophysiological studies have implicated SMA in movement planning, especially of learned movement sequences (48,54,55). Lesions of SMA in macaque monkeys result in deficits in bimanual coordination (56) and mild impairment in errors made during motor sequence tasks (57). SMA shares connections with PMd, PMv, M1, CMA, areas rostral to SMA, and PP cortex medial to the intraparietal sulcus (41,58–62). Thus, SMA connections are similar to PMd connections, in that parietal connections are primarily with more medial areas. One exception is that connections between SMA and S2 have been reported in some primate species (58,59).

Two SMA representations can be differentiated in primate species based on distinct cytoarchitecture, intracortical microstimulation, neuronal response properties, and connection patterns. These two areas, located on the medial surface of the cerebral hemispheres, are referred to as SMA-proper (or simply SMA; also called F3) and the pre-SMA (also called F6), situated more rostrally (63). In general, SMA proper is thought to be involved primarily in simple tasks, whereas pre-SMA is activated during relatively complex tasks (2). SMA and pre-SMA can also be differentiated in human neuroimaging studies; though until recently, reliable distinctions among the motor areas of the medial wall (SMA, pre-SMA, and CMA) were rarely possible. New approaches using diffusion tensor imaging may provide significant improvements in differentiating these areas (64–67).

DIFFERENTIAL PROCESSING STREAMS BETWEEN PARIETAL AND PREMOTOR CORTEX

To summarize, PMv, PMd, and SMA are strongly connected to parietal areas, though they receive differential input from separate sensorimotor-processing streams (Figure 7.2) (32,42). PMv is strongly interconnected with unimodal somatosensory areas of the anterior parietal lobe and with visual and polymodal areas in the lateral portions of the parietal cortex (7b, not shown). In contrast, PMd and SMA receive input primarily from visual and polymodal PP areas medial to the IP sulcus. Thus, except for the possible exception of S2 projections to both PMv and SMA, these premotor areas, PMv, and PMd/SMA appear to be involved in different aspects of motor control of the hand.

Cingulate Motor Areas

At least three cingulate motor areas—CMAd, CMAv, and CMAr—located on the medial wall, project directly to M1,

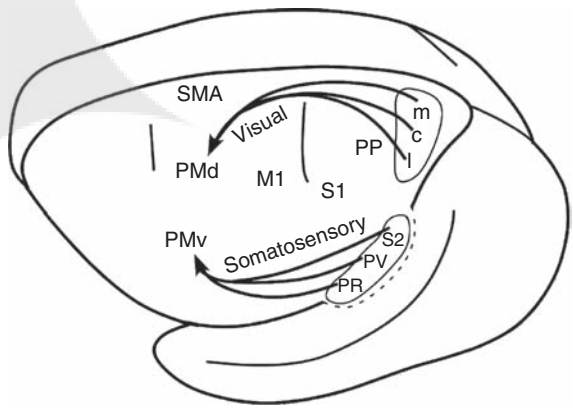

FIGURE 7.2 Sensory streams between parietal cortex and premotor areas of the frontal cortex. Recent tract-tracing results have revealed two distinct processing streams from parietal to premotor areas (*Source*: From Refs. (11,29)). PMv receives substantial inputs from somatosensory fields conveying cutaneous and proprioceptive information relayed from S1. These include PR, PV, and S2. In contrast, PMd and SMA receive substantial input from rostral, medial, and lateral aspects of PP cortex, conveying visual and polymodal information. These PP areas are probably homologous to areas 5, 7a, 7ip, 7m, and possibly MIP and PO of macaques (*Source*: From Ref. (29)). Thus, it appears that PMv and PMd/SMA process different sets of sensorimotor information and, thus, may have separate roles in motor control of the hand. Not shown in the figure are SMA connections with S2.

Abbreviations: m, c, l, medial, caudal, and lateral aspects of PP cortex; MIP, medial intraparietal area; PO, parietal occipital area; PR, parietal rostral area; PV, parietal ventral area.

other premotor areas, and directly to the spinal cord. It is thought that many of the functions originally associated with SMA may be mediated by CMA (47). Because it is less accessible for neurophysiological mapping studies and associated focal lesions, it is not a specific focus of this chapter.

Primary Somatosensory Cortex

Although not strictly a motor structure, the somatosensory cortex must be considered in the cortical control of movement, especially with respect to potential plasticity mechanisms involved in recovery after M1 lesions. Both primary (S1) and secondary (S2) somatosensory areas contain a large proportion of CS neurons; though most terminate in superficial and intermediate laminae of the spinal cord. Thus, CS neurons originating in the somatosensory cortex are thought to be involved primarily in modulating somatosensory inputs to the cord (68). Whereas stimulus-evoked motor output can be elicited by ICMS in S1, the effects are much weaker in magnitude and require higher currents (69). However, focal lesions in the S1 hand area result in deficits in motor skill, similar to those produced by M1 lesions (70). Further, neuroimaging studies in humans have demonstrated structural and functional plasticity in S1 after M1 injury (71–73). Thus, S1 should be included in any comprehensive study of cortical areas contributing to the recovery of motor function after M1 injury.

EXPERIENCE-DEPENDENT PLASTICITY IN CEREBRAL CORTEX

Over two decades of experimentation in the cerebral cortex have demonstrated many physiological and anatomical examples of cortical plasticity. Although these phenomena are triggered by many endogenous and exogenous events, one of the most potent modulators of cortical structure and function is behavioral experience (74–79). Emergent properties of each cortical area are shaped by behavioral demands, driven largely by repetition and temporal coincidence. For example, skilled motor activities requiring precise temporal coordination of muscles and joints must be practiced repeatedly. Such repetition is thought to drive the formation of discrete modules where the conjoint activity is represented as a unit (78).

One possible mechanism for mediating functional changes in the motor cortex is the modification of synaptic strength of horizontal connections (80). In slice preparations after motor learning, rats have larger amplitude field potentials in the motor cortex contralateral to the trained forelimb (81). Thus, the synaptic strength of horizontal connections in the motor cortex is modifiable and may provide a substrate for altering the topography of motor maps during the acquisition of motor skills. Structural alterations also occur in adult animals as a consequence of experience (82). Dendritic and synaptic morphologies of motor cortex neurons are altered by specific motor-learning tasks (83–87). Plasticity in the motor cortex is probably skill or learning-dependent, rather than strictly use-dependent. Tasks that require the acquisition of new motor skills induce neurophysiologic and neuroanatomic changes in the motor cortex, but simple repetitive motion or strength training tasks do not (85,88,89). New technological advances in microscopy such as transcranial two-photon microscopy allow the visualization of learning-dependent synaptic plasticity within the living brain by acquiring active images of axons and dendrites. For example, mice engaged in varying motor skill-acquisition procedures show task-specific clustering of dendritic spines as it occurs during skill acquisition. Only repetitive training on the same motor skill task resulted in task-specific clustering of new dendritic formations associated with motor memory (90,91).

Although the majority of our understanding of the relationship between behavior and motor cortex organization at the cellular and synaptic levels of analysis comes from rodent studies, the use of nonhuman primates has provided invaluable knowledge. Primates possess several unique advantages over rodents, including differentiated motor and sensory cortices, which can be subdivided into smaller regions similar to human sensorimotor cortical organization (11). This allows for the study of the differential contribution of various subregions to motor learning and allows for a more direct comparison to human studies. Furthermore, it allows for an understanding of how these subregions are functionally integrated through their extensive network of intracortical connections. In addition, primates possess the ability to perform complex behavioral tasks, especially those that require the use of fine digit manipulation. This digital dexterity is, with few exceptions, unrivaled in the animal kingdom (92) and is ideal for studying the acquisition of motor skills, as well as allowing for a large degree of control and detail in the design of behavioral training and testing paradigms.

The term "motor learning" is not rigidly defined in most experimental models, but instead thought of as a form of procedural learning that encompasses such elements as skill acquisition and motor adaptation. More specific is motor skill learning itself, which is often described as the modification of the temporal and spatial organization of muscle synergies, which results in smooth, accurate, and consistent movement sequences (93). Functional magnetic imaging studies in humans have led to the hypothesis that motor learning is a two-stage process (94). The first stage is rapid and results in within-session decreases in neural activity. The second, slower stage results in increases and expansion of activity in M1.

Although it is evident that numerous brain areas are involved in the production of complex motor movements, M1 has long been implicated in the acquisition and performance of skilled motor behaviors. Although originally believed to be involved in the activation of complex motor reflexes (95), the subsequent advancement of electrophysiological techniques revealed that movements could be elicited through electrical stimulation of the precentral gyrus (96). Based on these early findings, John Hughlings Jackson (1884) hypothesized that movement control was somatotopically organized. This hypothesis was later confirmed when

more systematic cortical stimulation studies were used to develop a somatotopic map of the precentral gyrus (97,98).

The development of the more sophisticated intracortical microstimulation (ICMS) technique in the late 1960s by Asanuma and colleagues allowed for the derivation of much higher spatial resolution maps within M1, which, in turn, revealed a more complex and dynamic cortical map organization, including the presence of columnar organization (99). The ICMS technique typically consists of applying a volley of short-duration cathodal pulses at a high frequency while using very weak currents (60 mcA), thus allowing for relatively little spread of cortical excitation. This greater spatial resolution revealed that although M1 is somatotopically organized on a macro scale, discrete cortical areas are comprised of a montage of representations of individual muscles and movements, which are repeated and highly overlapping. Based upon ICMS mapping experiments that define movements evoked by the lowest possible current levels, motor map organization resembles a fractured mosaic of movement representations, overlaid over a gross somatotopic representation.

Since the advent of ICMS, numerous studies have expanded our understanding of the relationship between motor maps and motor skill learning. Several general principles of motor map organization have been demonstrated that are thought to underlie the motor cortex's ability to encode motor skills (100). First, as mentioned above, motor maps are fractionated, in that they contain multiple, overlapping representations of movements. Second, adjacent areas within cortical motor maps are highly interconnected via a dense network of intracortical fibers. Third, these maps are extremely dynamic and can be modulated by a number of intrinsic and extrinsic stimuli. Together, these characteristics provide a framework that facilitates the acquisition of novel muscle synergies, at least in part, through changes in the intracortical connectivity of individual movement representations.

However, the dynamic nature of motor maps belies the issue of stable neural connections that must be maintained to respond to environmental demands and to retain acquired motor skills. Within the cortex, this balance is thought to be achieved through interactions of the excitatory and inhibitory connections of pyramidal cells and local inhibitory networks (101–103). This, in turn, requires an internal mechanism that is capable of shifting this balance toward strengthening relevant synaptic connections. Horizontal fiber connections have been shown to arise from excitatory pyramidal neurons and allow for the co-activation of adjacent and nonadjacent cortical columns. In addition to activating excitatory pyramidal cells, they also generate inhibitory responses via the activation of GABAergic interneurons (104). Furthermore, the activity of these horizontal fibers has been shown to be mediated by both long-term potentiation (LTP) and long-term depression (LTD) between distant motor cortical areas (80,105). LTP and LTD are persistent increases or decreases (respectively) in synaptic strength. These processes are thought to represent the synaptic mechanisms responsible for learning and memory.

Whereas the phenomena of LTP and LTD are now well established from experiments in slice preparations and intact animals, the concept of use-dependent modulation of synaptic strength was postulated much earlier by Hebb in the 1940s. Hebb proposed that synaptic efficacy can be increased by a presynaptic cell's repeated or persistent stimulation of a postsynaptic cell. This concept has taken on many forms and is pervasive in most theories of the synaptic basis of learning and memory. Many contemporary terms still honor Hebb's contribution to this field, such as Hebbian learning, Hebbian cell assemblies, and Hebbian engrams. Hebb's theories are often summarized in the now common phrase "cells that fire together, wire together." Specifically with regard to plasticity in cortical networks, alterations in synaptic strength in horizontal fibers provide a mechanism capable of both facilitating the activation of multiple novel muscle synergies that are required for motor skill acquisition, while likewise providing a mechanism, via inhibitory processes, of motor map stability that is required to maintain stable, neural representations in response to irrelevant (i.e., untrained) environmental events.

Utilizing manual dexterity training in combination with ICMS maps has been crucial in demonstrating the dynamic relationship between motor skill learning and cortical map plasticity. The first study to directly examine this relationship used varying behaviorally demanding tasks to selectively activate specific components of motor maps (78). In these tasks, monkeys were rewarded with small, banana-flavored food pellets for performing skilled movements with the hand. In one task, the pellets were placed one at a time into food wells of different diameters. The monkey simply was required to extract the pellet. Large food wells required minimal manual skill. Small food wells required the insertion of only one or two digits and, thus, maximal manual skill. Retrieval from the smaller wells required practice over the course of about 10 to 12 days for asymptotic performance to be achieved. In a second task, monkeys were required to reach through a narrow tube and rotate a key back and forth, requiring repetitive pronation and supination of the forearm. Posttraining ICMS mapping revealed training-induced changes in motor map topography that directly reflected the demands of the particular behavioral task. That is, the pellet retrieval task resulted in expansion of digit representations, whereas the key-turning task resulted in expansion of wrist and forearm representations.

In addition, an increase in ICMS-evoked multi-joint movements was observed. These movements consisted of simultaneous executions of digit and wrist, or proximal movements at low ICMS thresholds, and were only observed after training on the digit-use intensive manual dexterity task. Both before and after training, thresholds for evoking multi-joint responses were significantly lower than single-joint responses. These results imply that behaviorally relevant, simultaneous or sequential movements may become associated in the motor cortex through repeated activation.

A temporal correlation hypothesis has been proposed to explain these phenomena and derives from similar results

obtained from studies in the somatosensory cortex. For example, digit representations in the somatosensory cortex are typically individuated, with sharp boundaries between adjacent digit areas. If two digits are experimentally joined surgically in a so-called digital syndactyly procedure, then the representations of those digits become fused, with neurons displaying multi-digit receptive fields that cross the suture line. The hypothesis suggests that as inputs from the two separate digits are made temporally coincident by the syndactyly, the new multi-digit representations appear as an emergent property of the plastic somatosensory cortex. It is possible that this hypothesis is generalizable to the motor cortex as well. Thus, muscle and joint synergies used in complex, skilled motor actions may be supported by alterations in local networks within the motor cortex. As skilled tasks become more stereotyped in the timing of sequential joint movements, functional modules emerge in the cortex to link the outputs of different motoneuron pools.

These findings lead to the question of what aspects of motor skill learning drive the observed changes in map representations. It is possible that increased muscle activity alone produced the observed changes in map representations. To address this issue, a group of monkeys were trained exclusively on either the largest or the smallest well in the manual dexterity task described above. The rationale in this design is that the largest well allows for simple multi-digit movements for pellet retrieval, which does not require the subject to develop novel skilled digit movements since simply grasping for food is a normal part of their daily home cage behavior and already part of their behavioral repertoire. Small-well food pellet retrieval, in contrast, requires the monkey to manipulate one or two digits to retrieve the pellet, which is considerably harder, given that squirrel monkeys lack monosynaptic CS projections to motoneurons, which probably limits individuation of digit movements (106). Compared to pretraining maps, monkeys trained on the large-well pellet retrieval did not show an expansion of the digit representation, whereas those trained on the small well did exhibit an expansion of the digit representation (88). These findings strongly suggest that an increase in motor activity in the absence of motor skill acquisition is insufficient to drive neurophysiological changes in the motor cortex. Similar findings have been found in rodents during examinations of pellet retrieval vs. bar pressing. Rats that learned to retrieve pellets from a rotating platform displayed more distal movements in their motor maps. This expansion was associated with significant synaptogenesis (76,85).

PLASTICITY IN ADJACENT TISSUE AFTER FOCAL DAMAGE TO M1

Direct evidence that adjacent regions of the cortex might function in a vicarious manner after injury can be traced to studies by Glees and Cole in the early 1950s (107). Monkeys were subjected to focal injury to the thumb representation. When brains were remapped following behavioral recovery, the thumb area reappeared in the adjacent cortical territory. However, using ICMS techniques, somewhat different findings were observed by Nudo et al. in the 1990s. Small, subtotal lesions were made in a portion of the distal forelimb representation (DFL) in squirrel monkeys, and the animals were allowed to recover spontaneously (i.e., without the benefit of rehabilitative training) for several weeks. In contrast to earlier findings, the remaining DFL was reduced in size, giving way to expanded proximal representations (78). However, in animals that underwent rehabilitative training with the impaired limb, the DFL was preserved or expanded (108). In retrospect, it is quite possible that the re-emergence of thumb representations in the early study may have been driven by postinjury behavioral demands.

Studies in human stroke patients also suggest that the intact, peri-infarct cortex may play a role in neurologic recovery (109–111). Using transcranial magnetic stimulation (TMS) after stroke, it has been shown that the excitability of the motor cortex is reduced near the injury, and the cortical representation of the affected muscles is decreased (112,113). It is likely that this effect occurs from a combination of diaschisis-like phenomena and disuse of the affected limb (114). Further, after several weeks of rehabilitation, motor representations in the injured hemisphere are enlarged relative to the initial postinjury map (113,115). Also, when goal-directed movement with the impaired hand is encouraged, a significant enlargement of the representation of the paretic limb is produced (116), closely paralleling results in nonhuman primates.

Neuroanatomical changes also occur in the peri-infarct cortex. After middle cerebral artery occlusion in rats, Stroemer and colleagues examined immunohistochemical correlates of neuronal sprouting in the spared, peri-infarct tissue. Between 3 and 14 days after infarct, rats demonstrate increased GAP-43 immunoreactivity, suggesting significant neurite outgrowth in the peri-infarct region (117). Then, 14 to 60 days after infarct, synaptophysin staining is elevated, signifying increased synaptogenesis (117). The extent of injury-induced neural plasticity depends upon the extent and type of injury. For example, unlike ischemic brain injury, there is now evidence that synaptic plasticity and axonal sprouting may be constrained after severe to moderate traumatic brain injury (TBI) (118). TBI injuries also produced more persistent deficits than comparable ischemic cortical injuries (119). These differences further exemplify the role of enhanced plasticity in recovery as proposed by these earlier studies.

Although these experiments provided indirect support for neurite outgrowth and synaptogenesis in the peri-infarct zone after an ischemic cortical injury, direct evidence for local axonal sprouting has been obtained in experiments utilizing the so-called rodent cortical barrel field (120). This specialized region of somatosensory cortex in rats and many other species contains a somatosensory representation of the mystacial vibrissae, or simply, whiskers. The advantages of this system are two-fold: First, an individual "barrel" in the rat barrel field represents a single whisker, thus allowing precise experimental manipulation of the inputs to this

isolated region. Second, the barrel field, and individual barrels, can be identified in histological stains, allowing for precise identification of the barrel that has been manipulated. In studies by Carmichael and colleagues, focal ischemic lesions were made in the rodent barrel field cortex. A few weeks later, a neuroanatomical tracttracer was injected into the cortical tissue bordering the infarcted region, and the axonal projections of the labeled neurons were plotted. Rats with small ischemic strokes in barrel cortex had local, axonal projections arising from the peri-infarct cortex that were substantially different in orientation compared with control tissue. This result implies that new intracortical (horizontal) connections are formed in the peri-infarct tissue, at least over short distances of perhaps a millimeter in rats (120). There is also evidence that the rapid changes in the length of dendritic spines may also have neuroprotective effects by isolating excitotoxic events from reaching the neuronal soma (121). Whereas we are just beginning to understand the molecular events that drive local axonal growth after injury, the picture is now emerging of an evolving peri-infarct environment in which growth inhibition is suppressed for about 1 month after infarct. This period is followed by "waves" of growth promotion that may modulate axonal sprouting and, therefore, the brain's self-repair processes (122).

Based on the large number of paradigms demonstrating that the adult somatosensory cortex is plastic, it is not surprising that somatosensory organization is altered by cortical injury, as might occur in stroke. After small, ischemic lesions that destroy single-digit representations in S1 of adult monkeys, the destroyed representation re-emerges in the adjacent cortical territory (70). Neuroimaging studies in human stroke survivors suggest that structural plasticity accompanies somatosensory cortical reorganization. Cortical areas that undergo changes in activation response to tactile stimuli show increased cortical thickness (71).

FUNCTIONAL AND STRUCTURAL PLASTICITY IN REMOTE REGIONS AFTER FOCAL DAMAGE TO M1

Primate brains are endowed with a rich intracortical network that allows reciprocal communication among the various sensory and motor areas. Injury to the motor cortex results in a potent disruption of integrated sensorimotor networks, resulting in loss of fine motor control (77). Thus, even focal injuries produce widespread and persistent changes in areas that are quite remote from the site of injury. For example, injury to M1 in rats and nonhuman primates results in upregulation of NMDA receptors and downregulation of $GABA_A$ receptors throughout the ipsilesional and contralesional hemisphere (123). Therefore, it follows that intact motor areas outside of M1 may also contribute to recovery. As mentioned previously, the frontal cortex contains several areas that contribute to skilled motor behaviors in primates, including PMd, PMv, and SMA. All of these areas possess reciprocal connections with M1, contain numerous CS neurons, and contain complete hand representations. Thus, it is plausible that following an injury to M1, the remaining, intact motor areas play some role in functional recovery, via intracortical connectivity with other cortical regions and/or their direct CS projection pathways.

Experiments by Liu and Rouiller (124) showed in nonhuman primates that inactivation of the premotor cortex with the GABAergic agonist muscimol following an M1 ischemic lesion reinstated behavioral deficits. This reinstatement was not observed with inactivation of the peri-lesional or contralateral cortex. Thus, it follows that if the premotor cortex is capable of compensating for the loss of motor function following an M1 injury, there should exist physiological changes that accompany this recovery. In adult squirrel monkeys, ICMS mapping techniques have characterized representational maps of both M1 and PMv before and after experimental ischemic infarcts that destroyed at least 50% of the M1 hand representation (125). All subjects showed an increased hand representation in PMv, specifically in digit, wrist, and forearm sites. Further, the amount of PMv expansion was correlated with the amount of the M1 hand representation that was destroyed. In other words, the more complete the M1 hand area lesion, the greater was the compensatory reorganization in PMv (Figure 7.3).

Interestingly, when lesions were smaller than 50% of the M1 hand area, the PMv hand representation decreased in size (Figure 7.3). Thus, examining the entire spectrum of M1 infarcts of varying sizes, the linear relationship is maintained. This result occurred despite the fact that some of these subtotal M1 hand area lesions nonetheless destroyed nearly the entire terminal field of PMv-M1 connections. What possible compensatory changes in the neuronal network could account for proportional gains in premotor hand

FIGURE 7.3 Relationship between size of lesion in primary motor cortex (M1) hand representation and subsequent change in hand representation in ventral premotor cortex (PMv). The percentages refer to the proportion of the M1 hand representation that was destroyed by an experimental cortical infarct in squirrel monkeys. Note that as lesion sizes exceed 50% of the M1 hand representation, hand representations in PMv expand in a linear fashion.

Source: From Ref. (125). Frost SB, Barbay S, Friel KM, Plautz EJ, Nudo RJ. Reorganization of remote cortical regions after ischemic brain injury: a potential substrate for stroke recovery. *J Neurophysiol*. 2003;89(6): 3205–3214.

areas but losses with very small lesions? This phenomenon is reminiscent of Lashley's classic description of the relationship between cerebral mass and behavioral change (126,127). According to this hypothesis, lesion size is generally assumed to be associated with the severity of deficits, while lesion location is related to the specificity of deficits. Lashley also proposed the concept of equipotentiality, suggesting that each portion of a given cortical area is able to encode or produce behavior normally controlled by the entire area. In that vein, after smaller lesions, the surviving M1 tissue could potentially subserve the recovery of function. In that case, reorganization in distant, interconnected cortical areas would be a more "passive" process, resulting from the loss of intracortical connections. This reorganization could be compared to a "sustained diaschisis" of PMv. After larger lesions, reorganization of the adjacent tissue may not suffice for normal motor execution. Thus, learning-associated reorganization would need to take place elsewhere, resulting in greater PMv expansion. Accordingly, in rats, the contralesional cortex is thought to be involved in behavioral recovery only after large lesions (128). Lesion size appears to be a major factor involved in the initiation of some of the vicarious processes that purportedly play a role in recovery from CNS lesions.

Yet another form of postinjury sprouting of cortical projection pathways from PMv was discovered in the injured hemisphere of adult nonhuman primates. Five months after an ischemic injury to the M1 hand representation, most intracortical connection patterns of the PMv remain intact (129). This is despite the fact that the major intracortical target of PMv is destroyed by this procedure. However, after M1 lesions, monkeys display a remarkable proliferation of novel PMv terminal projections in primary sensory cortex (S1), when compared to uninjured control monkeys, specifically in the hand representations of areas 1 and 2. Likewise, this somatosensory area had a significant increase in the number of retrogradely labeled cell bodies, indicating an increase in reciprocal projections from S1 to PMv. In addition, intracortical axonal projections from PMv significantly altered their trajectory near the site of the lesion (Figure 7.4).

This finding is particularly interesting, given the direct intracortical connections between M1 and somatosensory cortex as well as the presence of direct CS projections originating from PMv. One hypothesis is that the postinjury sprouting represents a repair strategy of the sensorimotor cortex to re-engage the motor areas with somatosensory areas. In intact brains, M1 receives input from various regions of the parietal lobe that supply cutaneous and proprioceptive information that is largely segregated in the M1 hand area—cutaneous information arriving in the posterior portion of M1 and proprioceptive information arriving in the more anterior portion. The functional importance of this somatosensory input can be appreciated from studies employing discrete lesions in these subregions in M1. Lesions in the posterior M1 hand area lesions result in behavioral deficits akin to those seen after S1 lesions. These deficits appear to be similar to sensory agnosia, in which the animal reaches for food items but does not appear to know whether the item is actually in the hand (130). In contrast, anterior M1 hand area lesions result in deficits in metrics of the reach, perhaps indicating the disruption of proprioceptive information in the motor cortex (10). One lesson from these studies is that the motor cortex cannot be considered solely as a motor structure. Deficits result from sensory–motor disconnection, in addition to disruption of motor output. Thus, after M1 injury, there is a substantial reduction of somatosensory input to motor areas. Perhaps, the novel connection between PMv and S1 is an attempt by the cortical motor systems to reconnect with somatosensory input.

It is likely that this phenomenon of intracortical sprouting of remote pathways, interconnected with the injured zone, is not a unique event. It is more likely that many structures, both cortical and subcortical, that are normally connected with the injured tissue undergo substantial physiological and anatomical alterations. For instance, each of the other cortical motor areas (PMd, SMA, CMA) is likely to change its intracortical connectivity pattern since its targets are destroyed. If so, it follows that the brain with a focal injury is a very different system. It is not simply a normal

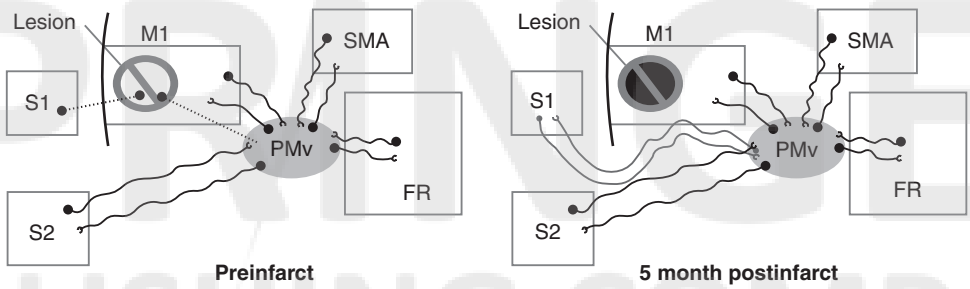

FIGURE 7.4 Rewiring of intracortical connections after M1 infarct. Normally, PMv provides a major input to M1. M1 shares significant connections with S1. Five months after an infarct in M1, novel connections form between PMv and S1. Other intracortical connections of PMv remain unchanged.

Source: From Ref. (129). Dancause N, Barbay S, Frost SB, et al. Extensive cortical rewiring after brain injury. *J Neurosci*. 2005;25(44):10167–10179.

system with a missing piece. If intracortical reorganization is a predictable process, as we think it is, then we may be able to begin to develop ways of enhancing adaptive, while suppressing maladaptive, connection patterns.

After stroke in humans, widespread changes occur in activation patterns associated with movement of the paretic limb in both the ipsilesional and contralesional hemispheres (131–133). Whether such bilateral activation is adaptive or maladaptive is still a matter of debate, but it appears that, as recovery proceeds, activation of the various regions in the ipsilesional cortex increases (115,132), possibly representing a restoration of excitatory/inhibitory balance between the two hemispheres (134). Increased ipsilateral activation after stroke is quite widespread, including spared premotor areas (135,136). In one longitudinal study, increased activation of SMA was correlated with better recovery (137). Stroke survivors with middle cerebral artery strokes that included lateral PM areas had poorer recovery (138), whereas increased lateral PM activity was associated with better recovery (139). In an experiment analogous to monkey secondary inactivation studies, the ipsilesional PMd of human stroke survivors was inactivated temporarily with low-frequency repetitive TMS. This procedure resulted in reaction-time delays that were not generated by inactivation of the contralesional PMd or the PMd of healthy subjects (140). From the results to date, it is not possible to determine if any one motor area is more important in the recovery of motor abilities after stroke. A likely hypothesis is that the entire cortical and subcortical motor system spared by the injury participates to varying degrees depending upon the extent and location of the injury and behavioral demands. At least some of the functions of the injured region(s) are thus redistributed across the remaining cortical and subcortical motor network.

An example of this can be seen after unilateral cortical lesions in rats where corticostriatal fibers, which primarily connect cortical motor areas with the striatum on the same side of the brain, sprout from the intact cortex on the opposite side of the brain and cross to the opposite striatum (i.e., on the side of the lesion) (141). In other words, unilateral lesions produce novel crossed corticostriatal pathways that originate in areas completely remote from the injured zone. Although still speculative, such plasticity in crossed fiber systems may provide one mechanism for the remaining intact hemisphere to participate in recovery by gaining access to the deafferented striatum in the injured hemisphere.

The benefit of compensatory axonal sprouting may be limited by the extent of brain damage as seen after a TBI (118). Various pharmacological, physiological, and behavioral interventions are being investigated to facilitate adaptive plasticity associated with recovery. These new innovations in rehabilitative therapy take advantage of the brain's natural ability to form new functionally adapted networks in response to environmental demands. Thus, the success of these new therapies depends on the quality of behavioral experience accompanying their implementation.

ROLE OF BEHAVIOR IN MODULATING POSTINFARCT RECOVERY

Several new approaches to improving functional recovery after stroke have been developed that are based on neuroplasticity mechanisms. Constraint-induced movement therapy encourages the use of the impaired limb, and engages it in functional tasks that purportedly drive adaptive plasticity in the intact portions of the ipsilesional hemisphere. Clinical trials support the efficacy of this approach over standard and usual care (see Chapter 20) (142). D-amphetamine administration, when combined with behavioral experience, appears to enhance recovery in rodent and nonhuman primate models, though clinical results have been mixed (143,144). D-amphetamine is known to induce increased synaptogenesis in the peri-infarct region in rats (see Chapter 12) as well as axonal sprouting from the intact hemisphere after a unilateral infarct to the deafferentated, red nucleus and cervical spinal cord when paired with rehabilitative training (145). Several studies have also found promising results with methylphenidate (146). Recently, new drugs have been developed to enhance cortical plasticity with more specificity than amphetamines. These drugs increase neural excitation by antagonizing heightened, tonic GABAergic inhibition within the peri-infarct zone induced by a stroke, thereby augmenting the beneficial effects of rehabilitation (147). Also, signaling pathways associated with axonal development after an ischemic infarct from the peri-infarct area and the homologous, contralateral cortical area have been identified as potential therapeutic targets to promote recovery (148). Other potential therapeutic targets are being discovered as postischemic expression of growth-promoting genes, associated with axonal sprouting, is revealed (149).

Cortical electrical stimulation, when combined with rehabilitative training, appears to have a positive effect on recovery in rodents and nonhuman primates (150,151). Although the mechanism is not well understood, the approach is thought to enhance excitability of the intact regions of the ipsilesional hemisphere. Noninvasive analogs of this approach are now being examined (152). What these approaches have in common is the importance of repetitive behavioral tasks, especially those that have high skill demands. Thus, although pharmacological and device-oriented approaches to increasing cortical excitability and growth of neuronal processes are clearly beneficial, their effects are modulated and shaped by behavioral experience.

Recent evidence from developmental and injury studies may suggest ways in which behavior may specifically influence neuroanatomical plasticity after injury. First, during development, guidance cues for axonal sprouting are activity-dependent. There are two phases in the maturation of thalamocortical connections. In the first phase, thalamocortical axons are directed to their cortical targets by axonal guidance molecules. This process may involve spontaneous neural activity (153). In the second phase, cortical activity guides axonal sprouting within the cerebral cortex, determining topological connectivity patterns (154). Postnatal axonal

branching patterns within the cerebral cortex have also been shown to involve sensory-related stimulus activity, possibly by initiating molecular retrograde signals such as brain-derived neurotrophic factor (155). After a focal ischemic infarct in rats, synchronous neuronal activity is a signal for postinfarct axonal sprouting to be initiated from the intact cortical hemisphere to periinfarct cortex and the contralateral dorsal striatum (156). Thus, evidence now supports the importance of cortical activity for axonal sprouting within the developing and adult brain.

The significance of neuroplasticity for rehabilitation is that it provides a mechanistic rationale for understanding therapeutic interventions. Thus, it may be possible to develop more effective recovery protocols if we can elucidate the effects of such interventions on physiological and anatomical plasticity in the injured brain. For example, technological advances in micro-electro–mechanical systems are now being utilized to develop "bridging devices" that can reconnect areas within a damaged cortical network to reestablish sensorimotor integration (157). Functional connections as well as behavioral skills are reestablished through activity-dependent stimulation during therapeutically relevant behavioral activity (158).

As demonstrated by the mapping studies after microinfarcts in nonhuman primates noted above, it is clear that behavior is one of the most powerful modulators of postinjury recovery. Behavioral interventions to enhance recovery after stroke have become increasingly popular because of the success of task-oriented functional therapeutic interventions, such as constraint-induced movement therapy (see Chapter 20). Whether such behaviorally driven changes in motor performance are caused by the reestablishment of original motor programs in spared tissue or by the compensatory use of unimpaired body parts remains a controversial subject. Nonetheless, plastic changes must take place in the spared neuronal substrate, whether the improvement is caused by the true restoration of function or compensation. Behavioral use clearly plays a role in the contralesional changes that take place in the uninjured cortex of rats following cortical infarction. Other studies have demonstrated that task-specific rehabilitative training is most effective in driving postinjury neuroanatomical changes (159). Thus, it would appear that CNS injury produces an environment in which the neuronal network is particularly receptive to modulation by specific behavioral manipulations.

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8

Functional Imaging and Stroke Recovery

Erin Burke and Steven C. Cramer

Stroke remains a leading cause of disability in the United States and many other countries, with the rate of survival increasing in recent years. Thrombolytic therapy has been approved for the treatment of acute stroke, but only 5.2% of Americans receive intravenous tissue plasminogen activator (t-PA) (1), and approximately half of those who are treated and survive show long-term disability (2). Stroke can cause deficits in a number of neurological domains, most commonly in the motor system (3,4). In most patients, the time when spontaneous behavioral recovery is seen is the first three months following a stroke (5,6), though this time period might be longer for neglect, aphasia, and other cognitive areas (7–11).

Although many patients show some degree of spontaneous recovery during the months after a stroke, the degree of this recovery is generally incomplete. In addition, the heterogeneous nature of stroke means that not all stroke survivors stand to achieve the same behavioral gains, making recovery highly variable. The best measures with which to establish prognosis and response to treatment are undetermined. The severity of initial deficits has traditionally been the measure most often used to predict the outcome after stroke (12–15). A number of other measures have been found to predict the degree of spontaneous recovery after stroke, including age (16), sensory or motor-evoked potentials (17–20), cognitive impairment and accompanying neurological deficits (21), and many more. That the list is so long is not surprising, however, given the large number of factors that influence brain function after stroke (22) (Table 8.1). However, a large amount of recovery variance remains unexplained using traditional clinical and demographic measures.

Exploring additional anatomical and physiological measurements in the stroke-affected brain is likely to provide greater insight into the likelihood of recovery. Animal studies have elucidated the cellular and molecular mechanisms (23), both near and remote from the lesion, that underlie spontaneous poststroke improvements. Because cellular and molecular measurements are generally inaccessible in human patients, a number of neuroimaging methods have been examined to better understand, predict, and guide poststroke recovery. MRI studies have shown that infarct volume, a global neural measure of neural injury, has value for predicting recovery (24–27), but much variance remains unexplained (28,29). More specific features of stroke-related injury, such as location (30,31) or effect on motor and sensory-evoked potentials (19,20,32), also have predictive value. In line with this, system-specific neural measures are more likely to predict system-specific behavioral outcome. Functional brain imaging is a useful tool that can elucidate the degree of activation and plasticity within the poststroke motor system. How such functional magnetic resonance imaging (fMRI) measurements predict behavioral outcome, as well as response to intervention, is discussed in this chapter.

METHODS FOR EXAMINING SPONTANEOUS BEHAVIORAL RECOVERY FOLLOWING STROKE

Animal Studies

A number of molecular and cellular events underlying spontaneous behavioral recovery after stroke have been identified. Available evidence suggests a range of processes including neurogenesis, axonal sprouting, synaptogenesis, and angiogenesis, many of which might be related to logical therapeutic targets in humans (33–39). Plasticity also occurs in response to treatments such as enriched rehabilitation (40), motor skill training (41–43), and exogenous pharmacologic administration (44–47). Importantly, some of these processes can be measured, directly or indirectly, with neuroimaging (48–51). Therefore, neuroimaging shows great promise in probing poststroke plasticity, both with and without treatment. Neuroimaging studies in human stroke patients are critical to optimal translation of preclinical findings, as they address some of the limitations of animal models. Some of these limitations (52) are ambulation on four legs, lack of comparable heterogeneity of injury and of preinfarct behavioral status, the nonphysiological nature of the injury induced in some models (53,54), limited modeling of stroke risk factors, limited modeling of psychosocial factors, and important differences in brain structure and function (e.g., the average brain weight is 2.5 grams for rats and 1300 grams for humans).

TABLE 8.1 Clinical Variables That Likely Modify Brain Function After Stroke

Stroke topography and sites injured
Time post stroke
Age
Hemispheric dominance
Side of brain affected
Depression and psychiatric comorbidities
Injury to other brain network nodes
Infarct volume
Initial stroke deficits
Arterial patency
Medical comorbidities
Prestroke disability, social function, experience, and education
Type and amount of poststroke therapy
Acute stroke interventions
Medications during stroke recovery period
Final clinical status
Stroke mechanism
Genetics

Human Brain Mapping

Insights into the brain events underlying stroke recovery can be obtained from studies of brain systems via human brain mapping. Several functional neuroimaging modalities have been used to probe systems-level neuroplasticity, including fMRI, positron emission tomography (PET), EEG, magnetoencephalography (MEG), transcranial magnetic stimulation (TMS), and near infrared spectroscopy (NIRS). Some of these methods provide useful insights into the topography of injury, data that usefully complement measures of brain function. In other cases, these techniques measure the volume of regional brain activation, the magnitude of this activation, and the balance of activation across hemispheres, often reported as a laterality index, during a task or at rest. Techniques such as fMRI, EEG, and MEG also provide estimates of functional connectivity (FC) and assess lesion effects on neural networks (55). Effective connectivity is a similar technique that evaluates not only changes in the temporal correlation of activation between regions, as with FC, but also the strength and directional influence of one brain region on another. As no single method is sufficient to examine all relevant aspects of neuroplasticity, multiple functional techniques are often used to achieve the most robust understanding of poststroke plasticity (56) and to help develop therapeutic protocols that best target these mechanisms (57).

Brain mapping data have provided insights into changes in brain structure and function arising after stroke, many of which are concordant with repair-related findings in animals. The current review considers these data, with an emphasis on fMRI of the motor system, which has received considerable study. One goal of these studies is to better understand reorganization of brain function to optimize restorative interventions and behavioral recovery, for example, by better predicting outcome, triaging, or defining measures of therapy at the level of the individual patient (58). This perspective is considered in the following text.

CHANGES IN BRAIN FUNCTION IN RELATION TO RECOVERY OF BEHAVIOR AFTER STROKE

Ample data from studies in animals and humans have shown that the brain has the capacity to change its function and structure, in association with behavioral recovery, in the days to weeks following a stroke. Several patterns of altered brain function have been described.

Increased Activation Across a Network

A common pattern described since the first functional imaging study of brain function after stroke (59) is increased activation within multiple nodes that together comprise distributed networks (60–71). This has been reported in numerous brain networks, including those related to motor, language, and attention functions. These studies converge on the conclusion that maintenance of behavioral output after injury to one node of a network is associated with increased activation within surviving network areas, a finding substantiated as studies have considered a broader range of behavioral outcomes (72,73). In healthy subjects, performance of an increasingly complex task is also associated with increased activation of multiple brain areas comprising a network, and so in this regard, brain function after stroke can be thought of as analogous to perpetually performing in a high-complexity/high-demand setting (74–79).

Additional studies have shed light on these overactivations that are distant from the site of stroke-related injury. Increased activation in distal sites is highest in those with the poorest behavioral outcome (72,80). However, studies using virtual lesion (81–87) and neurophysiological (88–91) approaches suggest that this change in brain function is nevertheless important to whatever behavioral recovery does occur spontaneously after stroke. Thus, these network-wide changes in brain function after stroke contribute to behavioral outcome and generally are most pronounced in association with incomplete restoration of function.

Diaschisis

Other changes can arise in injured areas distant from stroke, including diaschisis. *Diaschisis* refers to reduced activity and function, with consequent decreases in blood flow and metabolism, in uninjured brain areas that have rich connections with injured brain areas (92–95). In some studies, behavioral recovery is related to resolution of diaschisis, that is, restitution of brain activity in uninjured areas that are distant from, but connected to, the site of infarct (96,97). However, fMRI is likely not an ideal probe for the presence of diaschisis, as blood oxygenation level dependent (BOLD) activation may appear normal in areas of reduced blood flow (98), whereas PET is sensitive to blood flow and metabolism, depending on the

technique. The exact effect of diaschisis in humans, and the time period post stroke when this process is most relevant, requires further study.

Reduced Activation in the Injured Zone

In contrast to the often increased activation in distant areas after stroke, the injured ipsilesional hemisphere sometimes shows reduced activity, especially if injury is to the elegant/eloquent cortex or its efferents (99). For example, a study of subjects who had reached a plateau in motor recovery after paresis-inducing stroke found that primary sensorimotor cortex activation in the stroke-affected hemisphere during affected hand movement was smallest in those with lesser recovery, moderate in those with full recovery, and largest in healthy controls (100). These results are concordant with TMS studies of motor cortex after stroke (101), which show that, after stroke, motor maps are smaller, and corticospinal tract integrity is reduced in parallel with the severity of clinical deficits. Similar findings have been described with stroke affecting the language system, where aphasia is accompanied by increased activation in secondary cortical regions and decreased activation in the key dominant hemisphere's language regions (69,102–105).

Displacement of Function and Representational Maps

In some cases, depending on the topography of injury, the localization of particular cortical functions can be displaced to neighboring areas (106). A common example of this compensatory event in the motor system is the finding that after a stroke injures the motor system elements related to hand movement, hand representation on the primary motor cortex extends ventrally toward the face area. Weiller and colleagues described a ventral shift in the center of activation during motor task performance in recovered patients whose stroke affected the posterior aspect of the internal capsule (107). Subsequent fMRI studies reported the same finding (73,99,100). A shift of the motor cortex hand representation after stroke in the dorsal (108) or posterior (109–114) direction has also been described, suggesting that topographic shifts in cortical representation site might reflect survival of distinct subsets of corticospinal tract fibers. Some of these shifts might have functional consequences. For example, activation of primary sensory cortex after stroke along with therapy can support motor recovery (115), which may be partly because of increased responsiveness to sensory input (116). Different patterns of injury might thus invoke different forms of cortical map plasticity, a consideration that might explain the mosaic of reorganization patterns reported in some group analyses of stroke recovery (80).

Changes in Peri-Infarct Activity

One topic that requires further study is the evolution of function in surviving tissue that surrounds a cortical infarct. When examined histologically in animals, this zone shows the greatest levels of growth-related molecular change after stroke (33,40,44,45,117–127). Furthermore, in some cases, these specific peri-infarct events can be further amplified by therapeutic intervention, a phenomenon that has been associated with additional behavioral gains (44,120,128,129). Together, these observations suggest that this zone is of particular importance to the return of function after stroke and represents important therapeutic targets—assertions supported by human studies which found that the volume of threatened but surviving peri-infarct tissue is directly related to the final clinical outcome (130,131). Functional assessments of this zone in humans, using a range of functional neuroimaging modalities, have specifically noted activation in the peri-infarct region of patients with chronic stroke (62,104,111,132–139). The significance of these observations can be further clarified, for example, by assessing whether the extent of these events is related to behavioral status. An fMRI study of patients with cortical stroke did not find a significant correlation between the extent of peri-infarct activation and behavioral outcome after stroke (140). However, this correlation was complicated by the additional observation that the T2*-weighted MRI signal used to measure brain activation with fMRI was itself altered in the peri-infarct zone. This observation complicates the interpretation of peri-infarct fMRI data in patients with cortical stroke and suggests that functional neuroimaging methods besides fMRI might be important to best understand the contribution that peri-infarct activity has on the behavioral outcome after stroke.

Changes in Interhemispheric Laterality

Another finding in subjects with stroke is a reduction in the laterality of brain activity (60,68,107,141,142). For example, a right-hand motor task or language task that activates the left hemisphere in healthy controls will activate relevant regions within both the right and the left hemispheres in patients with a left hemisphere stroke. Indeed, a number of cases have been published where the main sites of brain activation are restricted to the nonstroke hemisphere, contralateral to findings in controls (62,68,143–145). This issue has also received considerable attention in the study of normal aging (146) and has also been identified as a pattern of cerebral reorganization in a number of other neurological settings, including epilepsy (147), traumatic brain injury (148), and multiple sclerosis (149). The shift in the balance of activation toward the contralesional hemisphere varies over time, being particularly common in the early days to weeks after a stroke (150). Subsequently, the activation balance shifts back toward the stroke-affected hemisphere, more so in patients with better behavioral outcome (69,71,73,150–154). In contrast to the motor system, recovery from poststroke aphasia may depend on right-hemisphere language areas in addition to preservation of left hemisphere (70,83).

Changes in fMRI laterality have been related to altered interhemispheric interactions, suggesting that improved

function of ipsilesional brain regions might be facilitated by normalizing the pathological interhemispheric interactions that arise after stroke (155,156). A shift in hemispheric lateralization might in part reflect changes in the balance of interhemispheric inhibition (157–161). Recent studies of connectivity have provided insight into the roles of interhemispheric changes in excitation and inhibition. The general consensus from studies of paired-pulse TMS is that the unaffected motor cortex exhibits abnormally high inhibition onto the affected motor cortex during movement after stroke (161,162). Indeed, this has been confirmed using fMRI-derived measures of effective connectivity: Greater inhibition from contralesional primary motor cortex (M1) onto ipsilesional M1 during movement of the paretic hand correlates with poorer motor performance (163). Yet, changes in interhemispheric connectivity might facilitate behavioral improvement in some cases (164). Interestingly, at rest, greater coupling of ipsilesional supplementary motor area (SMA) and M1 correlate with better motor performance of the paretic hand (163). Therefore, the neural correlates of better motor behavior may be different depending on whether a stroke patient is at rest or moving. The neural functional correlates may also be different depending on the stage of recovery (165). Reductions in corticospinal tract integrity and interhemispheric white-matter integrity are also associated with poorer outcome after stroke (166–169) and might underlie some of the observed changes in laterality of fMRI activation (170,171).

A number of factors have been found to modify the extent to which stroke is associated with a reduction in the degree of interhemispheric laterality. Examples include time after stroke, with laterality increasing toward normal as patients recover (69,96,150,152,172,173); hemispheric dominance, with motor task performance with the nondominant hand being less lateralized than with the dominant hand, in both healthy controls and after stroke (62,100,174); topography of injury, with reduced laterality being more common with a cortical, as opposed to subcortical, infarct (134,175); and greater injury and/or deficits, with reduced laterality present with larger infarcts and more severe behavioral deficits (73,152,176,177). Other factors relevant to laterality in normal subjects are also likely important after stroke, with less lateralization present with increasing task complexity (88–93), increasing subject age (146), lower task familiarity (178), and more proximal movement (179–181). One study also found that gender influenced laterality of brain activation (182).

Time is an important factor in the study of brain function after stroke, with many of the processes discussed here evolving rapidly, a finding that is likely to have therapeutic implications. Early after stroke, insulted brain areas show reduced function. Intact areas with strong connections to sites of injury sometimes show reduced function as a consequence of diaschisis. Laterality is shifted toward the nonaffected hemisphere. Over time, the shift of balance points back toward the affected hemisphere, with reduced activation in the nonstroke hemisphere and increased activation in the stroke-affected hemisphere. Some therapies have demonstrated value in increasing this shift back toward the affected hemisphere (78,81,94,106,143,144,146,156,160,169,170). The relationship between the degree of fMRI laterality and motor behavior may not change from the subacute to the chronic phase (183), suggesting that efforts to restore laterality could improve motor function regardless of time post stroke.

One principle apparent from a review of the literature is that changes in brain function after stroke for a given task are partly related to the normal functional anatomy for that task. Thus, swallowing (184), facial movement (73), and gait (185) are normally more bilaterally organized than distal extremity movements, and a shift in hemispheric balance after stroke occurs most often and with greatest clinical gains in these tasks. Similarly, movement of the nondominant hand is more bilaterally organized than the dominant hand normally, and this too remains true after stroke (100). This principle suggests the hypothesis that behaviors that are more bilaterally organized normally might benefit from a more bilateral approach to therapy. However, elegant and eloquent neocortical functions are generally highly lateralized (e.g., to the dominant hemisphere for language and fine motor skills); for these brain regions, the best behavioral outcomes are apparent when this remains true after stroke.

THERAPEUTIC INTERVENTION AND RECOVERY

Although many patients show some degree of spontaneous recovery during the months after a stroke, this recovery is generally incomplete. Restorative therapies aim to improve outcome not by salvaging threatened brain tissue but by promoting plasticity within surviving neural resources (186,187). Examples of such brain repair therapies include growth factors, cell-based therapies, antidepressants, noninvasive brain stimulation, devices such as robotics, and function-oriented physical therapy regimens such as constraint-induced movement therapy (CIMT) (44,45,129,188–201). However, there is currently no approved therapy for enhancing outcome after a CNS injury such as stroke. The maximum value of functional neuroimaging methods such as fMRI will be appreciated when used to improve application of an established restorative intervention.

One case for use of functional neuroimaging to improve application of restorative interventions is made from examining medical practice in nonneural systems. For many body systems, data on the functioning of an organ are used to inform and improve clinical decision making. Hypothyroidism is optimally treated by serial measures of pituitary–thyroid axis via serum TSH. Dosage in treatment of myeloproliferative disease and other hematological syndromes is based on serial measure of the cell population of interest. Other diagnostic approaches examine organ function before versus after a diagnostic stressor. For example, cardiac arrhythmias are sometimes treated by inducing tissue dysfunction in the electrophysiology laboratory and then evaluating the effectiveness of selected

drugs. Coronary artery disease is often assessed by stressing the heart with exercise, or with introduction of the sympathomimetic dobutamine. These practices suggest that some form of functional neuroimaging—possibly during introduction of a diagnostic stressor—might be useful for patient selection, treatment selection, or treatment dosing when introducing a restorative intervention, with the intent of modifying brain function and behavioral status.

Brain Mapping to Guide Poststroke Therapy

Some studies have already made strides in improving therapy with neuroimaging. One series of studies used fMRI to guide details of decision making during therapy (194,202). An fMRI scan was used to identify the centroid of primary motor cortex activation in patients with stroke. This information then guided neurosurgical placement of an investigational epidural cortical stimulation device. Using this approach, patients receiving stimulation plus rehabilitation therapy showed significantly greater arm motor gains than patients receiving rehabilitation therapy alone. A similar approach was used in studies that found repetitive TMS to be useful for improving motor function after stroke (193,203), in treatments that employed TMS to identify the optimal physiological representation site for hand motor function.

Brain Mapping to Predict Treatment Responses and Outcomes

The heterogeneity of stroke makes prediction of treatment responders, as opposed to nonresponders, a great challenge. The ability to predict response to therapy and prospectively separate subgroups could be useful for stratifying patients (58) to appropriate therapies to maximize behavioral gains, efficiently utilize rehabilitation and financial resources, and reduce variance to increase power in clinical trials.

Behavioral measures of motor impairment and function have been used most often to predict outcome after stroke (15), but pretreatment behavior alone is unlikely to sufficiently predict behavioral gains from restorative therapies. Several studies have used an assessment of brain function to predict behavioral response to a restorative intervention. For example, Cramer and colleagues (204) examined the ability of a baseline fMRI to predict behavioral gains. These patients each underwent baseline clinical and functional MRI assessments, received six weeks of rehabilitation therapy with or without investigational motor cortex stimulation, and then had repeat assessments. Across all patients, several baseline measures showed predictive value for trial-related gains in univariate analyses. However, multiple linear regression modeling found that, when controlling for other factors, only two variables remained significant predictors: degree of motor cortex activation on fMRI (lower motor cortex activation predicted larger gains) and arm motor function (greater arm function predicted larger gains). In the language system, fMRI activation within the right contralesional hemisphere is associated with greater behavioral gains from constraint-induced aphasia therapy (205).

In many areas of medicine, the response to a dynamic challenge is more informative than a single cross-sectional measure; the change in serum cortisol after introduction of IV ACTH is far more informative than is a single check of serum cortisol. Some studies suggest that this principle extends to stroke recovery. In two studies, early neurologic response to therapy significantly predicted long-term behavioral gains (206,207).

Recent studies have found that the motor system structure is also important for therapy response. A seminal study by Stinear and colleagues (208) generated a predictive algorithm of response to motor therapy. Although they found no predictive ability of fMRI, the structural and functional integrity of the corticospinal tract using diffusion tensor imaging and TMS, respectively, successfully predicted meaningful gains. The extent of overlap between an infarct and normal white-matter tracts descending from M1 and dorsal premotor cortex (PMd) is also a strong predictor, for example, of motor gains from a course of robotic therapy (209) (Figure 8.1). This study also highlights the importance of using a systems approach to predicting gains, as neither infarct volume (a general measure of neural injury) nor baseline behavior were significant predictors. Similar results have been found with a course of transcranial direct current stimulation plus physical therapy (210). Integrity of transcallosal fibers after stroke, as well as integrity of the corticospinal tract, may also hold predictive value (210).

These studies emphasize that an assessment of brain function or structure can be uniquely informative for clinical decision making in the setting of restorative therapy after stroke.

Functional Imaging of Treatment-Induced Recovery

The principles important to reorganization of brain function during spontaneous recovery from stroke might also operate in the setting of treatment-induced recovery. If true, brain mapping might be a useful tool to guide patient selection or choice of rehabilitation strategies, for example, by measuring the capacity of residual brain networks to respond to therapeutic challenges. In this way, such measures could serve as biomarkers of stroke recovery—one that reflects a brain event related to recovery and also correlates with the behavioral state. A biomarker of restorative therapy effects might be useful by providing a measure related to the treatment's mechanism (see Chapter 9). Differences in patients and their patterns of injury are likely associated with divergent neural responses to rehabilitation therapy. As with spontaneous recovery, functional imaging of therapy-induced recovery might be a unique source of insights. Published studies support this concept for CIMT.

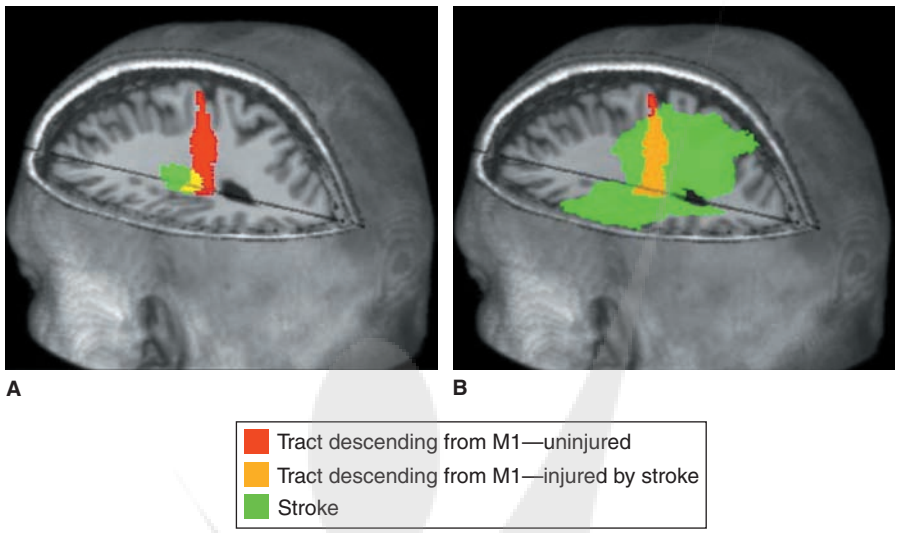

FIGURE 8.1 Examples of stroke injury to the tract descending from M1. (A) This subject had 37.5% of the M1 tract injured by stroke and had a gain of 11 points on the FM scale across the period of therapy. (B) This subject had 93.4% of the M1 tract injured by stroke and had a gain of 1 point on the FM scale across a period of therapy.

Source: From Ref. (209). Riley JD, Le V, Der-Yeghiaian L, et al. Anatomy of stroke injury predicts gains from therapy. *Stroke*. 2011;42(2): 421–426.

CIMT (211) is an approach to improve motor function that is effective in producing enduring motor gains in eligible patients in the setting of chronic (197), subacute (212), or acute (213) stroke. A range of functional neuroimaging methods, including EEG, fMRI, and TMS, have demonstrated changes in brain function that parallel treatment-related motor gains (214–219). Changes in brain function after CIMT include altered motor excitability, a shift in activated brain areas, a change in motor system interhemispheric laterality, and an increase in affected hand motor representation area (220,221). Importantly, cortical changes with therapy are likely to be specific to the training elements of the therapy. For example, a study of robotic therapy found that activation volume increased for a task that was part of the training, whereas activation volume did not increase during a task that was not part of the training (222) (Figure 8.2). In general, studies have typically diverged as to whether increased activation with CIMT is primarily in the ipsilesional or contralesional hemisphere (223).

The divergence in findings likely reflects differences in patient characteristics. For example, in chronic stroke patients, successful CIMT was associated with reduced interhemispheric laterality in a study of weaker patients (215) and increased laterality in a study of less impaired patients (219). A recent study found that patients with poorer baseline motor behavior and the largest behavioral improvements had the largest increases in ipsilesional sensorimotor cortex activation (224). However, whether the effect of a restorative therapy is beneficial or potentially maladaptive may also depend on the patient's baseline level of impairment (225). Greater injury to the corticospinal tract also affects treatment-induced cortical plasticity (224,226). Activation changes with therapy may also depend on intracortical excitability (227). Understanding these differences might be important when using functional imaging as a tool to guide poststroke rehabilitation therapy.

Motor Learning and Plasticity

Application of rehabilitation therapies might be improved if based on models of patterns of brain plasticity seen in healthy subjects. For example, some authors have drawn a parallel between brain events related to learning and those underlying rehabilitation-based motor gains after stroke (228). Motor learning theory is particularly important to the clinical application of poststroke therapies, such as CIMT, given that a goal of these approaches includes improved performance and retention of new motor skills. Studies of motor learning provide insights into the brain events underlying acquisition or refinement of movement skills, for example, with activity shifting from cortical to subcortical (229–232) or cerebellar (233) areas. Such changes can be short term (230,234) or long term (235), with both measures being potentially important to understand how structures of the brain motor system store kinematic details induced by motor training.

Implicit motor learning is an approach that might be particularly valuable for subjects with stroke, given the frequency with which concomitant deficits could impair explicit learning such as CIMT (236–240). It has been suggested that

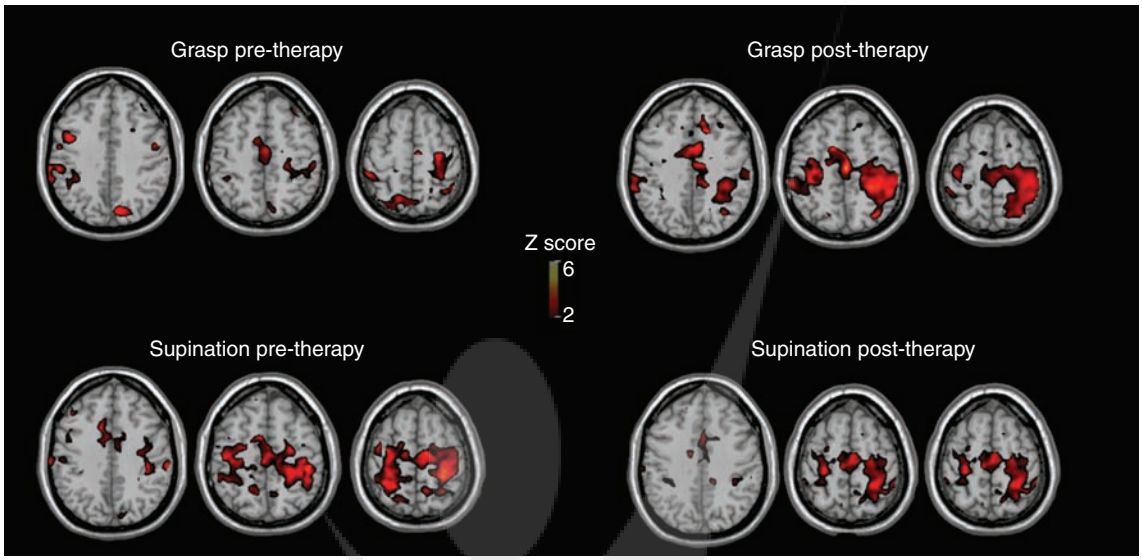

FIGURE 8.2 The grasp task that was central to therapy showed significantly increased activation volume over time within the left (stroke-affected) primary sensorimotor cortex, whereas the nonpractice supination task did not. This change in grasp task activation volume was not accompanied by a change in task-related EMG, suggesting that its basis was altered brain organization rather than altered subject performances.

Source: From Ref. (222). Takahashi CD, Der-Yeghiaian L, Le V, et al. Robot-based hand motor therapy after stroke. *Brain.* 2008;131(pt 2):425–347.

improved implicit learning is associated with decreased PMd activation and greater superior frontal cortex activation, findings not seen with such learning in healthy controls (241). These findings emphasize that the mechanisms of behavioral improvement will likely differ according to the nature of the restorative therapy.

Gray matter changes with learning, and treatment can be structural as well as functional. In healthy subjects, training on a dynamic balancing task increased gray-matter volume that correlated with the degree of behavioral improvement (242). Such studies are limited in stroke, but a study of CIMT administered to chronic stroke patients found a bilateral increase in sensorimotor cortex and hippocampi that was not identified in control subjects (243). Importantly, the volumetric increases correlated with the extent of increased use of the affected arm.

Abundant preclinical research indicates that white-matter structure and integrity are important to achieving behavioral gains with restorative therapies after stroke. However, this issue has been much less examined in human subjects. Studies of motor learning in healthy subjects have also elucidated some of the structural changes that occur in parallel with functional changes. Several examples of changes in white-matter integrity in parallel with training-induced behavioral gains have been described in healthy subjects (244–247). Recently, noninvasive cortical stimulation was found to alter white-matter integrity in chronic stroke patients with aphasia (248).

Considering the spectrum of functional and structural changes that occur in response to restorative therapies, multimodal neuroimaging studies are of high value, for example, because functional and structural changes can co-localize (242,244,249).

EMERGING CONNECTIVITY METHODS TO STUDY CORTICAL FUNCTION DURING STROKE RECOVERY

Newer methods have enabled researchers to move beyond fMRI activation metrics, such as percent signal change and activation volume, to evaluate cortical function as part of a network. Techniques such as resting-state BOLD MRI, EEG, and MEG can be used to provide estimates of FC, which can assess lesion effects on neural coupling across networks near the infarct and remotely (55) in ways that are more limited with traditional fMRI studies. Serial imaging of FC has the potential to unlock how stroke treatments alter functional connections between brain areas and how those changes are related to behavioral gains. Resting-state FC, reflective of neural coupling in the absence of active task performance, is an attractive means to evaluate network changes in clinical populations such as stroke because the patient does not need to perform a task. As such, the effect of task-related motion is minimized, and such motion is common during scanning of subjects with impaired motor control, producing substantial motion artifact in fMRI images. Increases in resting-state FC among several networks have recently been found to positively correlate with gains from both robotic and motor imagery training (250). Another measure, that of effective

connectivity, evaluates not only changes in the temporal correlation of activation between regions after stroke, as is done with FC, but also the strength and directional influence of one brain region on another.

Using connectivity measures to predict gains from restorative therapies has received limited study but is promising. Studies of spontaneous stroke recovery suggest that these connectivity measures will have predictive value. Such relationships may differ, however, when patients are examined in relation to introduction of a restorative therapy. Greater behavioral recovery from stroke is predicted by MEG- and fMRI-derived measures of resting FC within bilateral brain regions (251,252). Reduced effective connectivity from secondary ipsilesional areas onto ipsilesional M1 during a motor task has been found to correlate with recovery (165). Resting-state FC between ipsilesional M1 and several contralesional areas obtained near stroke onset positively correlates with motor improvement six months later (164). Recent findings encourage the use of such additional measures to probe functional changes across the brain during stroke recovery.

FUTURE STUDIES

The use of functional imaging is shifting from being employed primarily to study spontaneous recovery in a cross-sectional manner to longitudinal studies aiming to predict, and to evaluate mechanisms of, therapy-induced behavioral gains in a clinical trial setting. Despite advances, some key limitations still exist. Many of the studies to date have examined patients in the chronic phase. However, the brain is most primed to respond to treatment in the early days after a stroke (190,253,254). Therefore, further studies of predictors and biomarkers in the early days following stroke onset are critically needed. Also, many studies have enrolled patients with relatively mild impairments and those with subcortical infarct (255,256), but studies of the full spectrum of stroke-related deficits are needed to best understand the value of neuroimaging measures in this setting.

Evidence suggests that measuring brain function is useful for defining features of poststroke restorative therapies. A better understanding of the underlying neurobiological principles related to therapy-induced behavioral gains will likely improve this approach, and thus maximize gains derived from restorative interventions that aim to promote brain repair and thereby minimize impairment and reduce disability after stroke. A multimodal approach that incorporates measures of function and structure might provide the richest perspective on these issues.

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9

Anatomical and Physiological Predictors of Recovery

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GOALS OF BIOMARKER RESEARCH

Research in stroke rehabilitation is now actively testing new and more effective treatments, but is hampered in these endeavors by the complexity of primary outcome measures. It is acknowledged that the most important outcomes are those that affect quality of life and participation in society. However, it is unlikely that an intervention with effects on biological structures will have immediately measureable results at such a high level of analysis. To make this concrete, if we had an intervention that could reliably improve speech intelligibility by 20%, would we also find reliable changes in participation in family interactions? There might be other factors changing during the course of the study that would have an impact on the same high-level measure. But if we had a good measure of intelligibility and a mechanistic explanation for how the intervention improved it, then the intervention should be considered promising even if there were no significant changes at the level of participation.

The concept of a biomarker is, in some ways, a collection of old ideas under one label. The official National Institutes of Health (NIH) definition of a *biomarker* is "a characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention" (1). The biomarker is in one sense a substitute (or surrogate) for a clinical outcome that is too difficult or too remote in time to measure, and in another sense an indicator of a biological mechanism relevant to the intervention. The use of a surrogate can be problematic when there are other factors, which are important to the real outcome, that are affected by the treatment but not measured by the biomarker. This has led to actual problems in clinical trials and is an issue well worth considering in the choice of a biomarker in a field such as stroke recovery, which has a wide heterogeneity in the disease expression.

This has posed significant challenges in stroke rehabilitation research because there is no equivalent to the simple biomarkers used in many other fields, such as blood pressure, tumor size, or blood count. The development of biomarkers in stroke recovery is needed before studies can be as streamlined as in other fields of medicine. Work on biomarkers will have an added benefit of exploring the mechanisms underlying stroke recovery. In one sense, the mechanistic work of the past few decades has set the stage for the establishment of biomarkers in this field. This chapter reviews the work that has been done and makes some suggestions for the future use of biomarkers in stroke-related clinical trials.

Idea of Prediction

Although prognosis in stroke is an active area of research, issues of predication are sometimes ignored when new rehabilitation methods are developed. The ability to predict outcome, based on measures during the acute phase, has been recognized as having important implications in decisions regarding discharge planning and beyond (2). In one sense, biomarkers are already used in a practical way to generate discharge dates, although generally in a heuristic manner. That is, the impairment, age, social situation, and other factors collected on admission to inpatient rehabilitation are used to predict a date of discharge when the patient is expected to make a safe return home, or else reach a plateau that will necessitate transfer to a new setting.

Prediction of outcome is also very useful when considering interventions. Therapeutic approaches and techniques vary, and some may be more effective than others for particular patients. Newer rehabilitation approaches consist of focused types of task practice or neuromuscular stimulation, and often represent a significant commitment of time and expense. A set of biomarkers associated with good response to a particular intervention would allow these treatments to be targeted to those with expected outcomes, while saving predicted nonresponders' time and third-party payers' expense.

Correlation With Recovery

If a biomarker were to correlate with function, it would also be useful as a surrogate marker for recovery. That is, if function changed over some time interval, whether or not because of an intervention, then the biomarker would

change and the changes would be correlated with recovery. Conceivably that biomarker would be useful as a measure in clinical trials. It would be less useful in practice, given that it is actually function that we care about; no biomarker, however good, would substitute for real-life function. But during the course of treatment, if the biomarker were easier to obtain than a functional measure, it could help guide treatment, with decisions on therapeutic methods made on the basis of changes in that biomarker. An example would be surface EMG as a measure of specific muscle recruitment. If upper extremity function correlated strongly with specific activation of wrist flexors and extensors, then a metric of voluntary activation (and lack of coactivation) could be constructed as used on a daily basis to measure progress. If a particular rehabilitation treatment began to plateau for this metric, then a rational decision could be made about another intervention.

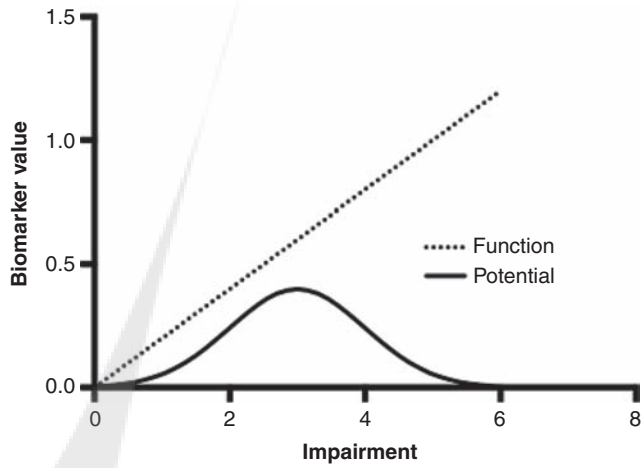

FIGURE 9.1 Two types of biomarkers in stroke recovery.

Motor Focus

This chapter deals mainly with biomarkers useful in rehabilitation of motor function, because this has been the primary focus of research in this field. Motor function has the advantage that it is relatively easy to measure with the cooperation of the patient. Of course, a patient may not understand the instructions in a motor task, may not give full effort, or may have other limitations in movement related to medical condition. In such a case, a biomarker could be useful. Such a biomarker would not have to depend on effort (unlike the preceding example of surface EMG activation) but could include something like white-matter tract integrity as measured by diffusion tensor imaging.

The Ideal Biomarker in Stroke Recovery

Would Help Define Normality. Because normal form and function are the goal of rehabilitation, it is no surprise that the ideal biomarker would have normal values in those patients most likely to recover normal function. Thus, there are two main classes of biomarkers useful in rehabilitation: (a) *functional* and (b) *potential*. The functional biomarkers correlate with function, whereas the potential biomarkers correlate with capacity to improve function.

But Normal Form and Function Are Possible Only in the Smallest Lesion. The functional biomarker would be close to normal values in only the smallest lesion, whereas the potential biomarker would likely have a bell-shaped distribution because of ceiling effects on one side, and substrate effects on the other (Figure 9.1). That is, there is no potential to recover in the undamaged situation, whereas large bilateral lesions would reduce the likelihood of meaningful recovery. So the potential biomarker would provide some insight into the substrate for recovery, namely the spared brain tissue that can participate in restoration of lost function. This situation is likely to be dynamic for the first several weeks or months after stroke (3) and related to functional status, so the potential biomarker will likely have to include input from both time and functional data.

Even if such a biomarker worked for recovery with usual clinical care and experience, it might not predict response to an experimental treatment. This results in a very complex situation in which many potential biomarkers may be associated with different prediction algorithms depending on:

1. Time
2. Functional status
3. Type of functional outcome being sought (e.g., general independence vs. specific impairment)
4. Type of intervention

ANATOMICAL MARKERS

Lesion Volume/Location

One of the most obvious biomarkers in stroke is the characterization of the lesion itself in location and extent. Yet lesion size is less useful than initial functional ability in terms of predicting outcome (4). Lesion location and the disruption of key areas for a function are most important—for example, the corticospinal tract and its impact on motor function or the dominant hemisphere perisylvian regions in language. Although there is likely to be a strong relationship between the amount of damage to these key regions, techniques are not yet available to allow good clinical correlation; however, there is some recent promise in this area (5). This may be because of variations in individual, structural, and functional anatomy. So, though the promise of imaging-based prognosis and prescription of therapy remains, it is a long way from reality.

Focus on the Corticospinal Tract

In the motor system, the corticospinal tract is the final common output from the cortex for movement of the distal extremities. There are other projections from the cortex that can produce movement, including corticorubral and corticoreticular projects. Of course, for movements of the face, it is more accurate to speak of the corticobulbar tract, because the lower motor neurons are in the brainstem. Studies have shown a relationship between number of corticospinal fibers and motor outcome (6). In the field of cerebral palsy, there has been a demonstration that anatomic assessment of the corticospinal tract is related to motor function (7) and that response to an intervention depends on physiological assessment (8).

Fractional Anisotropy as a Measure of White-Matter Integrity

Fractional anisotropy (FA) is a measure derived from diffusion tensor imaging. If water were equally free to diffuse in all directions, it would imply that there is no orientation of barrier (such as myelin sheaths) to diffusion. That would be a situation of complete isotropic diffusion. But when nerve fibers are oriented in a single direction, then water can diffuse most easily only in that single direction, and the anisotropy measure approaches 1. Whereas the relationship of myelination to FA values is baffling, in general FA has become synonymous with white-matter integrity.

FA as a Predictor of Response to Therapy

While FA is correlated with function, it also appears to predict response to treatment, perhaps by indicating that there is sufficient substrate to respond. Despite it being a white-matter measure, it may be more accurate than gray-matter measures because it better shows functional output and connectivity. An increase in FA value (or decrease in mean diffusivity) may occur after rehabilitation, and as such may serve as a potential biomarker for response to therapy (9,10).

Tractography

The data acquired from a diffusion tensor image (DTI) may be used to trace white-matter fiber tracts from one region to another. This technique, with the obvious name of "tractography," relies on the principle that axons tend to bundle when they are headed to the same place. They also tend not to take sharp turns, so a path can be inferred by following the main orientation of axons from one voxel to the next. Needless to say, the assumptions of bundling and smooth pathways can be violated, and automated methods to trace pathways may fail. However, this is an active area of research and continual improvement in methods for probabilistic tracing have overcome some of these limitations. But to have a chance of tracing a tract, the source images must contain precise measures of diffusion in many different directions. These high-quality scans can take up to 30 minutes.

Tractography can generate attractive and clinically useful images, but can also be used for quantitative measures. Therefore, the number of intact fibers in a tract can be estimated and then serve as a biomarker. Although it seems that increases in tract size would be unlikely in the adult human brain, recovery and experience do affect DTI measures. This may be because of a trophic relationship between activity and both myelination and axon size.

Another problem specific to the use of tractography as a biomarker is the effect of brain lesions on DTI data at the site of the lesion. In a very acute stroke, edema, blood, and other structural changes because of damage can reduce or even eliminate the ability to trace a tract through an injured region.

PHYSIOLOGICAL MARKERS IN MOTOR RECOVERY

The field of stroke rehabilitation is ultimately focused on improving quality of life and function, with rehabilitative efforts dependent on a strong understanding of the functional deficits that have underlying biological mechanisms (11). Anatomical markers have appeal because of their potential objectivity, sensitivity, and reliability, but of course they cannot address function directly. Alternatively, understanding the functional deficits, at best, provides speculation as to the biological underpinnings. A number of physiological measures have been tested for their relationship to function and recovery, and this section describes some of them.

Transcranial Magnetic Stimulation

Transcranial magnetic stimulation (TMS) is a technique that noninvasively stimulates brain regions and therefore is an excellent complement to methods that measure either anatomy or activity. It can evoke measureable outputs, such as limb movement, or transiently interfere with function in a specific brain region. In this way, it can both test *sufficiency* (ability to be involved in a function) and *necessity* (requirement for activity for that function).

Brief Introduction to Method

TMS uses pulsed magnetic fields to induce electrical fields in excitable tissue. In practice, this is accomplished with electromagnets with discharge of a high voltage into copper coils. The technique has been around for more than a century, but the development of high-voltage, silicon-controlled rectifiers has made possible compact, nonarcing devices that could be used in clinical and nonclinical settings. Some of the earliest uses have included stimulation of the visual cortex with inducement of phosphenes and stimulation of the motor cortex with induction of muscle activity.

MEP Presence and Recovery

One of the most basic measures in TMS is the motor evoked potential (MEP). The MEP is the electrical analog of

TMS-induced muscle activity caused by excitation of muscle fibers. Thus, it is a rather *indirect* measure of the upper motor neuron activity caused by TMS in the motor cortex, but it is more sensitive than measurement of movement, as a small amount of electrical activity may occur in the muscle without visible movement. Almost all normal individuals will have MEPs in distal upper-extremity muscles. The presence or absence of MEPs after stroke in such muscles is therefore a measure of damage to the motor system. Absence of MEPs in the affected upper limb within the first weeks of stroke correlates with poor recovery of arm and hand (12). Return of MEPs in hand muscles was associated with return of hand function, but as these authors noted, there was no such correlation between return of MEPs and return of movement in proximal arm muscles. This may be because of more mixed cortical/subcortical control of proximal upper limb muscles, or to the related fact that MEPs are not as reliably measured in some more proximal muscles. A meta-analysis reported strong evidence that the presence of MEPs is associated with better arm recovery, with at least 15 of 20 studies reporting significant associations (13).

Beyond the absence or presence of MEPs, MEP peak-to-peak amplitude is an objective metric that represents response of the corticospinal tract to stimulation at a particular intensity (Figure 9.2). The amplitude is considered in relation to the relative stimulation intensity or the change in amplitude as a function of increasing the stimulation intensity. This latter approach, known as the *recruitment curve* or *stimulus response curve*, is determined by measuring MEP amplitude with increasing stimulation intensity. Generally, MEP amplitude will increase as stimulation intensity increases to a point where a plateau is reached. Thus, these curves have a sigmoidal shape. The slope is considered to represent changes in synaptic excitability, with a steeper slope occurring as greater changes in MEP amplitude correspond to an increase in stimulator intensity. As a result, this slope can be considered as a measure of the integrity of the motor system and a potential indicator of recovery, with a steeper slope signifying that a greater number of upper motor neurons were recruited with lower stimulation intensity, that is, the motor system was more responsive or excitable to the stimulation. One of the inherent challenges with interpreting the slope of the curve as a potential indicator of recovery arises because the slope can be calculated by various mathematical methods such as a linear slope and a nonlinear, sigmoid function, and these two methods can be quite different (14). In addition, if not enough points on the curve are measurable to calculate a slope, the use of a recruitment curve as a marker for recovery can be limited. This suggests that use of the recruitment curve as a biomarker is limited to those survivors of stroke who have MEPs, and that it is better suited for distal muscles compared to more proximal muscles, similar to the presence or absence of MEPs proximally versus distally (14,15). Quantifying MEP amplitude provides a sensitive measure (16), but is useful only if MEPs are present in survivors of stroke. Thus far, recovery-related changes in recruitment curve have not been examined, and rehabilitation-related changes have not been found (17).

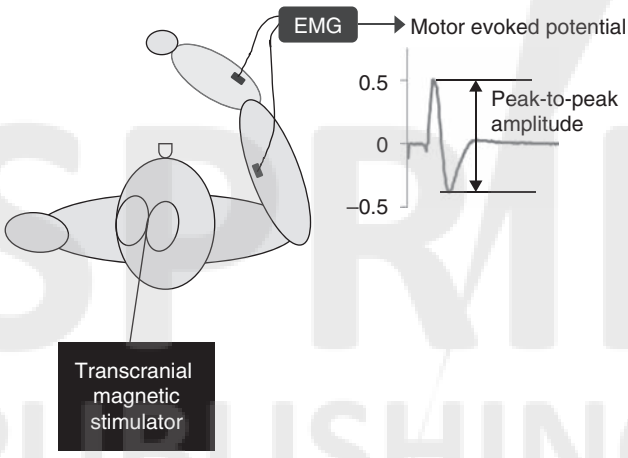

FIGURE 9.2 Schematic of TMS setup. The TMS is applied to the motor cortex with the motor evoked potential recorded by an EMG system. One of the most common metrics recorded is the peak-to-peak amplitude of the motor evoked potential.

Central Motor Conduction Time

Although most TMS studies in the motor system gauge the amplitude of the muscle response, it is possible to estimate the time for conduction within the upper motor neuron. This is done by measuring the difference in latency between TMS of the motor cortex and stimulation of the motor root, generally by magnetic stimulation over the spine. Whereas the latency difference includes somewhat more processes than conduction of the action potential from axon hillock to synapses of the upper motor neuron (UMN), peripheral nerve conduction time is effectively removed, and the resulting central motor conduction time (CMCT) can be used as a measure of central axon action potential velocity. This measure is used clinically in multiple sclerosis and cervical myelopathy to measure local or diffused demyelination and damage.

In stroke, the measure has been used to demonstrate the natural history of motor recovery, with abnormally slow CMCT increasing over time in some individuals (18) and slow CMCT indicating an intermediate progress between those with absent MEP (poor) and CMCT (good) (19). While CMCT has been suggested as a useful prognostic indicator (20), there has been little use over the past decade. This may be because its measurement is limited to patients with MEP, a category that already has a better prognosis, whereas other measures such as MEP size or recruitment curve slope offer an assessment of UMN health similar to that of CMCT.

Silent Periods

The *silent period* is the time during which voluntary lower motor neuron (LMN) activity is suppressed after stimulation of the motor cortex (21,22). Operationally, a silent period is

measured by asking for activation of a muscle at a constant and defined level followed by delivery of suprathreshold stimulation of the motor cortical representation of that muscle. The EMG response will show a MEP followed by absence of activity for several milliseconds, followed by resumption of activity, often with high levels of activity at first. The definition of the silent period, in the simplest form, is the duration in milliseconds from the stimulating pulse to the resumption of activity. But interpretation is complicated by technical issues, such as incompleteness of suppression, and the fact that the earliest part of the silent period is dominated by recurrent spinal inhibition. The first problem is how to handle a single motor unit that appears as an "island" during the silent period. This can be addressed by measures that reflect the loss of activity caused by stimulation, not just the period of complete silence. The second problem (that of recurrent spinal inhibition) does not generally require special consideration, because TMS results in a longer silent period than more direct methods of corticospinal tract stimulation, suggesting that it is more effective at activating cortical inhibitory interneurons. Therefore, the TMS-evoked silent period may be a good measure of the state of intracortical inhibitory networks.

After a stroke, the silent period is usually asymmetric, most often prolonged on the affected side but rarely shortened (23,24). Longitudinal studies have shown a predictive value of the relationship between voluntary activation and silent period duration, so that when the silent period was lost with voluntary activation, poor recovery was more likely (25). Other investigators also showed a gradual shortening of silent period duration over time, correlated with clinical recovery (26). Acute studies have been less positive about the prognostic value of the silent period (27) and silent periods do not appear to be affected after transient ischemic attack (TIA) (28).

In summary, the silent period is a sensitive measure of intracortical inhibition that may be most useful for prognosis in more mildly affected subjects. The general consensus is that the silent period, prolonged after stroke, also suggests that excess inhibition is a direct consequence of ischemia to the corticospinal system, and that reduction in inhibition is part of recovery.

Ipsilateral Silent Period. A different type of silent period is measured with stimulation to the motor cortex ipsilateral to the activated muscle (Figure 9.3). In the case of a stroke

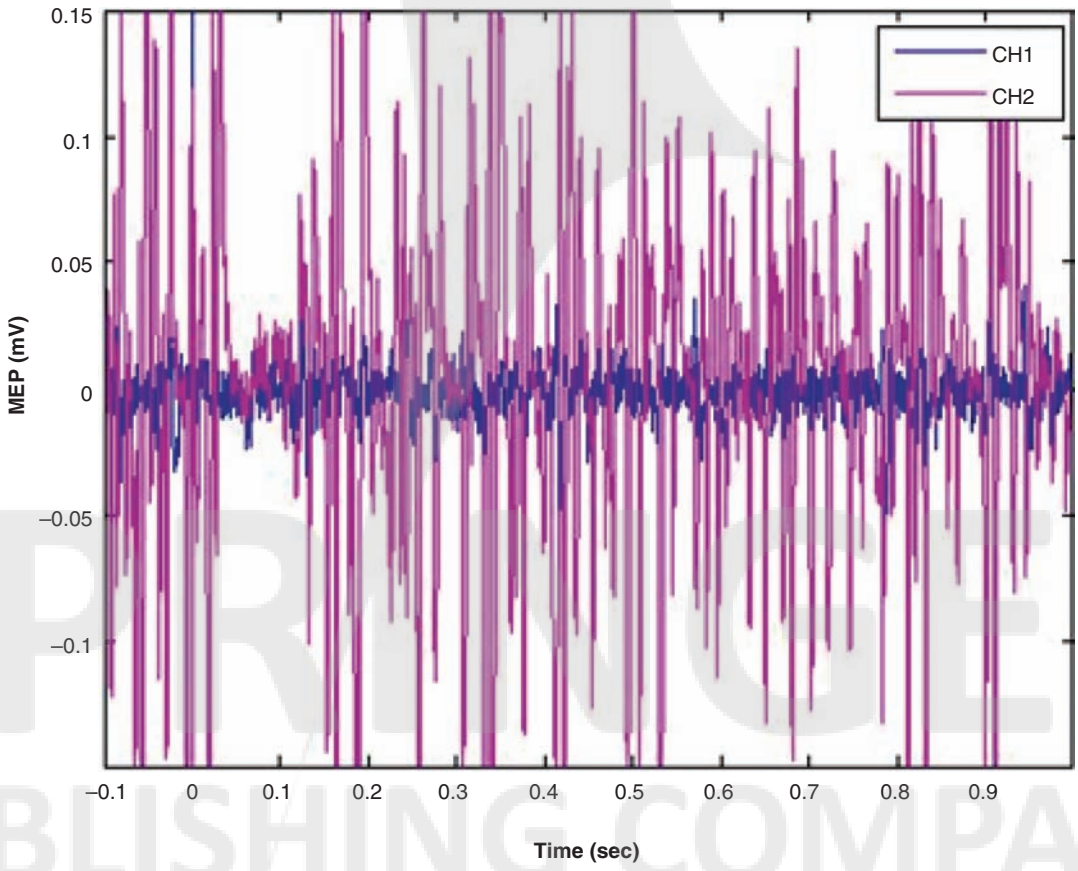

FIGURE 9.3 Ipsilateral silent period in a chronic stroke patient. Voluntary motor activity is present in a finger extensor (channel 1) and biceps muscle (channel 2) in the affected hemisphere prior to stimulation of the unaffected hemisphere, at time = 0. *Note*: reduction in activity for >100 ms after stimulation.

patient, this would mean stimulation of the unaffected cortex with activation of the affected side. Such a silent period is called "ipsilateral" and reflects contralateral interhemispheric inhibition. It has an advantage in that it more directly tests the inhibitory effects of interhemispheric connections (rather than a mix of inhibitory influences that operate intracortically). One disadvantage is that the level of inhibition is often not as complete as with the contralateral silent period. In many cases of stroke, stimulation of the unaffected side will result in an ipsilateral MEP, in which case the silent period no longer represents a purely interhemispheric phenomenon.

The length of the ipsilateral silent period has been shown to be proportionally related to impairment in a moderately affected range; training-related improvements are associated with reduction in duration (29).

Problems With Silent Period Interpretation. Because the silent period depends on voluntary activation, which is often difficult after stroke, the measure may have a very different meaning in severe cases, where voluntary activation through cortical mechanisms is poor. In our experience, ipsilateral silent periods are often absent in severely affected subjects, defined as those with absence of MEP following stimulation of the lesioned hemisphere. This is perhaps not surprising, except that many of these subjects can voluntarily activate the target muscle as part of a synergy pattern. However, synergistic activation may result from subcortical output that is not subject to cortical inhibition. In the right range of subjects, both types of silent period measurement appear to be methods that are related to both impairment and recovery. They have the advantage of requiring only a single TMS stimulator as well as a method to standardize voluntary motor activation. Further work is required to develop the silent period biomarker and evaluate it as a measure independent of impairment.

Paired-Pulse Inhibition and Disinhibition as a Recovery Mechanism

Recurrent inhibition, negative feedback through inhibitory interneurons, is a common theme in neural systems. It may serve several purposes, including preventing runaway excitation, such as might lead to seizures; and sharpening responses in time and space. While recurrent inhibition is a feature of systems that are functioning normally, it presents an opportunity for plasticity in that disinhibition can enhance function of intact areas to compensate for damaged ones. This is analogous to removing a car's muffler when the engine has lost a cylinder. Although you may get back some power, it will have other undesirable effects.

Disinhibition following injury to the brain can be studied using TMS. Stimulation of the motor cortex induces inhibition to further stimulation with a particular time course. Although most studies have examined the phenomenology of such *paired-pulse* stimulation, a variety of evidence demonstrates that short-interval (2–5 ms) effects are because of cortical GABA-B interneurons, and the phenomenon is thus termed SICI, for short-interval cortical inhibition. SICI is affected by pharmacological interventions and is strongly affected by stroke, with a dynamic course after the initial insult (30) eventually resulting in less inhibition in the affected hemisphere (31).

Though inhibition appears to be an important factor that is affected by both stroke and stroke recovery, it has several features that lessen its attractiveness as a biomarker. Measurement of paired-pulse inhibition requires more equipment and adjustment of parameters, making it more difficult, time consuming, and operator dependent. Furthermore, in severe stroke MEPs cannot be elicited with paired-pulse stimulation, making measurement of inhibition impossible.

Response to Stimulation of Nonprimary Areas, Unaffected Hemisphere

The primary motor cortex, M1, is not the only source of input to the contralateral lower motor neurons. Other, predominantly frontal, cortical areas project to the spinal cord, although many of these projections are on spinal interneurons that then synapse with spinal motor neurons. The potential role in motor recovery for the nonprimary motor areas, such as the premotor area and supplementary motor area, has long been recognized (32). Elegant studies have shown that these areas have a key role in voluntary movements after stroke.

Although TMS can be used to stimulate nonprimary cortical areas and the cerebellum, the measures do not have characteristics of good biomarkers. Often the effects are in the context of voluntary or TMS-evoked motor output, and require precise coil placement and timing. However, this work is an active area that promises to elucidate mechanisms of recovery.

There are also spinal projections of brainstem areas, including the pontine reticular formation. The role of these areas in recovery of function is being actively investigated. While once thought to be related mainly to posture and proximal movement, they appear to play a role even in finger movement (33), as well as in reaching (34,35). It is a familiar finding after stroke that voluntary movement of the upper limb is limited to a flexion synergy pattern, and these muscle synergies may be modulated by postural interventions (36) that likely originate from reticulospinal neurons. One method for studying the output of the reticulospinal system noninvasively is the acoustic startle. However, it cannot be assumed that all motor output from a startle comes directly from reticulospinal pathways, as there are reticulocortical connections as well (37,38). Thus far, the acoustic startle response has not been developed as a biomarker for recovery.

EEG/MEG

Electroencephalography (EEG) is one of the oldest techniques for measuring brain activity noninvasively. The principle is simple: electrical currents in the brain cause electrical potentials in the scalp, although the size of these potentials is reduced by the resistance of the head and the filtering properties of the brain, CSF, and other cranial contents.

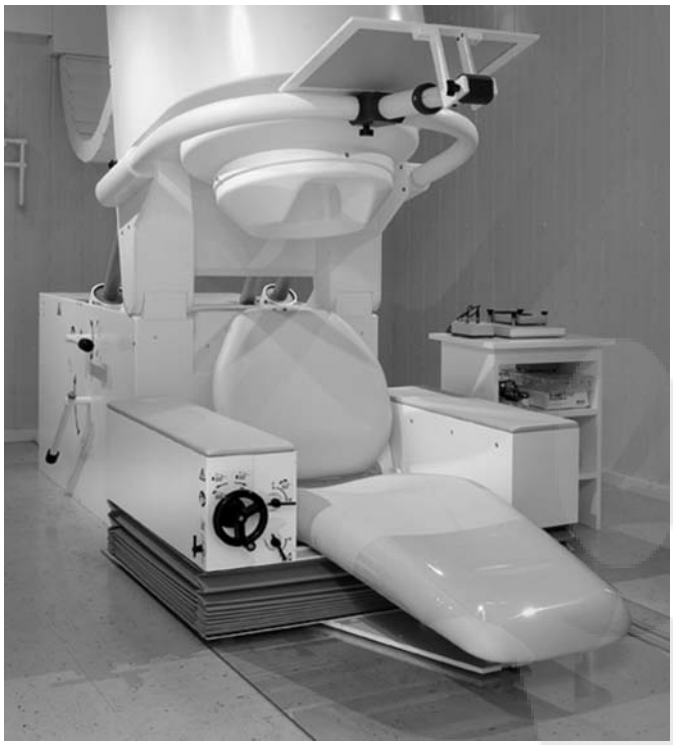

FIGURE 9.4 275-channel biomagnetometer (MEG) that measures the magnetic fields generated by neuronal activity of the brain. The magnetic fields are then analyzed to determine the neural sources in the brain and are then superimposed on an MRI image. Brain recordings can be obtained while an individual is seated or supine.

Photo courtesy of MEG International Services, Ltd, Coquitlam, BC, Canada.

This leads to problems with localization in space, and brain activity is not recorded equally by surface electrodes. Magnetoencephalography (MEG; Figure 9.4) is another way to record electrical activity. Because MEG is sensitive to the magnetic fields generated by electrical currents in the head, the skull does not present much of a barrier. However, it still has limitations in that electrical currents in the brain are not represented equally in the magnetic fields at the scalp surface, and some currents may not produce measurable potentials at all.

EEG

The late Joseph Green was a pioneer in the use of high-resolution EEG to study changes in the motor system after stroke and spinal cord injury (39,40). However, these studies were not conclusive with respect to changes in timing of motor-related potentials, but they did show changes in localization consistent with functional imaging. Later studies also showed a correlation between NIH Stroke Scale and an index of resting EEG activity called the delta-change index (41). The advantage of this method is that it does not require high-resolution electrode arrays and does not depend on motor performance. These findings have, so far, led to little work on a practical EEG biomarker for impairment or responsiveness to rehabilitation. In aphasia, a correlation has been noted between slow wave activity and function (42), and recovery has been related to changes in alpha location (43).

The promising aspect of EEG is its applicability to almost any patient and setting. Although spatial localization is inherently limited, as mentioned earlier, the potential to use time and frequency domain information does offer something different from other functional imaging methods.

MEG

Given the spatial limitations of EEG, alternate neurophysiological techniques are surfacing as potentially more precise measurements of the millisecond temporal coherence between brain regions. Such insights into the spatiotemporal propagation of neural signals can broaden the understanding of restorative mechanisms. MEG is a tool used to evaluate the timing and, in turn, the hierarchical role of brain regions with respect to the onset of movement. In addition, MEG can be used to produce a spectral profile of rhythmic neural activity and more accurately describe modulations in resting-state networks. For example, functional connectivity is greatest in somatosensory, visual, and language cortex within the alpha frequency band in healthy subjects (44). Within the sensorimotor network, activity in a combination of primarily low-frequency bands has been found (45,46). Therefore, assessing shifts in bandwidth representations may provide an additional important biomarker for the pathophysiological mechanisms of recovery after neurological insult.

Resting-state functional connectivity has also been proposed as a useful biomarker of sensorimotor impaired brain states, such as in Parkinson's disease (47,48), amyotrophic lateral sclerosis (49), multiple sclerosis (50,51), and brain tumors (44). Evaluating the dynamics of neural networks in a task-free model provides valuable information about the intrinsic function of the brain and can account for variation in motor performance. MEG studies provide hints of a disrupted local resting neural network after stroke, with abnormally increased activity in the delta and alpha frequency bands of acute perilesional areas (52,53). The value of functional connectivity within a widely distributed network, both local and remote to the stroke lesion, has also been identified. In particular, motor recovery was found to be predicted by increased connectivity in the ipsilesional somatosensory area, supplementary motor area, and cerebellum, contrasted with reduced connectivity of contralesional motor regions, after controlling for age, stroke onset time, and lesion size (Figure 9.5). These findings define brain regions in which the extent of network participation may become an important surrogate marker to identify poststroke recovery potential (54).

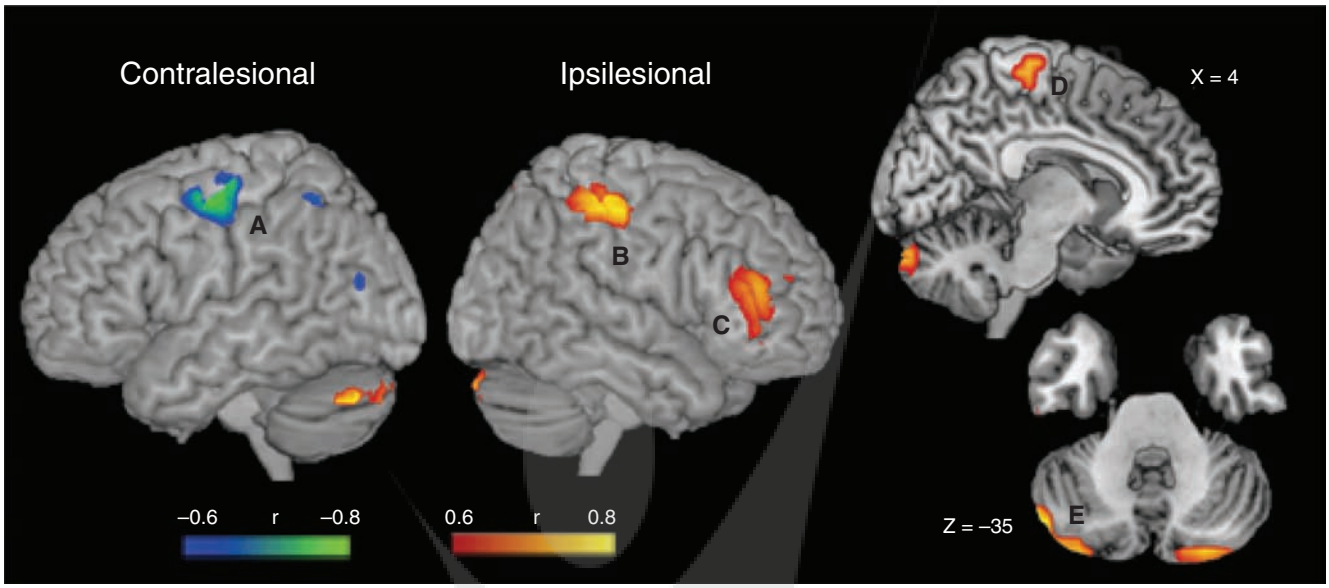

FIGURE 9.5 Predictive value of resting-state functional networks using MEG. Brain regions of neural networks at 1-month poststroke demonstrated positive (orange–yellow) and negative (blue–green) correlations with clinical recovery of the affected upper extremity by 6 months after stroke. A, B: sensorimotor cortex; C: prefrontal cortex; D: supplementary motor area; E: posterior cerebellum.

Source: From Ref. (53). Westlake KP, Hinkley LB, Bucci M, et al. Resting state alpha-band functional connectivity and recovery after stroke. *Exp Neurol.* 2012;237(1):160–169.

EEG/MEG Motor Coherence

The measurement of *coherence*, which is a normalized measure of correlation between each frequency band of a time-varying signal, is helpful in determining the causal role of one signal to another. This is because the phase relationship of the two signals is also determined. If the power in a particular band in one signal reliably precedes that of another, there is likely to be either a causal role for the first signal or at least the presence of a common driver for both. The most relevant measure in motor rehabilitation is motor cortex–muscle coherence (55). This is a relatively new measure, first demonstrated in epileptic patients, using electrocorticography, then in normal subjects with MEG, and finally in EEG. Although this connection involves at least two synapses (UMN-LMN and LMN-muscle), demonstration of temporal coupling between EEG signals from M1 and EMG, with the M1 signal leading the EMG, presents a strong suggestion of the causal role of M1 in muscle activation. This has been used to demonstrate the role of the nonlesioned hemisphere in movement (56).

In general, coherence can be used to suggest connectivity between brain networks (57), and a number of studies have used this measure after stroke and in response to rehabilitation (58,59). However, it is still essentially a research method, with its mechanisms and utility as a biomarker as yet unestablished.

PET/fMRI

Brain imaging techniques that are sensitive to functional activity have been used for a few decades to demonstrate brain activity during task performance. The data that they generate is, in a sense, easier to interpret, as activity is localized in particular brain regions and in the context of a defined activity. The temporal resolution of such techniques is in general poor, and high noise-to-signal ratios necessitate the discarding of much temporal information observed. Two main techniques utilized are positron emission tomography (PET) and functional MRI (fMRI). Though the basic principles underlying these imaging techniques are unrelated, they both may be used to detect the increase in blood flow that occurs with brain activity. PET uses the infusion of water labeled with oxygen-15, and in MRI flow changes are inferred from changes in the blood oxygenation level dependent (BOLD) signal. Therefore, the MRI measure is more indirect because it is not the blood flow itself that is detected, but the increase in oxygenation that occurs because the blood flow increase exceeds that needed to maintain constant oxygenation. This phenomenon is called "luxury perfusion" and may be absent in pathological conditions in which autoregulation of blood flow is disrupted. Because patients with stroke have, by definition, a deficit in blood flow, one might think that BOLD signals are not useful. However, even when infarction damages one brain region, most other regions still have sufficient autoregulation to produce luxury perfusion, although uncertainty remains as to whether this is true for all uninjured brain regions or in all cases of stroke.

PET can also be used to measure glucose metabolism using fluorine-18 radiolabeled fluorodeoxyglucose, but these measures are limited by the much longer half-life of ^{18}F. Current fMRI methodology is becoming more diverse, and includes techniques to measure blood flow directly, such as with arterial spin labeling. While there have been numerous

demonstrations of the feasibility of performing functional imaging with this technique, it has other limitations that have prevented it from replacing BOLD imaging.

In most cases, the signal values are measured relative to a reference value, which in the simplest case is in the resting condition. Typically the task condition results in an increase in BOLD signal, but some brain regions have decreased signal in response to any task (the so-called default mode network) or are suppressed by other brain regions (contralateral inhibition between homologous regions.)

M1 Activation

Although one of the advantages of whole-brain functional imaging is the large amount of data collected in each scan, this volume of information can make identifying a biomarker difficult. Data can be quantified within regions of interest (ROI), which helps create metrics that can be tested for their correlative and predictive value. Because deficits in motor function are most related to damage and reorganization of activity in the primary motor cortex, measures of M1 ROI have been tested as biomarkers. The measure that appears to have the most utility is the laterality index (LI) for a contralesional limb motor task (60). This measure has several definitions, but usually it is the difference between the M1 ROI activation of each hemisphere, divided by their sum. Thus the formula is:

$$LI = M1_{ipsilesional} - M1_{contralesional} / M1_{ipsilesional} + M1_{contralesional}$$

The LI index is defined as being positive when there is more activity in the affected hemisphere. As long as no brain area reduces activity during rest, the LI will be between –1 and 1. However, because ROI values can also represent deactivation, and have negative values, the denominator can approach zero, with the resulting absolute value of the LI becoming larger than one. (In older applications, activation was measured as a volume of significantly activated voxels, and this problem could not occur.)

But the meaning of the LI is the degree of normal lateralization of motor function. When LI is close to 1, it implies activation of the normal M1 contralateral to the limb being moved, with little or no activation in the ipsilateral M1. When it is close to –1, it implies activation only of the ipsilateral M1, and therefore potential localization of motor activity only on the contralesional cortex. A complicating factor in LI measures is the occurrence of mirror movements, involuntary movements of the unaffected side when attempting to move the affected one (61). There have been two interpretations of the abnormal LI value. One is that it represents useful reorganization of activity (60), with a decrease in LI after therapy (62). The other view is that it reflects degree of damage, with an increase (normalization) in LI after therapy (63,64). The second viewpoint has taken hold, and it is suspected that LI may predict response to therapy. But there is no example of a clinical trial in which LI was used prospectively. LI remains an interesting biomarker, but one that still requires both better definition and testing.

Bilateral and Nonprimary Areas

The LI is measured in the primary motor cortex, but many other areas are also activated during motor tasks. These include other areas on the hemispheric convexity (premotor areas) and on the medial wall (supplementary and cingulate motor areas). Because many of these areas have strong bilateral influences on movement, they are potential candidates as substrates for recovery, and have been studied extensively. However, to our knowledge, none of them has been tested as biomarkers.

Resting State

Despite the potential usefulness of the LI, consideration must be given to the fact that activated areas provide focal information about M1 and overlook the dynamic and integrative neural mechanisms contributing to these signal changes (65). Moreover, subjects are typically studied because they are able to perform a standardized task, thereby limiting the generalizability of findings to the function of the particular task and to subjects with moderate to good motor recovery (66,67). Such activation maps cannot be derived from subjects who are unable to perform a task. Therefore, one promising alternative to a task-based neuroimaging biomarker is to evaluate brain connectivity from a resting state. Functional connectivity of the resting or anesthetized brain is represented in fMRI by synchronously fluctuating, low-frequency (<0.1 Hz), BOLD signals (fcfMRI). Emerging from these intrinsic signals are consistent, spatially distinct neural systems that mirror spatial representations found in task-based studies (68,69). These slowly oscillating resting-state hemodynamic signals are thought to reflect the propagation of transient neural signals between structurally connected regions (70–72). However, a consistent relationship between the neural correlates of stroke recovery and functional connectivity findings has not yet been established, thereby confounding its interpretability as a biomarker.

Near Infrared Spectroscopy

Near infrared spectroscopy (NIRS) is an optical technique that probes cortical activity based on neurovascular coupling. This approach continuously monitors changes in oxygenated hemoglobin and deoxygenated hemoglobin in response to a motor task. One of the limitations is that NIRS provides limited spatial resolution and depth of measurement (i.e., only the superficial cerebral cortex can be monitored), but has moderate temporal resolution with resistance to motion artifact. NIRS is more convenient and appropriate in the rehabilitation setting because it is more tolerant to movement, has a lower cost than other imaging techniques, is portable, and has fewer restrictions (e.g., it can be used in patients with metal implants). Measurement recorded using NIRS was in agreement with findings using fMRI and may be useful as a biomarker of poststroke recovery (73).

Motor Synergies/EMG/Kinesiological Markers

The many examples of physiological markers described so far in this chapter have appeal because of their relationship to function and recovery. Another potential avenue for biomarkers relates to the ability to generate voluntary movement or motor markers. The potential advantage of this type of marker is that they are closer surrogate measures of participation in society, that is, the ultimate measure of recovery from stroke.

Traditionally, movement impairments observed post-stroke were defined within a synergy framework. For example, the Fugl-Meyer is perhaps the most widely used clinical assessment of impairment based on subjective ratings of movements in/out of synergy patterns (74). An increasing trend in stroke rehabilitation, however, has been the use of kinematic motion analysis to precisely and quantitatively measure voluntary movements and elucidate differences between recovery and compensation (75). Although different data acquisition systems exist for recording voluntary movements, data are typically recorded as a time-series of coordinate data (x, y, z) that are used to define segments of interest, such as an arm or a hand, and analyzed to determine joint angles, accelerations, and trajectories. These analyses can be described as kinematic and kinetic, although kinematic measures (joint angles, ranges of motion, spatial–temporal parameters) are applied more commonly as markers for upper-extremity movements compared to kinetics (forces, inverse dynamics, etc.), which are more commonly applied to gait and lower-extremity tasks.

Movement Parameters

One of the benefits of using kinematic motion analysis is the vast number of movement parameters that could potentially be used as markers of recovery. These are most commonly separated into segmental kinematics (how the body is generating movement) and end-point kinematics ("performance" on the task). Segmental kinematics is often calculated as a range of motion to accomplish a task. For example, survivors of stroke often use the trunk to accomplish a forward reaching task; this has been suggested as a common compensatory movement. End-point kinematics can take on many forms, including how quick movements can be made (e.g., peak velocity, movement time) or how smooth movements are (e.g., path length ratio, smoothness of movement). These types of measures have been implicated as important motor control factors and have been shown to be altered following a stroke. For example, Rohrer suggested that the smoothness of movements is disrupted after stroke and changes with recovery or following intervention, thereby making it a potential useful marker of motor function (76,77). One of the limitations of kinematic motion analysis is the sophisticated data acquisition units currently required, but advancements in technology such as accelerometers will expedite availability for clinical use.

NONMOTOR FUNCTIONS

This chapter has focused on biomarkers that relate mainly to motor function, but other areas have been studied as well, particularly aphasia, visual function, and neglect. We will briefly comment on aphasia.

Aphasia

Because of the usual strong, left hemisphere lateralization of language, it was apparent from early functional imaging studies that left hemisphere damage could lead to abnormal language localization (78). Soon afterward, conflicting results were published regarding whether the right hemisphere activation was compensatory and supported recovery (79) or was uncorrelated with performance (80,81). In the later studies, left hemisphere perilesional regions appeared to be more related to linguistic performance. In fact, current research indicates that right hemisphere activation is more related to linguistic errors and may reflect a failure of the damaged language system to deal with the task (82). This makes right hemisphere activation during naming or other word generative tasks a possible biomarker for aphasia.

Arcuate Fasciculus Integrity

A potential anatomical marker that may be a simpler biomarker for aphasia after stroke is the arcuate fasciculus, which has long been known to be involved in classical aphasias (those with impaired repetition), although that view is being challenged (83). Diffusion tensor imaging of the arcuate fasciculus has been shown to predict aphasia recovery (84) and should be evaluated in larger studies to determine the sensitivity of the method.

CONCLUSIONS

Establishing biomarkers is a critical step for stroke rehabilitation to facilitate the development of interventions that positively affect functional ability and quality of life. The appropriate biomarker will be a substitute (or surrogate) for clinical outcomes that can be difficult to measure. The mechanistic work of the past few decades has advanced the field to explore a multitude of potential biomarkers for recovery that can be quantitatively measured. In return, biomarkers can also be an indicator of a biological mechanism relevant to the intervention. The appropriateness of potential biomarkers, however, is not simple or straightforward. Anatomical markers have a high degree of sensitivity and reliability, but may have limited functional relevance, whereas motor markers are more functionally relevant but may have less sensitivity (11). Physiological markers, such as the presence of MEPs, represent a potential biomarker that is associated with function and the underlying anatomical structure. Continued work in the stroke rehabilitation field to more fully understand the underlying biological processes of recovery will aid in the development of biomarkers, and ultimately the development of effective interventions for survivors of stroke.

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10

Genetics of Stroke Recovery

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Genetic factors have been found to be associated with many features of stroke in humans, including severity, recovery, brain plasticity, and treatment efficacy. Across patients, the same degree of injury can be associated with a high degree of variability in spontaneous behavioral recovery and in response to therapy. It is likely that genetic factors contribute to some of this inter-individual variation. Understanding factors related to motor recovery, neurological disorders, and pharmacological and therapeutic response could increase the efficacy of rehabilitation strategies and drastically improve quality of life for many. Further, genetic differences might also influence the amount or type of rehabilitation therapy required to induce optimal levels of brain plasticity and thereby achieve the best functional recovery. Understanding the relationship that genetic factors have with stroke recovery could therefore inform many aspects of clinical decision making.

FORMS OF GENETIC VARIATION

Genetic variation takes a number of different forms and can be studied in several ways. One nucleotide in a gene may be altered, which can result in an amino acid change in the protein or in altered transcription or translation efficacy if the nucleotide change occurs in a promoter region. Alternatively, a nucleotide may be inserted or deleted, or a segment of the gene may be repeated. A *genetic mutation* is a form of genetic variation that is rare in the population and causes a significant change in function. Examples include the single nucleotide mutation that causes sickle cell anemia or the expanded CAG repeats found in Huntington's disease. When a genetic variation occurs commonly and has a relatively small effect on behavior or phenotype, it is termed a *polymorphism*. A polymorphism may be a single nucleotide polymorphism (SNP), a variable number of tandem repeats (VNTR), or an insertion/deletion (ins/del).

The most common approach to studying the impact of genetic variation to date has been to study *single polymorphisms* and their association with diseases or traits or with endophenotypes such as brain function. A *candidate gene approach* may be used in this context, in which a polymorphism is chosen a priori based on its likely association with the condition of interest. Alternately, a *genome-wide association study* (GWAS) may be done, during which all known polymorphisms, or a very large number of them, are assessed (1). Another approach utilizes a *gene score* that sums the effects of multiple polymorphisms across a particular biological system (2–5). Other approaches include examination of exome sequencing, epigenetics, and epigenomic and transcriptomic variation (6).

GENETICS OF NEURAL PLASTICITY AND RECOVERY

Many molecular events, and therefore a number of genes, have been associated with brain plasticity and recovery from neural injury (7,8). Well-characterized genetic polymorphisms on the genes for brain-derived neurotrophic factor (BDNF), apolipoprotein E (ApoE), the serotonin transporter (5HTT), and catechol-o-methyltransferase (COMT) have been studied in relation to stroke recovery and brain plasticity. Other genetic polymorphisms are just beginning to be characterized and studied in this context.

One highly studied genetic variant is a polymorphism in the gene for BDNF. BDNF is a growth factor important to many forms of development, plasticity, learning, and repair. At position 66 in the BDNF gene, the more common valine may be replaced with methionine, resulting in 18% to 30% less activity-dependent secretion of the BDNF protein (9,10). Another highly studied genetic variation is in ApoE, which is the most abundant brain lipoprotein. A combination of polymorphisms results in the ApoE2–ApoE4 genotypes (11), which are correlated with differences in several neural repair processes as well as with the risk of Alzheimer's disease (for more in-depth review, see (8)). A third major genetic variant is located in the promotor region of the serotonin transporter gene (5-HTTLPR) and modulates gene expression. The 5-HTTLPR sequence has a 44-bp ins/del and hence occurs in either a short form (s) or long form (l). The short form is associated with susceptibility to stress and depression, including poststroke depression (12,13). Several polymorphisms related to dopamine neurotransmission have been studied, including an amino acid alteration from valine to methionine at position 108/158 of the COMT enzyme. This amino acid change results in a protein with three to four times less enzymatic activity, and thus higher synaptic dopamine availability (14).

Several of these polymorphisms have been associated with differences in outcome after neural injury in patients with stroke. These findings in human subjects are concordant with preclinical investigations, for example, in rodents, where BDNF levels have been associated with CNS repair (15–18), and treatment with exogenous BDNF can improve motor recovery (19). In humans, a study of 255 acute stroke patients found that the presence of the ApoE4 allele and BDNF Met allele were associated with poorer behavioral recovery and with greater disability after stroke (20), similar to prior findings in patients with subarachnoid hemorrhage (21). Further, the BDNF Met allele may be linked to early neurological deficit, specifically in those who have suffered a hemorrhagic stroke (22). Regarding ApoE, some data show a relationship with outcome following intracerebral hemorrhage (23). However, a meta-analysis found a relationship between ApoE genotype and outcome following subarachnoid hemorrhage but no overall relationship with death or long-term dependency in other forms of stroke (24). Data from patients with traumatic brain injury (TBI) suggest a relationship between ApoE genotype and outcome. For example, a prospective cohort study found that patients with the ApoE4 allele were more than twice as likely to have an unfavorable outcome 6 months after TBI as were those without this allele (25). A meta-analysis found that the presence of the ApoE4 allele was associated with increased risk for poor long-term outcome following TBI (26).

The choice of metric used to probe genetic associations is important. The studies mentioned here examined genetic association with stroke recovery defined by global outcome scales that measure patient function in a broad sense. However, such scales capture the final phenotype in a manner that reflects a complex collection of diverse biological processes, and therefore dilute the effect of genes on specific recovery-related processes and more distinct traits. Such traits can be behavioral (27) or anatomical, and can provide a more direct demonstration of genetic effects. As an example, in a study of patients with Alzheimer's disease, presence of the COMT Val allele, which is known to be associated with lower synaptic dopamine, was correlated with reduced gray matter in several dopamine-related structures (28). The specificity of location of these anatomical changes supports a model whereby genetic effects on the COMT enzyme result in local changes in dopamine-innervated structures.

Genetic associations might not always be apparent when the behavior of interest is evaluated in isolation, as in many cases genetic differences are most apparent through an interaction with experience or training, or when examined as a function of time. This has been suggested in many studies of 5-HTTLPR, as well as with the classic studies that described an association of genetic variation in monoamine oxidase A (MAO-A) with antisocial behavior. The importance of such interactions and distinctions is highlighted in the case of ApoE, where the E4 allele is associated with long-term functional outcome, but not initial injury severity, following stroke (20) or TBI (29). This suggests that ApoE influences the neural plasticity related to recovery rather than initial response to injury. Such studies underscore the importance of considering genetic variation in relation to experience and time, a point of particular importance when studying stroke recovery. Note that a great number of experience-related factors might be important, including features of acute care, rehabilitation therapy, home life, and psychosocial factors; these experiences may differ greatly across individuals.

IDENTIFICATION OF NEW GENETIC VARIANTS

Other polymorphisms, in addition to commonly studied genetic variants such as BDNF and ApoE, have been implicated in stroke recovery. Some are related to acute injury and early repair events. For example, recent evidence suggests an important role for inflammation-related genes in stroke outcome, including those related to leukocyte activation (interleukins) and prostaglandin production (cyclooxygenases). Marousi et al. (2011) found that SNPs in interleukin 4 and interleukin 10 were correlated with the likelihood of a recurrent ischemic event and predictive of functional outcome, respectively (30). The cyclooxygenase gene alleles COX-2 rs5275 C and COX-2 rs20417 C were associated with better outcome 90 days after stroke (31), concordant with animal model data suggesting better stroke outcomes with reduced COX-2 activity. One new polymorphism that may greatly affect stroke recovery and poststroke plasticity is found in the gene for tissue-type plasminogen activator (t-PA). The t-PA protein, known for its role as an acute reperfusion therapy after stroke, is also thought to be highly involved in neurotransmission and cortical plasticity (32). A study of postmortem human brains found a large difference in t-PA mRNA between carriers of the –7351C and T alleles (33). Thus far, this polymorphism has not been studied for its relationship to cortical plasticity in humans, but evidence from animal and postmortem studies suggests a potential modulatory influence. More research is needed to determine the exact biological consequences of these genetic variations.

GWAS are particularly helpful for identifying new genetic associations (1). A large GWAS has found and replicated an association of an HDAC9 gene variant with large vessel ischemic stroke (34). As the mechanism is not known, this association would not have been found with a candidate gene approach. Although this study pertains more to stroke pathophysiology than to poststroke repair, it highlights a point critical to any study of human stroke: genetic associations might be most accurately identified when studied in relation to distinct forms of cerebrovascular pathophysiology. Numerous, divergent biological events can result in very similar clinical phenotypes, but identification of genetic associations might necessitate identifying different pathophysiological states separately. This perspective can probably be more extensively applied to genetic studies of stroke recovery.

In addition to GWAS, gene expression studies are also useful for identifying new variants. Such an approach profiles the expressed genes from peripheral whole blood to identify unique gene-expression patterns that are associated

with a neurological disorder and its phenotypic subtypes (35). Evidence from an animal TBI model suggests that gene-expression regulation could help monitor injury progression and thereby help identify novel protein targets for future pharmacotherapy development (36); similar approaches could be extended to a restorative therapy focus. For many forms of neural injury, there has been limited clinical trial success in pharmacologically improving outcome. Examining the progression of a gene expression profile across the timecourse of recovery could uncover new recovery-related genes and pharmacological targets.

Studying these new variants, such as in the t-PA gene, along with methods for discovering new recovery-related genetic polymorphisms, such as GWAS and genetic profiling, offers promising directions to extend current research.

RELEVANCE OF GENETIC POLYMORPHISMS

The study of genetic polymorphisms related to stroke might provide insights into disease pathogenesis and outcome prediction, but the greatest clinical benefit from genetics research might come from the identification of polymorphisms that can guide details of therapy such as treatment choice, dose, or duration. Such an approach is being used in oncology, where the BRCA1 and BRCA2 mutations are used to direct the management of breast cancer in some patients (37). Similarly, variations in the CYP2C19 gene, coding for the cytochrome P450 2C19 protein, may be considered when prescribing the platelet-aggregation inhibitor clopidogrel (38–40). Barriers to effective implementation of pharmacogenomic insights include cost, awareness, and ethical concerns (41).

A number of potential opportunities exist whereby genetic factors might influence pharmacotherapy after neural injury. Although evidence is often incomplete, several drugs are commonly used following neural injury, including the dopamine precursor levodopa, selective serotonin reuptake inhibitors (SSRIs), serotonin-noradrenaline reuptake inhibitors (SNRIs), and acetylcholinesterase inhibitors (42). Genetic variations have been shown to interact with many of these drug families (8). For example, one recent study found that dopamine genetics modulated the effects of levodopa on skilled motor learning and motor cortical plasticity (43). SSRIs are given primarily to treat comorbid depression (42), but some data suggest a favorable influence on recovery as well (44). The 5HTTLPR s/l polymorphism, along with others, modulates response to antidepressant drugs in major depressive disorder (45) and may have an impact on SSRI and SNRI response in poststroke depression and rehabilitation. Genetic variations in drug-metabolizing enzymes can alter drug responses to a wide variety of pharmacological agents, including most antidepressants (46). In addition to modulating drug efficacy, genetic variation has been associated with the likelihood of medication side effects in conditions such as epilepsy (47), diabetes (48), rheumatoid arthritis (49), cancer (50), and depression (45). The increased likelihood of side effects owing to genetic variation will be a consideration during the development of drug treatments for neural injury. Particularly in conditions when multiple drugs or classes of drugs could potentially be used, pharmacogenetics might shorten the process of finding the best drug for the patient and thus reduce the number of drugs the patient must be exposed to before settling on the appropriate treatment (51). However, several ethical concerns exist, including, but not limited to, obtaining informed consent from patients who are not competent, maintaining confidentiality of such sensitive data, and balancing the uncertainty of genetic associations versus tested or standard clinical practice (51).

An understanding of genetic factors might also influence the method of treatment for neural injury through nonpharmacological forms of intervention. For example, several forms of brain stimulation, whereby cortical excitation is focally modulated, are under investigation for the treatment of stroke (52–54). Polymorphisms in genes coding for proteins key to neural plasticity could influence response to such treatment. Polymorphisms in the NMDA NR1 and NR2B subunit genes (55) and the BDNF Val66Met polymorphism (56,57) have been shown to affect experimentally induced cortical excitability and plasticity. In addition, recent evidence has found a significant positive relationship between homozygosity of the G allele in a common SNP of the transient receptor potential vanilloid 1 channel (TRPV1) gene and increased cortical excitability (58). These findings suggest differential cortical plasticity patterns across genetic groups and warrant further work studying the effects of these genotypes on cortical plasticity and motor task performance in neurologically compromised populations. As methods for modulating cortical excitation such as transcranial direct current stimulation receive increased study as a treatment for neural injury, an increased need will arise to study genetic variants related to neural plasticity and their relationship to treatment response.

OTHER FACTORS THAT INFLUENCE RECOVERY

Genetic factors, in addition to a direct influence on the mechanisms of stroke recovery, could modulate other processes that are strongly linked to recovery, such as depression, vulnerability to stress, cerebral blood flow (CBF), and cognitive impairment.

Depression

Depression has a serious negative impact on stroke recovery (59), and its clinical presentation may be modulated by several genetic and environmental factors (60,61). The 5HTTLPR s/s genotype has been robustly associated with an increased risk for depression (60,62,63), including poststroke depression (13). Studies of this polymorphism with treatment response have found that the s allele, compared to the l allele, is associated with poorer response to antidepressant drugs (45) but improved response to psychosocial therapy (61). Thus, knowing a patient's 5HTTLPR genotype may be useful for treatment planning in the management

of poststroke depression. Several other genetic factors and gene–environment interactions are being explored in the context of depression (60,62,63). In particular, polymorphisms in interleukin genes have been associated with nonremission, emotional processing, and response to pharmacological agents in subjects with depression (64,65). The overall significance of these genetic studies on understanding and treating depression remains to be clarified, however, as there are also many negative studies. In the 1,953-patient STAR*D (Sequenced Treatment Alternatives to Relieve Depression) study, 768 SNPs were examined for their relationship to major depression, and only one SNP in the gene for serotonin receptor 2A was significantly associated with treatment response (66). As the relationship between genetic factors and major depression becomes better understood, treatment and prevention of depression can become a factor in a patient's overall rehabilitation strategy. Patients with genetic susceptibility to depression might benefit most from in-person rehabilitation therapy and might also be less likely to comply with self-motivated telerehabilitation. Such patients might also be proactively prescribed an SSRI or psychosocial therapy, based on 5HTTLPR and perhaps other genotypes.

Stress

Stress is a key environmental variable brought on by the recovery process following neural injury. Vulnerability to stress has been found to have a genetic component (60). Experimental stress paradigms resulted in worse working memory performance for COMT Met/Met homozygotes than COMT Val/Val homozygotes (67,68). Of possible relevance to interpreting such findings is a study in children which found that the COMT Met allele is associated with a higher cortisol response to stress (69). Animal studies have found that the BDNF Met allele confers significant vulnerability to stress (70); consistent with this, one study suggested that meditation might indeed be more helpful for BDNF Met carriers (71).

Cerebral Blood Flow

CBF is affected by functional variants in the gene for nitric oxide synthase (72), and individuals with such polymorphisms may have a decreased ability to maintain adequate CBF following TBI (73). Using PET, it has recently been found that the BDNF Val66Met polymorphism increased resting CBF in the prefrontal cortex and hippocampus (74). Modulation of CBF could be a contributory mechanism of action for some restorative therapies, or may be a useful biomarker for some treatments, and hence such results might be useful for brain repair after stroke.

Plasticity

Neurorehabilitation relies heavily on brain plasticity, or the capability of the brain to alter function or structure in response to a range of learning and environmental events (75). Throughout the early phases of stroke and rehabilitation, perilesional neural networks are revised and restored, whereas brain regions in distributed networks are often recruited to progressively compensate and, depending on the extent of damage to a given region, adopt some of the functions of the damaged area (76–80). A large number of genetic factors may be related to the cellular and molecular mechanisms underlying CNS plasticity, with the greatest evidence amassed in relation to BDNF and ApoE (8).

CONCLUSION

With evidence from various studies suggesting that particular genetic polymorphisms may affect the extent and timecourse of spontaneous behavioral recovery following neural injury such as stroke, the need arises for strategies to modify therapy—pharmacological or otherwise—to optimize outcome in relation to genetic risk for individual patients. Understanding the role of genetic factors in relation to comorbid conditions such as major depression may also be important, including aspects with respect to preventative strategies. The ever-increasing knowledge of genetic variants holds promise to provide clinicians and researchers with useful avenues of insight for improving brain repair after stroke.

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11

Physiological Basis of Rehabilitation Therapeutics in Stroke

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In the past decade stroke rehabilitation research has shifted its focus from empirical evidence to biological targets. Physiology, especially neurophysiology, has identified a number of potential mechanisms that can be accessed by rehabilitation interventions. These physiological targets focus upon the potential for neuroplasticity at multiple CNS levels including the sensorimotor cortex, subcortical networks, the cerebellum, and the spinal cord. Moreover, a synthesis of clinical and animal research suggests that diverse biological mechanisms, including alterations in selected neurotransmitter pathways, and growth factors that modulate neuroplastic adaptations may interact to promote recovery. Although the evidence based on randomized clinical trials is currently insufficient to generate consensus practice recommendations, increasing experimental evidence supports a rationale for further research combining pharmacotherapeutic strategies with task practice to optimize sensorimotor recovery after stroke. Finally, the biological targets to optimize stroke recovery must go beyond the CNS to include skeletal muscle and metabolic function. Following stroke there are major body composition abnormalities including structural and metabolic abnormalities in hemiparetic muscle that can worsen disability, constituting important targets for physical rehabilitation, and, potentially, for pharmacological therapies. In the following sections, we discuss these biological targets and the interventions designed to interact with them. A focus is maintained on current knowledge in human rehabilitation, followed by a brief overview of some clinical and translational research in animal models that may help to define future research directions. Rehabilitation can and must access different elements of the nervous system and body functional systems to be effective. Table 11.1 gives an overview of the biological targets and the related treatments. The text further elucidates some of the neurobiological mechanisms and derived treatments that target the brain, the spinal cord, and muscle.

CENTRAL NERVOUS SYSTEM

Stroke damages the central nervous system (CNS). The CNS is therefore the prime target for therapies aiming for cure at the origin of the disease. Three properties in the organization of the CNS theoretically allow for recovery—redundancy, plasticity, and regeneration of neural tissue—the last of these still being a theoretical capacity about which far too little is known to develop a therapeutic intervention. Redundancy implies a certain over-capacity of the CNS so that limited tissue loss can immediately be compensated. Plasticity is a double-edged sword: it can be beneficial but also detrimental if re-growing neurons reach false targets and cause additional motor impairment. Detrimental plasticity is commonly referred to as "maladaptation." In the following, redundancy and plasticity are discussed.

Studies in patients with brain lesions demonstrate that the CNS has, albeit limited, redundancy. The brain's redundancy is not like that of other organs, such as liver or kidneys, where removal of a part is easily and instantly compensated by the remaining tissue. Within a theoretical neural network, the drop-out of a limited number of single cells or cell-to-cell connections can be tolerated without much dysfunction (1). Clinically unnoticed lacunes in eloquent brain regions, that is, regions that lead to immediately detectable symptoms like hemiparesis, document this scenario. Because over-capacity declines with age, compensability also decreases.

In contrast to lesions that injure a few cells, territorial lesions that affect entire or large parts of neuronal networks, cannot go unnoticed. Compensation for such lesions can only come from parallel networks that provide the same function but are underused in the healthy, for example, because their capabilities were replaced by more potent systems during evolution. Such parallel systems could be recruited after failure of the dominant system and may provide slow functional compensation. One example for a parallel system is the rubrospinal system compensating for corticospinal injury (2). However, the number of parallel systems is certainly limited. Another form of redundancy exists between the two hemispheres of the brain. Certain lateralized functions mainly executed by one can be adopted by the other hemisphere. Swallowing is an example (3). Dysphagia typically recovers faster than other impairments due to interhemispheric compensation.

TABLE 11.1 Biological Targets and Treatment Strategies

BIOLOGICAL TARGET	MECHANISM	TREATMENT STRATEGY
Brain (cognitive systems)	Adaptations in emotional, reward, and other cognitive systems. Reorganization of speech and language networks	Psychological and motivational therapies providing reward and emotional support, social and occupational therapy Therapies based on reinforcement learning paradigms Physical therapies combining multiple tasks to train attention and distractability Speech and language therapy
Brain (sensorimotor system)	Neuroplasticity in cortical and subcortical motor systems, motor skill learning	Repetitive task-oriented physical and occupational therapy Action observation and mirror training-based approaches (see Chapter 20)
Spinal cord	Adaptations in spinal reflex circuits preventing spasticity and maladaptive reflex behaviors	Classical physical therapies (neurodevelopmental, sensory feedback)
Muscle	Reversal of muscle atrophy and phenotype alterations (stroke causes shift to fast muscle fibers), relief of spasticity	Repetitive resistive and aerobic exercise Botulinum toxin injections
Cardio-respiratory	Fitness	Aerobic exercise therapy

Plasticity of neurons is an alternative mechanism that enables recovery of function. Plasticity is the "reprogramming" of neuronal circuits by modifying their firing patterns (synaptic efficacy or weights) and/or architecture. The stimulus for plastic reorganization can occur through the use of damaged circuits, such as through active training (skilled use dependent plasticity). An alternative stimulus may arise from the stroke lesion itself, for example, through lesion-induced expression of plasticity related genes (4).

Plastic phenomena have been observed in a variety of different brain regions including cortical and subcortical areas. Depending on the research methodology used, the phenomena may reflect structural or functional plasticity or both. After lesioning CNS motor areas or their descending tracts, motor recovery is associated with plastic adaptations in motor cortex (see Chapter 7). Cortical representations of body parts, as determined by stimulating different areas of the cortex, reduce in surface area after an infarct. Motor training prevents this shrinkage of cortical maps and can even expand representations in monkeys (5). Well-recovered stroke survivors with descending tract lesions have motor cortical activation patterns that differ substantially from healthy controls (6–9) and change longitudinally over time reflecting the reorganization of the cortical motor system (10–12). Similar to animal studies, motor cortex stimulation has documented adaptations in the input-output organization of the motor cortex after stroke (13). Areas other than the motor cortices (primary motor cortex, premotor cortex, SMA, and cingulate motor areas), such as the somatosensory cortex (14) and temporal and parietal regions, may also contribute to recovery but are not as consistently involved in recovery-related plasticity processes. Functional imaging in stroke survivors with different degrees of impairment also suggests a role of the cerebellum. In well-recovered subjects cerebellar activation during movement of the affected side is stronger than in the impaired (15).

Hence, motor cortices and cerebellum are brain targets that can mediate recovery or functional compensation if properly triggered. This triggering may be a particularly successful approach considering that the lesion itself attracts neuroblasts to migrate from the subventricular zone to the cortex (16), which in turn could be "reprogrammed" by active use. This could be a first step toward a relevant regeneration of neural tissue.

Genetic determination may affect how apt the motor system is to plastic changes. The Val66met polymorphism in the BDNF gene (brain derived neurotrophic factor) was shown to be associated with reduced reorganization of motor cortex somatotopy after learning in rodents (17). The Val66met genotype in conjunction with the catechol-O-methyltransferase (COMT) Val158Met homozygous genotype was found to have reduced cortical plasticity and implicit learning in humans (18).

Rehabilitation Training Techniques Targeting CNS

Specific training therapies aim at inducing neuroplastic adaptations in the CNS. Constraint induced movement therapy (CIMT) is an effective intervention that provides sustained benefits to stroke survivors with long-term disability (19). CIMT combines active training with the paretic arm by constraining the unaffected arm; the latter helps to overcome learned nonuse of the paretic side (20). CIMT is associated with changes in cortical physiology. The representation of the paretic hand in the ipsilesional hemisphere as determined by transcranial magnetic stimulation (TMS) increases

in size after therapy; this increase correlates with improved arm function (21). The enlargement occurs into areas with decreased intracortical inhibition (22) indicating a role for a GABAergic mechanism in this form of plasticity. Plasticity mechanisms may depend on lesion location. A patient with a lesion in the primary motor area or its descending pathways (as defined by an abnormal motor evoked potential in response to TMS) showed an increased area representation and decreased cortical excitability (or increased inhibition); patients without such lesions show the opposite pattern (23). Functional imaging studies indicate that CIMT can induce plasticity in other brain areas, such as the contralesional primary motor area (reduction of activation), cerebellum, supplementary motor area, and frontal gyri (24–26).

Bilateral arm training with rhythmic auditory cueing (BATRAC) is an effective therapy for most patients (27,28). Some patients despite improving their reach do not gain movement abilities relevant for daily life. Bilaterality and rhythmicity are elements adopted from motor learning techniques possibly acting through interhemispheric signaling and movement sequencing. Patients who improve in motor impairment as measured by the Fugl–Meyer score show increased recruitment of bihemispheric premotor and motor areas (Figure 11.1) (27). In contrast, patients without functional improvement demonstrate no cortical reorganization suggesting a mechanistic link between recruitment of ipsi- and contralesional motor cortices and improved arm function.

In a larger cohort, as compared with dose matched physical therapy exercises, bilateral arm training did not mediate greater improvements but similar behavioral effects did lead to different brain reorganization patterns (29). These findings indicated that different mechanisms can be utilized to achieve similar functional improvement—raising the possibility of additive effects of different forms of therapy.

Other upper extremity training regimens also utilize neuroplasticity to improve function. Task-specific training of tracking waveforms with the paretic index finger leads to a shift in the activation of sensorimotor cortices (primary sensory, motor, and premotor cortex) from the contralesional to the ipsilesional side (30). Similar results were obtained by using a home-based task-oriented training protocol (31). In another study, a task-oriented arm training program led to increases in the activation of ipsilesional primary motor cortex as well as inferior parietal and premotor cortex (32). Activation changes were not observed in either healthy controls undergoing the same training program or in patients subjected to conventional physiotherapy techniques.

Gait training on a treadmill while facilitating paretic leg movements using somatosensory stimulation produces "healthy" patterns of cortical activation; patterns that are closer to those of healthy controls during unfacilitated treadmill walking (33). In contrast, unfacilitated treadmill walking in stroke patients is associated with abnormal activation patterns. While this observation provides no evidence for neuroplastic adaptations in the brain, it demonstrates that specific physiotherapy techniques can reverse abnormal brain activation. It is possible that the entraining of "normal" activation patterns leads to long-term encoding and a persistent functional benefit. A randomized controlled study comparing aerobic treadmill exercise to stretching demonstrated a

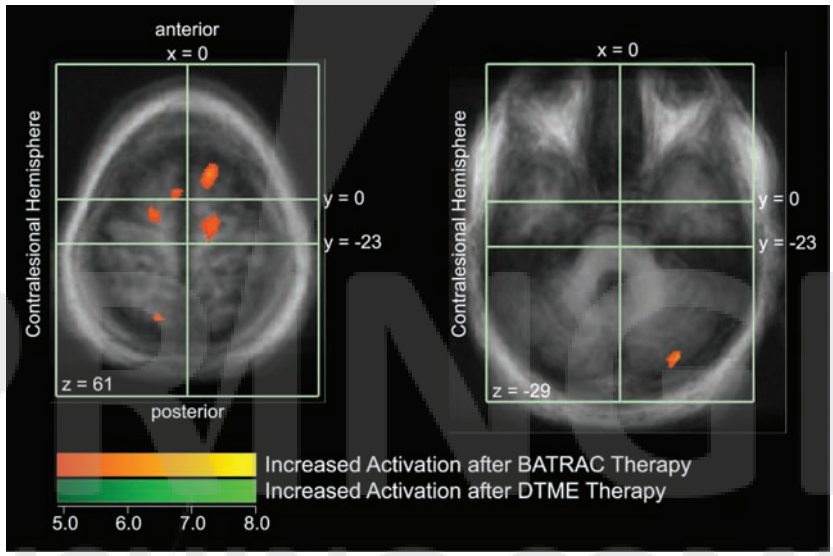

FIGURE 11.1 Evidence for neuroplastic reorganization after BATRAC. Bilateral arm training with rhythmic auditory cueing (BATRAC) recruits brain areas in both hemispheres to control the paretic limb (orange areas represent foci of novel activation after training in the BATRAC group, no increased activation was found after control dose matched physical therapy exercises).

Source: From Ref. (27). Luft AR, McCombe-Waller S, Whitall J, et al. Repetitive bilateral arm training and motor cortex activation in chronic stroke: a randomized controlled trial. *JAMA*. 2004;292(15):1853–1861. With permission of JAMA.

superiority of the treadmill interventions with respect to walking velocity and fitness. Increases in walking velocity were correlated with recruitment of subcortical brain networks, namely cerebellum-red nucleus circuits (34). This study demonstrated that subcortical networks can be modified by specific interventions that improve ambulation for chronic stroke survivors.

Other Interventions Supporting CNS Plasticity

Cortical Stimulation

CNS-neuroplasticity can be facilitated by certain adjunct treatments. One of these emerging interventions is cortical stimulation. Stimulation can be delivered transcranially either via magnetic fields (TMS) or by applying weak direct current (transcranial direct current stimulation [tDCS]). Cortical stimulation alters cortical excitability. For example, applying tDCS to the primary motor cortex (anodal stimulation) in the lesioned hemisphere, enhances excitability and results in improved use of the paretic arm (35). Also, associated with increased cortical excitability is a reduced intracortical inhibition suggesting changes in gamma-aminobutyric acid (GABA) and glutamatergic neurotransmission as the likely underlying mechanism (36). Interestingly, downregulation of excitability by applying cathodal stimulation to the contralesional hemisphere also improves arm function (37). This observation indicates that transcallosal interhemispheric signaling is part of the pathophysiology of hemiparesis. Similar results have been shown with repetitive TMS (38–40). Excitability changes that are observed following cortical stimulation are short-lived, and improve motor performance only for minutes to hours (35). In motor skill learning tDCS has been suggested to promote consolidation of a motor skill (41). Additionally, in cortical slices of mice tDCS-induced N-methyl-D-aspartate (NMDA) receptor-dependent long-term potentiation enhances BDNF secretion and activation of its receptor TrkB (tropomyosin-receptor-kinase) (42). Daily application in combination with training may provide persistent effects that are greater than those induced by training alone (38,43), but this remains to be confirmed in larger trials.

Pharmacotherapy

Systemic administration of Levodopa in combination with physiotherapy was superior to physiotherapy alone (44). In this trial, the combination treatment was given for 3 weeks during subacute recovery after a stroke that occurred 3 weeks to 6 months earlier. Amphetamines have been suggested to provide similar benefits (45), but conflicting evidence has been reported (46) (see Chapter 12). A meta-analysis based on 10 trials acknowledges benefits for motor function but found the evidence to be insufficient to allow definitive conclusions or guidelines (47). The mechanism of action for dopamine and amphetamine is thought to be the enhancement of cortical norepinephrine, but direct effects of dopamine have also been suggested (48). Inhibiting norepinephrine reuptake by reboxetine has been shown to enhance learning of a motor skill (49,50).

Sensitive animal models are necessary to better understand how certain substances affect recovery or learning. Only this knowledge will lead to optimized use by defining the delivery method, the time to use, the duration of treatment, and so on. In a rat model of motor skill learning, evidence exists that dopaminerigc neurotransmission in primary motor cortex is crucially important for successful movement learning and possibly recovery. Dopamine may take this role by mediating long term potentiation (LTP) of cortical neurons and by modulation of intracortical inhibition (51). The dopaminergic projection to motor cortex originates in the midbrain's ventral tegmental area (52).

SPINAL CORD

The spinal cord harbors reflex circuits that are inhibited by a pathway from the motor cortex to the brainstem ventromedial reticular formation (53). If a stroke injures this pathway, the reflex circuits become hyperactive leading to "upper motor neuron" (UMN) signs such as clonus and positive extensor plantar reflexes, as well as spasticity. However, these symptoms develop over time suggesting that it is not simply the removal of corticoreticulospinal signaling that causes symptoms of the UMN syndrome. Instead, slow plastic changes within the spinal cord must be involved (53). Little is known about these changes that are a deleterious form of spinal plasticity. Potential mechanisms are the sprouting of afferent axons, which in turn connect to previously inhibitory synapses converting them to excitatory synapses, or upregulation of receptor sensitivity as a consequence of denervation (53). Spasticity and muscular hypertonus leads to adaptations in muscle tissue and has biomechanical consequences, such as contractures and impaired posture.

Deleterious plasticity or "maladaptation" can occur because neurons lose their targets after injury and then rewire inappropriately. Rewiring may be maladaptive because the patterns of activation that occur during active use are missing. It has been hypothesized that maladaptive rewiring leads to the inability of newly formed synapses to undergo lasting modification of synaptic strength, and hence, learning (54). The basis for this hypothesis is that in the normal state, an oscillating balance exists between learning and recall, that is, between plastic change of synaptic strength or interneuronal connections and their stable maintenance; studies on the mechanisms of consolidation and reconsolidation after an early recall of stored information support this idea (review in (55)). By the destruction of part of the neuronal network as a result of stroke, this delicate balance is disturbed. Maladaptive rewiring leads to a permanent disruption of this balance. As a consequence, the neuronal networks are locked in a so-called "stability-plasticity dilemma" which leads to "catastrophic forgetting" of the information that was previously stored in these networks (54). This forgetting may contribute to motor paralysis in stroke survivors, that is, the forgetting of preexisting movement patterns. The classical pathophysiological

model of paralysis that emphasizes de-efferentiation is a result of interruption of CNS-muscle pathways, probably contributes as well, but is clearly not the sole explanation for paralysis; that stroke patients demonstrating plegia in neurological examinations, sometimes move their arm "subconsciously or automatically" when they wake up in the morning, underlines this idea.

Rehabilitation Training Techniques Targeting Spinal Cord

Original neurorehabilitative techniques, such as the Bobath neurodevelopmental technique (56), aim at avoiding UMN syndrome maladaptations at the level of the spinal cord. Whether or not they achieve this goal has not been demonstrated. They may also produce benefits by targeting other elements of the motor system. Proof of clinical efficacy of these techniques comes from experience more than from clinical investigations (57,58).

The spinal cord harbors "central pattern generators" that produce automated movement, such as stepping, and are under cortical and subcortical control. In animal models with spinal cord injury, these pattern generators can be modulated by gait training on a treadmill possibly reflecting spinal plasticity (59). In humans, body weight supported treadmill training (BWSTT) is advocated for spinal cord injured patients. A randomized controlled trial comparing BWSTT with overground training has shown clinical benefits for both interventions (60). This is expected assuming that any task, that is, gait-specific training whether on a treadmill or on the ground will induce activity-dependent adaptations. In humans whether these adaptations occur at the spinal level or in the brain remains to be investigated.

Spinal cord networks are specifically targeted by the antispasticity drug baclofen applied via continuous intraspinal infusion using an implanted pump. In a controlled double-blinded trial (n = 21) comparing a one-time bolus injection of baclofen versus saline, significant improvements in spascticity were documented in favor of the active drug (61). Responders to the bolus were then offered an implantation of a baclofen pump. At 12-months follow-up spasticity scores were markedly decreased.

SKELETAL MUSCLE

There are a number of skeletal muscle alterations that could propagate disability and increase cardiovascular risk after stroke. These skeletal muscle alterations include muscular atrophy and increased intramuscular adiposity (62), fiber phenotype shift (63), and changes in muscle metabolism that are linked to insulin resistance (64). Stroke leads to profound cardiovascular deconditioning that relates to gait deficit severity and body composition changes. Reduced muscle mass is fundamentally related to poor fitness and physical performance capacity after stroke (62,65).

Skeletal muscle fibers have great adaptive potential. Myosin heavy chain (MHC 1) is an important structural and regulatory contractile protein that is expressed in different isoform profiles, and thereby imparts functional diversity to muscles. Slow (MHC 1) isoform fibers are rich in mitochondria, resistant to fatigue, and less pH sensitive because of their highly oxidative metabolism (66). Fast-twitch fibers have glycolytic metabolism, have faster force generation capacity, but fatigue easily. The structural and functional characteristics of muscle fibers can be modified in response to several physiological and pathological conditions. Muscle phenotype is regulated by hormones, growth factors, changes in load, innervation patterns, aging, hypoxia, as well as electrical stimulation, and exercise. After stroke, skeletal muscle responds to altered use, loading states, and neural activation pattern. The most comprehensive study of muscle pathology reveals a shift to greater fast twitch fiber proportions in hemiparetic leg *vastus lateralis* (VL) based on ATPase staining, and a reliance on anaerobic metabolism with rapid lactate generation during isolated hemiparetic limb exercise, in contrast to oxidative metabolism during nonparetic leg exercise (67). These findings are similar to a recent study that finds a major shift to fast MHC by routine ATPase staining at pH 4.6 and MHC gel electrophoresis of hemiparetic leg *VL* muscle biopsies in 13 chronic stroke patients (63). The hemiparetic leg has elevated proportions of fast MHC isoforms compared to the nonparetic leg. These findings that are restricted to the hemiparetic leg suggest that neurological alterations may be partially responsible for the shift of muscle phenotype. The proportion of fast MHC isoform, only in the hemiparetic limb, is negatively correlated with self-selected walking speed. The shift to fast MHC after stroke in the hemiparetic leg muscle would be expected to result in a more fatigable muscle fiber type that could be more insulin resistant. Interestingly, spinal cord injury results in a parallel shift to fast MHC muscle composition, which can be reversed with partial weight suspension treadmill training (68).

Tumor necrosis factor alpha (TNF-alpha) has been implicated in muscular wasting in models of disuse, cachexia, sarcopenia, and insulin resistance. TNF-alpha may cause atrophy and insulin resistance through a number of mechanisms. It inhibits protein synthesis, reduces transcriptional factors regulating myofiber gene expression, induces protein breakdown through activating ubiquitin proteases and induction of apoptotic cell death, and alters insulin signaling (69–73). TNF-alpha mRNA expression is elevated in hemiparetic VL compared to the nonparetic leg of stroke patients and age-matched controls (64). TNF-alpha mRNA levels are 2.8-fold higher in hemiparetic muscle and 1.7-fold higher in nonparetic *VL* compared with matched controls. The findings of elevated TNF-alpha in both the hemiparetic and nonparetic muscles suggest systemic, as well as local inflammation could augment muscular atrophy and increase insulin resistance after stroke. This inflammatory mediator can negatively impact muscle mass, structural proteins, performance, and metabolism. These secondary biological abnormalities in body composition and skeletal muscle should be considered as potential targets for rehabilitation and therapeutic exercise after stroke.

Rehabilitation Training Techniques Targeting Muscle

In a small trial (n = 32) comparing robot-assisted gait training (Lokomat, Hocoma, Inc., Volketswil, Switzerland) to conventional physiotherapy (training of trunk stability, gait symmetry, and step initiation) in subacute stroke patients, Husemann et al. showed beneficial changes in whole body composition with robot training (74), that is, increase in muscle and decrease in fat mass compared to the control group over the 4 week intervention. Functional benefits were comparable between groups, but, the trial may not have been sufficiently powered to show such differences. These findings indicate that specific physiotherapy interventions can differentially affect body composition—the benefit for the stroke survivors remains to be assessed.

A systematic meta-analysis covering 21 trials using various strengthening methods—including electrical stimulation, biofeedback, muscle re-education for very weak acute or chronic stroke survivors and, in addition, resistance exercise for weak participants—demonstrated an overall benefit on strength and activity. The benefit was greater in acute than chronic and in weak than very weak subjects. The carryover between strength and activity was comparably low which was explained by the selection of muscles for strength training. Daily tasks, instead, consist of movement sequences that require the synergistic and timed action of different muscle groups. Strength training did not increase spasticity (75).

Spasticity is limiting active training to induce plastic adaptation. It is therefore desirable to relieve spasticity either through physiotherapy or pharmacotherapy. Brashear and colleagues compared butolinum toxin injections into flexor muscles with placebo in a randomized multicenter trial (76). At 4, 6, 8, and 12 weeks of follow-up, butolinum toxin was beneficial in improving muscle tone and self-reported disability without producing adverse events. It remains to be investigated whether butolinum toxin which has a time-limited effect, may enable specific training interventions that recover motor ability and prevent a relapse of spasticity.

SUMMARY

Rehabilitation training approaches for motor recovery after stroke can target all levels of the motor system (Table 11.1). Many patients require psychological and cognitive training targeting higher cognitive and language systems to understand and motivate themselves for rehabilitation and to cope with disability and related social stressors. Repetitive and task oriented training therapies target the brain's motor systems to induce neuroplastic changes that provide recovery of motor function or compensation for disability. These training therapies may be supported by pharmacological, for example, dopamine, or electrical therapies that render the motor cortex more apt to plastic changes. Spinal cord reflex mechanisms are targeted by conventional rehabilitation therapies but little is known about the ability for lasting changes in the spinal cord after stroke. Maladaptive changes in spinal cord may lead to spasticity, which together with muscle degeneration can be a limiting factor to CNS training therapies. Therefore measures to reduce spasticity, such as butolinum toxin injections and sensory feedback therapy, may be a prerequisite to further training. Muscle degeneration may be reversed by resistive and nonresistive exercise. Finally, reduced cardiovascular fitness after stroke can limit any movement effort. Aerobic exercise therapies targeting the cardiovascular and respiratory systems may enhance fitness and provide sufficient energy reserve for enduring daily life activities.

The neuroscience of rehabilitation is just at its beginning. Much needs to be learned about the brain's ability to adapt and recover, including the use of restorative approaches (e.g., via stem cells). Because a plethora of therapies already exist and will be expanded in the future, it will be crucial to learn about efficacy, prerequisites for response, treatment intensity, and sequence. Most likely we will have to tailor the rehabilitative protocol to the individual patient.

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12

Medications and Stroke Recovery

Larry B. Goldstein

Despite decades of laboratory-based research showing that a variety of systemically administered drugs can have a profound influence on poststroke functional recovery, consistent data from prospective clinical trials demonstrating a similar effect in humans is lacking. This discrepancy between laboratory-based and clinical studies is not unique to putative poststroke pharmacologic restorative treatments. A similar disparity between the results of animal model experiments that were designed based on an understanding of a drug's neurobiological actions and the demonstration of similar effects in humans has plagued attempts to identify clinically relevant neuroprotective interventions (1,2). There are likely a variety of reasons for these failures of translational medicine, and despite the setbacks, there is reason to believe that the identification of effective pharmacological approaches for improving functional outcomes after stroke may be possible (3–5). A plethora of novel strategies, such as stem cell transplantation (6–8), hormonal administration (9–11), exogenous growth factors (12), and statins (13–15), hold promise; these, and several other therapeutic avenues, are being actively pursued. This discussion focuses on the potential effects on the recovery process of medications acting through central neurotransmitter mechanisms.

CONCEPTS AND MECHANISMS

Arguably, amphetamine is the most extensively studied systemically administered drug with the potential to modulate the recovery process after stroke or other forms of central nervous system injury. Experiments suggesting that the administration of amphetamine might affect measures of neurological function after damage to the brain or spinal cord date to at least the 1940s (16,17); however, the therapeutic potential of amphetamine was not widely recognized until publication of a series of experiments by Feeney and coworkers nearly 40 years later (18,19). These experiments showed, that when combined with task-relevant training, a single dose of *d*-amphetamine given 24 hours following unilateral sensorimotor cortex ablation increased the rate of locomotor recovery in rats. The observations were subsequently confirmed in other laboratories (20–23). Other studies found that postinjury administration of amphetamine was associated with recovery of otherwise permanent neurological deficits. For example, in cats, amphetamine given after unilateral or bilateral frontal motor cortex ablations led to a restoration of both locomotor ability (24–26) and tactile placing (27). After occipital lobe injury, amphetamine combined with visual experience resulted in the recovery of stereoscopic vision (28,29) in addition to tactile placing (30). Consistent with the data from cortical ablation models, beneficial effects were observed for the recovery of sensory function after ischemic injury to the barrel cortex in rats (31–33), as well as for recovery of motor function after middle cerebral artery distribution infarction (34), traumatic brain injury (35), and skilled reaching after both cortical ischemia (36,37) and ablation injury (38). Dextroamphetamine combined with training also led to long-term improvements in motor task performance after cortical infarction in squirrel monkeys (39). Experimental conditions and behavioral measures may, however, be critical, as not all studies found similar effects (40–43).

If administration of *d*-amphetamine can positively affect functional recovery after brain injury, understanding its pharmacology is important. Amphetamine use can be associated with cardiovascular toxicity even when given to young persons without known vascular disease to treat attention deficit disorders (44). Cardiovascular side effects may be reduced if the drug's action on recovery could be isolated from its effects on blood pressure, cerebral blood flow, and cardiac function. Although amphetamine may affect the release and activity of several neurotransmitters, including dopamine, serotonin, and norepinephrine (45), several lines of evidence suggest that its action on recovery is mediated through norepinephrine.

In rats, intraventricular infusion of norepinephrine has an effect on motor recovery similar to that of amphetamine (46). There is no effect of dopamine infusion if its conversion to norepinephrine is blocked by dopamine-beta-hydroxylase (46). Selective depletion of central norepinephrine with (N-(2-chloroethyl)-N-ethyl-2-bromobenzylamine; DSP-4) impairs motor recovery after a later injury to the cerebral cortex (47,48). Selective injury to the locus coeruleus, the primary source of central noradrenergic projection fibers, also affects motor recovery after a subsequent injury to the rat sensorimotor cortex, although the effect varies between experiments (49–52). When performed at least two weeks

before a unilateral sensorimotor cortex ablation, bilateral, contralateral, and ipsilateral locus coeruleus lesions block locomotor recovery (52).

If the administration of *d*-amphetamine can facilitate poststroke recovery, understanding the neurobiological substrate of its action could have implications for selecting patients for treatment in clinical studies. Because each locus coeruleus has widespread projections, selective lesions of the ipsilateral and contralateral dorsal noradrenergic bundle were used to determine whether norepinephrine levels in the damaged or undamaged hemisphere correlated with recovery. In one experiment, the locus coeruleus fibers innervating each hemisphere were lesioned two weeks prior to a unilateral sensorimotor cortex injury (53). Locomotor recovery was impaired by contralateral but not ipsilateral dorsal noradrenergic bundle lesions. Further implicating norepinephrine and its effects in the opposite, noninjured hemisphere, the overall rate of recovery was correlated with norepinephrine content in the contralateral but not ipsilateral cerebral hemisphere. The observation is intriguing, as studies with functional MRI in humans find changes in the cerebral hemisphere contralateral to a stroke that correlate with motor recovery (54,55).

The neurobiological processes underlying amphetamine (and norepinephrine) modulated recovery remain uncertain. One theme that arises from laboratory experiments is that the effect of *d*-amphetamine on recovery depends on concomitant training. In the original experiments by Feeney and colleagues, the amphetamine effect was blocked if the rats were not allowed to walk rather than being trained in conjunction with drug administration (19). There was also no effect if rats were handled rather than trained, suggesting that specific locomotor experience was required (56). The drug effect on motor recovery in cats was not observed in the absence of training, and there was no reinstatement of depth perception in cats after visual cortex ablation if they were kept in the dark after being given *d*-amphetamine (25,28).

As the effect of amphetamine is long-lasting, administration might be expected to affect anatomic neuroplasticity. *D*-amphetamine, given in addition to training, led to neuronal changes in both the ipsilateral and contralateral cerebral cortex (57). The combination of postinjury training and amphetamine administration was associated with an increase in projection fibers from the contralateral, noninjured cerebral cortex to the pontine motor nuclei (38). Therefore, amphetamine may induce long-term changes in neuronal structure that could, in part, underlie its impact on recovery.

In addition to the importance of concomitant experience/training, drug effects on recovery may also depend on drug dosing and timing relative to the injury. For example, *d*-amphetamine's effect on locomotor recovery after sensorimotor cortex injury in the rat is dose-dependent (58). There was progressive benefit as the dose was increased but a progressive loss of benefit as the dose was increased further. In cats, motor recovery after cortex injury was facilitated when a series of amphetamine/training sessions were provided every four days for two weeks as compared to a single session (25). Amphetamine improved binocular depth perception in visually decorticated cats when given beginning 10 days after injury, but there was no benefit if treatment was delayed for 3 months (28).

Several principles arise from these experimental studies. Some systemically administered drugs such as *d*-amphetamine may modulate recovery after brain injury. The effect depends on concomitant behavioral experience/training. Timing and dosing are critical. For *d*-amphetamine, at least part of the drug effect appears to be exerted in the cerebral hemisphere contralateral to the injury.

PRECLINICAL PHARMACOLOGY

Noradrenergic Agents

Given the hypothesis that *d*-amphetamine acts through norepinephrine, other centrally acting noradrenergic drugs would be anticipated to affect recovery after brain injury. Motor recovery was accelerated by the norepinephrine precursor L-threo-3,4-dihydroxyphenylserine (L-DOPS) (59,60). Effects on recovery similar to amphetamine also occurred after administration of phenylpropanolamine (61), phenteramine (62), and (depending on dosing regimen) methylphenidate (63). Further illustrating the complex interaction of dose and experience, the effect of methylphenidate depended on the number and timing of treatment sessions (63). Single doses of the alpha$_2$-adrenergic receptor antagonists idazoxan and yohimbine, which act to increase synaptic norepinephrine release, facilitated motor recovery when given to rats after unilateral sensorimotor cortex injury (64–66).

Antihypertensives

Antihypertensives that cross the blood–brain barrier act on central noradrenergic receptors and have the potential to affect recovery after brain injury. The alpha$_2$-adrenergic receptor agonist clonidine (67) and the alpha$_1$-adrenergic receptor antagonists phenoxybenzamine (65) and prazosin (65,66) interfere with locomotor recovery after cortex injury. Deficits also transiently reemerge in animals that had recovered motor function when given either clonidine or prazosin (66). In contrast to drugs active at alpha-adrenergic receptors, the beta-adrenergic receptor antagonist propranolol had no effect on locomotor recovery (65).

Major Tranquilizers and Related Drugs

In Feeney's original experiments, he and co-workers not only reported that *d*-amphetamine coupled with training facilitated locomotor recovery in rats, but also that haloperidol impaired recovery (19). It was also found that haloperidol blocked *d*-amphetamine-facilitated recovery of stereoscopic vision in visually decorticated cats (29). Butyrophenones, such as fluanisone and droperidol, can reinstate neurological deficits in rats that recovered motor function after cortex injury (68). These observations raise the possibility that

dopamine, in addition to norepinephrine, might modulate recovery after brain injury. Arguing against this hypothesis, intraventricular administration of norepinephrine improves recovery similar to *d*-amphetamine, but intraventricular dopamine is neutral (46). Because haloperidol and other major tranquilizers also have effects on noradrenergic receptors (69,70), it is hypothesized that their impact on recovery is noradrenergically mediated. The relative dose-dependent detrimental effects of haloperidol and clozapine on post-sensorimotor cortex injury in rats are related to their relative potencies at noradrenergic receptors (71).

Antidepressants

Antidepressants affect the reuptake and metabolism of a variety of central neurotransmitters, including norepinephrine. Serotonin, a target of several antidepressants, modulates the release of norepinephrine through activation of 5-HT3 and possibly 5-HT1C receptors in rat hippocampal neurons (72). In addition, various antidepressants, including fluoxetine, induce neurogenesis in the hippocampus, an effect thought to underlie their delayed impact on depression (73). Facilitation of neurogenesis might have a favorable impact on recovery after brain injury. The administration of a single dose of trazodone, however, transiently slows motor recovery in rats with cortical injury and reinstates the hemiparesis in recovered animals (74). In contrast, desimpramine facilitated, whereas fluoxetine and amitriptyline had no effect on, motor recovery in experimental animal studies (74,75). Another study found that administration of fluoxetine after traumatic brain injury in rats had no impact on memory, balance, or gait (76), and chronic fluoxetine negatively affected assessments of memory and had no effect on electrophysiological measures after dentate gyrus injury in rats (77). Thus, there are only limited preclinical data supporting a direct effect of antidepressants on poststroke recovery, and the data that are available are inconsistent.

Anxiolytics

Diazepam, an indirect gamma-amino butyric acid (GABA) agonist, has a permanent and severe detrimental impact on recovery of sensory function when given after anteromedial neocortex damage in the rat, an action associated with neuroanatomical changes in the thalamus and substantia nigra (78,79). Co-administration of a benzodiazepine antagonist blocks this harmful effect (80). Because anxiolytics that do not act through the GABA/benzodiazepine receptor are neutral with respect to recovery, the detrimental actions of benzodiazepines seem to be due to a specific, receptor-mediated action (81).

Anticonvulsants

The harmful effect of diazepam and other benzodiazepines on recovery after brain injury raises concern for similar actions of other anticonvulsants. Phenobarbital delays recovery from somatosensory deficits after unilateral injury to the cerebral cortex (82), and phenytoin administration worsens sensorimotor deficits after cortex injury in rats (83). In contrast, chronic administration of carbamazepine does not affect recovery (81).

Possible Mechanisms of Neurotransmitter-Modulated Recovery

Diaschisis, a term referring to the remote metabolic depression that occurs in brain structures anatomically and functionally linked but not adjacent to the area of primary injury, can be demonstrated in both animal models (84–86) and humans (87–90). Because *d*-amphetamine's effect on recovery is evident within hours in some animal models, it was hypothesized that drugs that prolong or worsen diaschisis would be detrimental, whereas those that reverse diaschisis would be beneficial (86). Resolution of crossed cerebellar diaschisis in humans, however, is not directly associated with recovery after hemispheric stroke-related hemiparesis (91).

Long-term potentiation (LTP) refers to a change in synaptic efficiency following specific types of neurotransmitter exposure and is thought to represent a physiological mechanism for learning and memory (92). Because the initial effects of *d*-amphetamine on recovery after brain injury occur within hours, and because of the need for concomitant training, induction of LTP is an attractive potential mechanism underlying the effects of at least certain classes of drugs on recovery. LTP is mediated through the N-methyl-D-aspartate (NMDA) receptor complex and leads to activation of both pre- and postsynaptic mechanisms, resulting in a long-lasting effect on synaptic strength. In addition to the hippocampus, LTP (and its correlate, long-term depression) occurs in a variety of brain regions, including the motor (93,94) and visual cortexes (95,96). In addition to amphetamine (97–99), neurotransmitters including norepinephrine (97,98,100–103), serotonin (104), dopamine (105), GABA (106–108), and acetylcholine (100,109–111) can affect the induction of LTP. Further, the impact on recovery of a variety of drugs acting on central neurotransmitters can be explained based on their effect on LTP (112–114). The effects of norepinephrine on synaptic function and plasticity, however, are complex and may vary in different brain regions (115).

Pharmacological Effects on Poststroke Recovery in Humans

Reduction in Dependence and Disability

There have been several clinical studies assessing the effects of amphetamine on poststroke recovery in humans (Table 12.1).

The studies were small and have important differences in methodologies. An initial "proof-of-concept" study randomized eight subjects with stable poststroke motor deficits to receive either 10 mg of *d*-amphetamine or placebo

TABLE 12.1 Comparative Clinical Trials of the Effects of Amphetamine on Poststroke Motor Recovery

STUDY	N	STROKE-TREATMENT INTERVAL	*d*-AMPHETAMINE DOSE/ TREATMENT FREQUENCY	DRUG-THERAPY SESSION INTERVAL (DURATION)	OUTCOME ASSESSMENT
Crisostomo et al. (1988) (116)	8	<10 days	10 mg, one session	<3 hour (45 min)	1 day
Reding et al. (1995) (118)	21	>1 month	10 mg daily for 14 days, then 5 mg daily for 3 days	Same day (? Duration)	1 month
Walker-Batson et al. (1995) (152)	10	16–30 days	10 mg every 4 days for 10 sessions	"Peak of drug action" (? Duration)	1 week and 1 year
Sonde et al. (2001) (119)	39	5–10 days	10 mg twice weekly*	1 hour (30 min)	3 months
Martinsson et al. (2003) (120)	30	<96 hours	5 or 10 mg once or twice daily for 5 days	Same day** (15 min vs. 30–45 min)	3 months and 1 year
Treig et al. (2003) (121)	24	<6 weeks	10 mg every 4 days for 10 sessions	1 hour (45 min)	90 days and 1 year
Gladstone et al. (2006) (122)	71	5–10 days	10 mg twice weekly for 10 sessions	90 min (1 hour)	6 weeks and 3 months

**dl*-amphetamine.
**Duration of physiotherapy varied (both groups received *d*-amphetamine).
Source: From Ref. (153). Goldstein LB. Amphetamine trials and tribulations. *Stroke*. 2009;40(Suppl 1):S133–S135.

coupled with physical therapy within 10 days of ischemic stroke (116). As assessed 24 hours later, the *d*-amphetamine-treated group had a significant improvement in motor performance compared to the placebo-treated group. The study, however, involved only a small number of highly selected patients and the clinical significance of the effect was uncertain.

A second double-blind, placebo-controlled trial included 5 *d*-amphetamine- and 5 placebo-treated patients with treatment given in conjunction with physical therapy once every 4 days for 10 sessions beginning 15 to 30 days after stroke (117). Amphetamine-treated patients had significantly greater improvements in motor scores compared to placebo-treated patients, with a consolidation of the benefit after treatment was completed.

Other studies using different or similar trial designs have failed to confirm these observations. In one study, a set of randomized 24 subjects received 10 mg of amphetamine daily for 14 days followed by 5 mg for 3 days or placebo (118). The subjects were enrolled more than one month after stroke, and there was no tight coupling between drug administration and physical therapy. Compared to the previous studies, there was a longer delay between stroke and treatment, and physical therapy was not temporally linked to drug exposure. Other negative studies evaluated *dl*- rather than *d*-amphetamine (119), or used different dosing regimes, intervals between treatment sessions and treatment durations, or only included subjects with severe deficits (120). Two additional trials using a treatment and dosing regimen similar to the single positive study with longer-term follow-up also failed to find benefit (121,122).

Overall, the results of clinical trials evaluating the effect of *d*-amphetamine combined with physical therapy on poststroke motor recovery have been disappointing and have not fulfilled the promise anticipated from the extensive preclinical data. Although a meta-analysis based on 6 studies (176 patients) found a better relative change from baseline to last follow-up in motor function (weighted mean difference –6.1 points; 95% CI –10.4 to –1.9), baseline imbalances may have led to a trend for more deaths at the end of follow-up among subjects randomized to amphetamine treatment (OR 2.8, 95% CI 0.9 to 8.6) (123). As mentioned earlier, it was concluded that "too few patients have been studied to draw any definite conclusions about the effects of amphetamine treatment on recovery from stroke."

Methylphenidate is used as a psychostimulant and antidepressant in apathetic patients to improve their participation in physiotherapy (124,125). As reviewed earlier, preclinical data suggested benefit in improving motor recovery after brain injury, but the dosing and treatment schedule is critical (63). Two clinical studies did not find any treatment-associated improvement in motor recovery with methylphenidate, although cardiovascular side effects occurred (126,127).

An uncontrolled study of L-DOPS combined with physiotherapy was conducted in a group of subjects with chronic, stroke-related motor deficits (128). The subjects' average Fugl-Meyer motor score improved by 4.4 points ($P < .001$), and 10-minute walk time was shortened by 16% ($P < .001$) after 28 days of drug administration. Because the study was not controlled and physiotherapy alone can improve motor function even in the setting of established

deficits (129,130), the clinical significance of the observation is not certain.

Poststroke depression is common, and antidepressants of various classes are used not only to treat the attendant psychiatric symptoms but also to improve the patient's participation in rehabilitative interventions (131). The effects of two norepinephrine reuptake blockers (i.e., nortriptyline (132), maprotiline (133)) on poststroke disability were neutral when given chronically. Drugs increasing norepinephrine levels are anticipated to facilitate recovery based on the reviewed preclinical pharmacology. Dosing, however, may be critical. Brain norepinephrine content is reduced after chronic but not acute administration of desipramine (134). Trazadone is an antidepressant that blocks alpha$_1$-adrenergic receptors and interferes with motor recovery after cortex injury in rats (74). A small clinical trial, however, found that its chronic administration to depressed stroke patients receiving physical therapy led to improvements in their activities of daily living (135). The discrepancy could be due to different pharmacological effects of one-time versus chronic administration on norepinephrine levels, or related to its action on serotonin levels, or due to its antidepressant effects.

As noted earlier, there are scant preclinical data showing an effect of serotonergic drugs on recovery after brain injury. Despite this, a small clinical study suggested that the selective serotonin reuptake inhibitor (SSRI) fluoxetine might facilitate poststroke recovery (133). This was followed by the fluoxetine for motor recovery after acute ischemic stroke (FLAME) trial that randomly assigned 118 fluoxetine 20 mg daily or placebo for 3 months beginning 5 to 10 days after symptom onset (136) to subjects with stroke-related moderate to severe hemiparesis. Improvement at 90 days was greater in the fluoxetine group (adjusted mean 34.0 points on the Fugl-Meyer score [95% CI 29.7–38.4]) than in the placebo group (24.3 points [19.9–28.7]; $P = .003$). There was also benefit as assessed by the modified Rankin score (mRS) at 90 days, with 26% of those treated with fluoxetine compared to 9% of those who received placebo being independent (mRS 0–2, $P = .015$). The effect was independent of depression. The trial, however, included only a small number of subjects, and whether the benefit is sustained over time is not known.

A meta-analysis of the effects of SSRIs on poststroke disability included data from 13 trials of fluoxetine, 1 trial of sertraline, 3 trials of citalopram, and 5 trials of paroxetine (n = 1,310) (137). Treatment with an SSRI was superior to controls (standard mean difference 0.92, 95% CI 0.62–1.23; number needed to treat = 3) with no evidence of differences among the antidepressants. Many of the trials were small, and there was significant heterogeneity among the studies due to methodological and other differences. It was concluded that SSRIs might be associated with improved poststroke recovery but that much of the evidence is of poor quality and that larger, high-quality studies are needed.

Recovery From Aphasia

Although this discussion is primarily focused on poststroke motor recovery, clinical studies have also evaluated pharmacological approaches for reducing stroke-related language impairments (138,139). A double-blind study randomized 21 subjects who had poststroke aphasia to 10 mg *d*-amphetamine or placebo between 16 and 45 days after stroke, using a treatment schedule similar to the trial that was found beneficial for motor recovery (117). Improvement, assessed with the Porch Index of Communicative Ability, was greater one week after treatment was completed in those who received *d*-amphetamine ($P = .015$). The difference between the groups, however, was no longer significant after six months ($P = .048$) after correction for multiple comparisons. Two randomized trials found no benefit of bromocriptine on any measure of aphasia (140,141). Although there are a variety of potential explanations for this negative finding, the results are not surprising, because preclinical studies suggested that recovery is mediated through noradrenergic rather than dopaminergic mechanisms.

Piracetam is a derivative of GABA that has no effect on the synthesis, release, or uptake of GABA and has no effect on GABA postsynaptic binding but does have effects on the cholinergic system and increases synaptic norepinephrine release (142). It also has diverse effects on blood flow and platelet reactivity, but its specific mechanism of action is unknown, and there are virtually no preclinical studies assessing its potential impact on poststroke recovery. Despite this, it has been described as the first *nootropic* (cognition-enhancing) agent, and has been evaluated for improving cognition in patients with dementia (143,144), with several trials assessing its impact on recovery after stroke in humans. A small trial found a transient improvement in aphasia in subjects randomized to receive piracetam (145), with a second small study finding benefits in some language subtests at the end of six weeks of treatment (146). A third found only trends toward benefit (147). It remains unclear whether piracetam treatment results in a clinically meaningful, long-term benefit.

Impairment of Recovery

Several of the centrally acting drugs with the capacity to negatively affect poststroke recovery are commonly given to patients who have had an ischemic stroke to treat comorbid and concomitant medical problems (148). These include various antihypertensives, anti-epileptics, anxiolytics, and major tranquilizers. Whether these drugs have a detrimental effect on recovery in humans can only be assessed in retrospective studies, which have a series of inherent limitations, including unmeasured confounding. With this caveat, a retrospective cohort study (n = 58) found that the motor recoveries of stroke patients who received one or a combination of the antihypertensives clonidine or prazosin, major tranquilizers, benzodiazepines, or the anticonvulsant phenytoin had poorer recoveries than those who did not receive one of these drugs, even after adjustment for other factors,

including initial stroke severity (149). Similar results were found in a retrospective analysis of data from a prospective clinical trial focused on poststroke recovery in which nearly 40% of 96 control subjects received one or a combination of potentially harmful drugs (72% in the "detrimental" group received a benzodiazepine, 22% a major tranquilizer or related drug, 14% an alpha$_2$-adrenergic receptor agonist, 8% an alpha$_1$-adrenergic receptor antagonist, and 6% phenobarbital or phenytoin) (150). There were significant differences in recovery based on the drugs the subjects had received, with recovery being impaired in those who had received a "detrimental" drug. The finding was further replicated in an analysis of a third independent cohort (151). This study included 154 patients admitted to a rehabilitation hospital within 2 months of stroke. In this group, 19% received a benzodiazepine, 13% a major tranquilizer or related drug, 3% an alpha$_2$-adrenergic receptor agonist, 8% phenobarbital, and 3% phenytoin. After multivariable adjustment, those who received a potentially detrimental drug were found to have significantly poorer recoveries.

CONCLUSION

Preclinical studies provide clear and consistent evidence that a variety of centrally acting drugs affecting specific neurotransmitters can either favorably or unfavorably modulate recovery after brain injury. Although at least some studies suggest similar effects in humans, results have been inconsistent. The impact of important factors such as drug dose, duration and intensity of physiotherapy, and timing between injury and treatment are difficult to translate from preclinical studies. Issues related to variability in stroke severity, involved structures, and comorbid conditions further complicate trial design and could obscure a true treatment effect. Because of these and other issues, the design of efficacy trials assessing putative neurorestorative interventions is not trivial. Although a proven pharmacological approach resulting in a clinically meaningful improvement in poststroke recovery remains elusive, it is reasonable to avoid medications that may have harmful effects in patients who have had a stroke. It is also important to control for these possible harmful effects in future clinical trials assessing the outcomes of stroke patients after the acute period.

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III

NEUROLOGIC IMPAIRMENTS AND THEIR TREATMENT

13

Aphasia, Apraxia of Speech, and Dysarthria

Leora R. Cherney and Steven L. Small

Speech and language problems are common sequelae of stroke that significantly impact the daily lives of stroke survivors. Reduced speech and language skills have negative ramifications for the individual's social, vocational, and recreational activities, often leading to social isolation, loneliness, loss of autonomy, restricted activities, role changes, and stigmatization (1–7). Given the importance of communication to the stroke survivor's quality of life, it is essential that rehabilitation professionals recognize and address the speech and language disorders associated with stroke.

Normal speech and language are extraordinarily complex. A number of steps are required, some accomplished sequentially and some in parallel, that incorporate the following: (a) conceptualization of an idea and generation of a communicative goal; (b) formulation of a grammatically structured sequence of verbal symbols (words), each consisting of an interacting set of ordered sounds; (c) selection of a series of neural commands or sensorimotor "programs" that will activate the speech muscles at appropriate coarticulated times, durations, and intensities; and (d) central and peripheral nervous system innervation of muscles of respiration,[1] phonation, resonance, and articulation to produce the intended acoustic signal.

Stroke can disrupt any of the stages of speech and language, resulting in one or more of the disorders of aphasia, apraxia of speech (AOS), and dysarthria. Disruption to the initial stage involving the structure and rules of the linguistic message results in *aphasia*. Impairment of the capacity to plan and program sensorimotor commands for the positioning and movement of muscles for the volitional production of speech results in AOS. It can occur without significant weakness or neuromuscular slowness and in the absence of disturbances of conscious thought or language (8). *Dysarthria* results from abnormal neuromuscular execution that affects the speed, strength, range, timing, or accuracy of speech movements. Dysarthria can affect respiration, phonation, resonance, articulation, and prosody, either singly or in combination.

Although by definition the disorders of aphasia, AOS, and dysarthria are distinguishable, in practice they often co-occur, making it challenging for even the experienced clinician to distinguish between them. Yet, distinguishing aphasia from dysarthria and both disorders from AOS can be important not only because of the neurologic implications regarding underlying pathology, but also because a specific diagnosis can have implications for selection of the appropriate management techniques and strategies.

This chapter, therefore, is divided into three parts, each of which addresses the primary characteristics of aphasia, AOS, and dysarthria, as well as assessment suggestions and management strategies. It will become obvious that the section on aphasia is far more detailed than the sections on the other two disorders. There are several reasons for this disparity, including differences in the incidence and prevalence of these disorders following stroke, the severity and persistence of the disorders, and their impact on the stroke survivor. The disparity also reflects our current knowledge of these disorders following stroke. For example, though there is a large body of literature about the characteristics of dysarthria and its assessment and treatment in general, relatively little pertains to dysarthria resulting specifically from stroke. There is far more research on the diagnosis and treatment of dysarthrias that are caused by Parkinson's disease, amyotrophic lateral sclerosis (ALS), and other progressive neuromuscular disorders. By contrast, stroke is the leading cause of aphasia, and most of the literature on aphasia relates to aphasia that is caused by stroke. Furthermore, as vascular lesions are not functionally selective—the same arteries and arterial branches supply brain areas that mediate functions important for all three disorders—the diagnosis and treatment of aphasia often must take into consideration these other disorders concomitantly.

APHASIA

Aphasia has been defined as a multimodality language disorder resulting from damage to brain areas that subserve the formulation and understanding of language and

[1] *Respiration*, by strict definition, refers to the exchange of gases between the bloodstream and the environment, whereas *ventilation* refers to the exchange of air between the lungs and the environment. However, it is customary for speech–language pathologists to refer to the breathing muscles of inhalation and exhalation as the muscles of respiration. Therefore, the term *respiration* rather than the term *ventilation* is used in this chapter.

its components (i.e., phonology, syntax, morphology, and semantics). Although it is beyond the scope of this chapter to provide a tutorial on language, it is important for those involved in aphasia rehabilitation to have a basic understanding of these different components of language to clarify the definition and to provide some basis for the discussion of rehabilitation.

Language Components

Phonology

Phonology refers to the linguistically important speech sounds or phonemes of a language and the rules for combining them. It is contrasted with *phonetics*, which is involved with the physical production of these sounds. Each consonant or vowel in a language may take a number of different pronunciations. For example, the letter *c* can sound like *k* or like *s*, and each pronunciation within that language is considered a *phoneme*. Many patients with aphasia have problems at the phonological level of processing. On the production side, they may substitute one phoneme or one syllable (combination of phonemes) for another, and on the comprehension side, patients can misinterpret particular phonemes or syllables, thereby hearing an unintended word and misinterpreting what is being said. Obviously, ascertaining these phonological errors in production is easier than in comprehension.

Syntax and Morphology

Syntax (or *grammar*) is the set of rules that governs the structure of sentences in a particular language, whereas *morphology* refers to the internal structure of words. In both cases, the structural rules have specific impacts on meaning. In English, for example, the addition of *-ed* to many regular verbs changes their tense, and the addition of *-s* to many regular nouns changes them from singular to plural. Word order plays an important role in syntactic processing in English, unlike other languages (e.g., Italian, German) where word order plays less of a role, and affixation or even semantic context are more important (9). This can lead to differences in the manifestations of aphasia across languages.

Syntactic impairments are common in aphasia. Some observers believe that grammatical processing problems are characteristic of patients with damage to the frontal part of the left perisylvian region and have called this disorder *agrammatism*. Such patients are more likely to say and understand single meaningful words, called *content words* (e.g., nouns and verbs), than they do the small *function words* (e.g., prepositions, articles). Importantly, the content words of a language form an *open class* (i.e., one to which new items can be added), whereas function words form a *closed class*. Function words do not denote objects, actions, or locations but rather play a role similar to word affixes and word order in guiding sentence production or interpretation. A less common syndrome called *paragrammatism* involves grammatical processing problems and results from damage to the posterior (temporoparietal) portion of the left perisylvian region (10,11).

Semantics

Semantics is meaning, and conveying meaning in context is the fundamental goal of communication. The study of word meanings is called *lexical semantics*. The study of sentences and their different meanings—conveying entire "thoughts" or statements—is called *sentential semantics*. The meanings of sentences are built up from a combination of the meanings of the individual (content) words in the sentence, the syntactic aspects of word order, function words, word affixes, and the higher linguistic context (i.e., the entire conversation or discourse).

Lexical semantic processing is often disrupted in aphasia. Many patients with stroke cannot find the names of objects and actions that they understand visually and functionally. They may substitute a related but unintended word for the target word. Patients with agrammatism sometimes cannot distinguish the subject from the object of a sentence, particularly if word order is less common (e.g., in a passive sentence) and the subject and object words are both able to perform the actions (e.g., the boy was kicked by the girl). This is a problem of syntax and sentential semantics.

Working Memory

Certainly it is not possible to use language without various types of memories, including memory for words, grammatical rules, affixation rules, and so forth. Separating out language-specific memory from other types of memory is a topic of significant controversy, and one that we do not address here. However, one type of memory is particularly important in the understanding of aphasia and that is *working memory*, the memory that is required to maintain the partial fragments of what is being heard or said to ensure completion of the comprehension or production of the desired word, phrase, or sentence (12). All language computations require this type of very short-term memory, and it is commonly disrupted in aphasia (13,14).

Language Modalities

As aphasia is a multimodality disorder of language, it impairs, in varying degrees, the understanding (input) and expression (output) of both oral and written language modalities. Producing and understanding oral speech requires mechanisms for encoding and decoding auditory waveforms and mechanisms for encoding and decoding the words and sentences that constitute the message. As oral speech is both the phylogenetic and ontogenetic backbone of language—it is learned first and in some cases exclusively—it is thought to be the evolutionary foundation and architectural core of the neural circuits involved in language. Patients with disorders of spoken language production and comprehension usually have concomitant problems in the written modality, reinforcing the ontogenetic coupling of these two neuroanatomical systems.

Consequently, aphasia is defined in terms of impairments in oral expression (speaking) and understanding,

and a preponderance of treatment approaches are aimed directly at this form of communication. To the extent that the oral and written modalities share underlying mechanisms, such as lexical retrieval and sentence syntax and semantics, treatment need not be modality specific. However, when the language deficit is inextricably entwined with modality-specific problems, such as AOS, treatment that targets the specific modality might be preferable.

Producing written language requires neural and motor mechanisms for encoding a message in letters and visual words and performing the somatic motor movements to write or type the visual product. Understanding written language requires distinguishing particular visual stimuli as linguistic and then decoding them into letters, words, and sentences. There is also neural circuitry to convert these visual stimuli into phonological forms. Although it has not been completely determined when and how such circuitry is used, it seems to play its most important role in the case of less common (or pretend) words with regular spellings. It can also play a role in certain reading disorders caused by stroke. Disorders of reading and writing are an integral part of the aphasia, suggesting a significant degree of common underlying neural substrate for language processing from the oral and written modalities. When a writing disorder occurs that is disproportionate to the degree of impairment in speaking, it is called *dysgraphia* (or *agraphia*). The analogous reading disorder is called *dyslexia* (or *alexia*).

Anatomy of Language

In 1861, Pierre Paul Broca presented a paper to the Anatomical Society of Paris discussing the autopsy findings of his patient with a language disorder (15). Broca found a large brain lesion in the left inferior frontal region (the frontal "convolutions") and postulated a role for this region in the physiology of language. Although neurologists prior to Broca had suspected and even published similar arguments (16), Broca is generally acknowledged as the initiator of the modern study of language and the brain through the method of clinicopathologic correlation (*lesion analysis* or *neuropsychological localization*) (17,18). Following this work, a number of additional papers were published on the brain mechanisms of language, including those by Wernicke (1874), Lichtheim (1884), Grashey (1885), and Freud (1891) (19–22). Their work led to the general notions that (a) the left perisylvian region is anatomically responsible for most of the neural mechanisms of language; (b) the codes and processes of the language output channel are anatomically instantiated by structures in and around the opercula of the left inferior frontal gyrus; and (c) the analogous codes and processes for the language input channel are anatomically centered around the posterior aspect of the superior temporal gyrus (20).

Thus, the classical zone of language, as defined by Dejerine in the late 19th and early 20th centuries, was located in the left hemisphere within the distribution of the middle cerebral artery, surrounding the sylvian fissure on the lateral surface of the hemisphere and incorporating portions of the frontal, parietal, and temporal lobes (23). The zone includes Broca's area (in the premotor region of the frontal lobe) anteriorly and Wernicke's area (auditory association cortex in the posterior portion of the superior temporal gyrus) posteriorly. Connecting Wernicke's and Broca's areas is a subcortical white matter pathway (i.e., the *arcuate fasciculus*, which is a portion of superior longitudinal fasciculus) that passes through the angular gyrus and supramarginal gyrus at the posterior rim of the sylvian fissure, where the temporal and parietal lobes come together (23). The location of these critical language areas is illustrated in Figure 13.1.

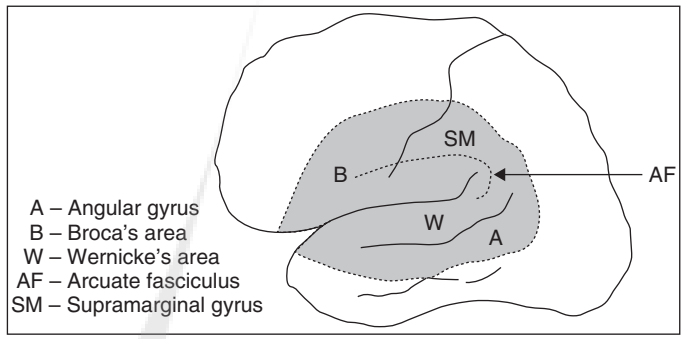

FIGURE 13.1 Diagrammatic representation of the cortical areas that are critical for language.

Source: Reprinted from Ref. (32). Albert ML, Helm-Estabrooks N. *Manual of Aphasia and Aphasia Therapy*. 2nd ed. Austin: Pro-Ed; 2004, with permission.

Since that time, much research has been done within the lesion analysis method, and some of the finer functional structures of these areas have been determined. Most recently, the development of noninvasive in vivo neuroimaging techniques, such as computer tomography (CT), positron emission tomography (PET), static and functional magnetic resonance imaging (sMRI and fMRI, respectively), electroencephalography, transcranial magnetic stimulation, and magnetoencephalography, has transformed the study of the neurologic basis of language.

In some ways, though, the anatomical localization of function has become more rather than less muddled. For example, there is a yet unresolved debate about the specific role of Broca's area during language processing (24,25). One line of research suggests that Broca's area plays a specific role in syntactic processing (26,27), whereas another line of research suggests that it serves a more general function and is responsible for a variety of tasks including working memory (24).

Behavioral data have been supplemented by functional neuroimaging (28) with increasing evidence having accrued to challenge the concept that small regions of the brain are specifically responsible for language functions such as comprehension or naming. This is not to say that brain regions do not have specific functions or that there are no neural circuits to perform these classically determined functions.

It simply appears that the homomorphic relationship between historically important brain regions and functions has broken down. The same problem holds for other brain regions, such as the thalamus, basal ganglia, and the inferior parietal lobule, and other functions (29).

Current theory therefore rejects the notion of a one-to-one correspondence between specific linguistic structural elements and focal segments of the brain. Rather, it recognizes the existence of distributed anatomical circuits, interactivity among regions, and different types of functions (28,30,31). It takes into account evidence that multiple complex and overlapping neuronal systems most likely are involved in language processing. As Albert and Helm-Estabrooks explain, the networks include cortical and subcortical components, some of which are near each other providing the basis for regional contributions to language; others are more distant, providing the basis for widely distributed parallel processing of aspects of language (32). All the regional and widely distributed networks are multiply interconnected.

Within the classical zone of language, there is extensive superposition of the neural networks critical to language. These areas of multiple overlap may correspond to what in classical neurology were called the "centers" of language (20). As these areas likely represent "critical crossroads, points of intersection, or points of integration for processing selected elements of language," a focal lesion in one of these critical locations could potentially result in a predictable aphasia deficit (32).

The Aphasia Syndromes: Assessment and Differential Diagnosis

Over the past 150 years, aphasiologists have developed several taxonomies for distinguishing various aphasia subtypes. These classification systems range from simplistic severity systems to more complex syndrome approaches (33). Perhaps the most widely used classification system is the Boston classification system, so named because it was based on early classical descriptions of aphasia subtypes and brought to the fore in the 1960s by Boston-based aphasiologists including Geschwind, Benson, Goodglass, and Kaplan (34,35). This classification system applies the early connectionist descriptions of aphasia subtypes and cortical syndromes and is still in use today by many practitioners.

Although there are compelling arguments both for and against classifying in aphasia, the use of some common classification system helps the clinician understand the basic relationships between the aphasia syndrome, various patterns of language impairments, and their source in the central nervous system (32). In addition, it provides a common language for the efficient communication of patient information within and across professional disciplines. Therefore, the assessment and differential diagnosis of the aphasia subtypes is presented first, and cautions about the application of the classification system are discussed in the following section.

Syndrome Classification of Aphasia

Three language behaviors are helpful in classifying aphasia by syndrome: fluency of verbal output, auditory comprehension, and repetition.

Assessment of Fluency

Nonfluent aphasia is characterized by language output that is slow, labored, and effortful. The individual may have difficulty initiating speech, and agility of the articulatory movements is reduced. Phrase length is short, and agrammatism is typically present. In contrast, fluent aphasia is characterized by normal prosody, easy articulation, adequate phrase length, and varied syntax.

Phrase length has been defined as the number of words produced continuously without a significant pause. However, there is variability in aphasia fluency, which is affected by several factors including the emotionality of the topic, memory demands, and vocabulary constraints. To more objectively determine phrase length, using the best average phrase length from three different narrative tasks such as describing a picture, responding to an open-ended question (e.g., What happened to you?), and responding to a historical question of emotional significance (e.g., Where were you on September 11, 2001?) has been suggested (32). A best average phrase length of five words or less is categorized as "frankly nonfluent," whereas a best average phrase length of nine words or more is categorized as "frankly fluent." Patients who are nonfluent usually have a lesion anterior to the central sulcus, and these include Broca's aphasia, transcortical motor aphasia, and global aphasia. Those with fluent aphasia typically have a lesion posterior to the central sulcus. The fluent aphasias include Wernicke's aphasia, conduction aphasia, transcortical sensory aphasia, and anomic aphasia. A third group with a best average phrase length of 6 to 8 words is called "borderline fluent" and may include individuals with nonfluent aphasia who have demonstrated some degree of recovery as well as individuals with aphasia resulting from subcortical strokes (32).

Assessment of Auditory Comprehension

The second differentiating language behavior is auditory comprehension. Auditory comprehension is poor in individuals with global aphasia, Wernicke's aphasia, and transcortical sensory aphasia. Although auditory comprehension is relatively good in the other types of aphasia, difficulties may occur with understanding more complex information such as multistep commands or a lecture. Therefore, assessment requires several tasks that range in difficulty from the single word to lengthy complex materials. Auditory comprehension is often assessed with questions that require a "yes/no" response. In these cases, it is important to ensure that the person does indeed have a reliable "yes/no" response—either verbal or nonverbal (e.g., nodding the head, thumbs up or down, pointing to the written word *yes* or *no*). As there is always a 50% chance of getting the response correct, some tests present pairs of questions, both of which must be

answered correctly for credit to be given. At the single-word level, comprehension tasks usually include identification of different objects, actions, body parts, colors, and numbers, as word frequency and semantic class influence comprehension. The ability to follow single and multistep commands should also be assessed; however, when responses require body movements or object manipulation, some individuals may fail because of their motor/limb apraxia and not because of their aphasia. At the level of complex, lengthy material, it is important to consider the familiarity of the topic, the context in which the material is presented, and whether the questions or discussions are based on factual or implied and inferential information.

Assessment of Repetition

Repetition is the third language behavior that can assist with the classification of aphasia. In particular, the presence of relatively preserved repetition skills can help identify the transcortical aphasias, whereas relatively poor repetition skills in an individual with fluent aphasia may help differentiate conduction aphasia from anomic aphasia. Repetition tasks should include words of different semantic categories and frequencies and different syllable length and phonological complexity as well as phrases and sentences of different length and complexity. When making a differential diagnosis, the examiner should consider the relative preservation or disturbance of repetition skills as compared to spontaneous conversational speech. Many problems with repetition appear to relate to limited working memory for different types of linguistic fragments.

Table 13.1 describes each of the classical aphasia syndromes and illustrates how fluency, comprehension, and repetition are differentially impaired in each type of aphasia.

Assessment of Aphasia: Other Considerations

Word Retrieval. Word-retrieval problems are a core feature of aphasia. However, as they are present in all aphasias, they do not serve to distinguish among aphasia types. Nevertheless, assessment of their severity (which may range from mild difficulty in producing a desired word during conversation to virtual inability to produce the target word in any conditions) and an analysis of the types of naming errors that occur are important for treatment planning. In addition, it is important for the practitioner to ascertain that the word-finding problems are independent of other causes such as memory problems, thought disorders, or confusional states (32). There are several ways to assess word retrieval, including presentation of objects and pictures for naming, using pictured scenes and free recall tasks such as conversation, or explaining directions for a familiar route or the procedures for completing a familiar task (e.g., making a sandwich), which allow the clinician to observe the naming difficulties in connected language. Generative naming or word-fluency tasks in which the person is asked to name as many items as possible within a particular category (e.g., animals, words starting with a specific letter) may also be used.

Reading and Writing. Similarly, virtually all individuals with aphasia display reading and writing problems, although the assessment of reading and writing skills does not contribute to the differential diagnosis of the classical aphasias. Most standardized tests of aphasia include tasks that assess reading comprehension and written expression at different levels of complexity beginning with single letters and moving to word, phrase, sentence, and paragraph levels. In addition, there are tests that are specifically aimed at assessing these skills, and a comprehensive treatment plan for aphasia should address treatment of the reading and writing problems.

Standardized Tests of Aphasia. A variety of standardized tests have been developed specifically for the assessment of aphasia. Table 13.2 lists those that are commonly used in clinical practice and characterizes the language functions that they assess. In addition to these formal tests, clinicians also use informal tasks to assess functional everyday performance; selection of these tasks depends on the individual patient's communication needs and goals.

Cognition. Although aphasia is a language disorder, examination of all domains of cognition is important for successful rehabilitation of the person with aphasia. The ability to maximize the use of residual language, compensate for language deficits, and return to independence depends to a large extent on the integrity of other aspects of cognition, which can be used to assist with communication and other functional activities of daily living. However, accurate assessment of cognitive skills in the presence of aphasia is a challenge, as many neuropsychological tests depend on language skills to varying degrees, thereby making them less reliable for use with patients with aphasia. The Mini-Mental State Examination (36), commonly used in the assessment of dementia, has poor validity for patients with aphasia who, for example, may be fully oriented to place and time but are unable to state or write the month, day, facility name, and so forth.

A commonly used test of nonverbal cognitive ability is the Ravens Colored Progressive Matrices (RCPM) (37), a test of visual analogic thinking that uses design patterns and requires a pointing response. In fact, a portion of this test has been integrated into the Western Aphasia Battery (38,39), which, in addition to yielding an aphasia quotient, also provides a cognitive quotient (CQ) score. The CQ represents a summary of scores from the RCPM together with constructional, visuospatial, and calculation tasks. In addition, the Cognitive Linguistic Quick Test (40) was designed for individuals with aphasia and provides a screening of the areas of attention, memory, and executive skills.

Classifying Aphasia Syndromes: Cautions

There are as many reasons not to use classification systems in aphasia as there are arguments in its favor; even the authors of this article are not in agreement on this issue. However, use of such systems represents a valuable shorthand, and even if these systems do not have strong validity for neurolinguistic research (41–43), they may have some advantages in the clinical setting.

TABLE 13.1 Characteristics of the Cortical Aphasias

TYPE OF APHASIA	FLUENCY	ORAL EXPRESSION: OTHER FEATURES	AUDITORY COMPREHENSION	REPETITION
Broca's aphasia	Nonfluent. Slow and effortful output. Short phrase length (less than 4 words). Disrupted prosody of speech.	Agrammatism—uses primarily substantive content words (nouns, verbs) with few function words (pronouns, prepositions, articles). Most sentences are simplified. May have an associated apraxia of speech.	Relatively good comprehension except for sentences that involve syntactic complexity.	Poor.
Wernicke's aphasia	Fluent. Well-articulated speech, often produced at an increased rate. Phrase length greater than four words.	Paraphasic errors (sound substitutions). In the severest cases, neologisms may dominate so that output consists of prosodic fluent-sounding jargon. In other cases, speech may be characterized as empty (lack of content words, perseverations).	Poor. Do not self-monitor and are often unaware that they are not communicating information.	Poor.
Anomic aphasia	Fluent. Word-finding pauses may interrupt speech flow, but average phrase length is within normal ranges.	Uses grammatically correct sentences. Clear difficulty finding words. May circumlocute or use nonspecific terms (e.g., thing, this, that) when they cannot find the word they want.	Good.	Good.
Conduction aphasia	Quite fluent with normal average phrase length. May be word-finding pauses. Attempts to self-correct phonemic paraphasias may also disrupt the fluency of speech.		Good but may show verbal short-term/working memory deficits.	Poor. Major deficit is the inability to repeat.
Global aphasia	Nonfluent. Severely impaired.	Stereotypic utterances may be present. They are produced during attempts to verbalize and consist of repetitive nonsense syllables or real words, often well articulated with prosodic variation.	Severely impaired.	Severely impaired.
Transcortical motor aphasia	Nonfluent. Slow and effortful output. Short phrase length (less than 4 words). Disrupted prosody of speech.	Impaired initiation of verbal output. Agrammatic.	Relatively good comprehension, except for sentences that involve syntactic complexity.	Major characteristic is the good repetition in relation to speech output.
Transcortical sensory aphasia	Fluent. Well-articulated speech, often produced at an increased rate. Phrase length greater than four words.	Paraphasic errors—includes both sound and word substitutions.	Poor. Do not self-monitor and are often unaware that they are not communicating information.	Major characteristic is the good repetition.
Mixed nonfluent aphasia	Nonfluent. Verbal output may be limited to stereotypic utterances, but sometimes meaningful speech is produced with articulatory effort.	Phonemic paraphasias and perseverations. Severity lies somewhere between global and Broca's aphasia; may occur as the patient recovers from global aphasia.	Auditory comprehension poor but not as severely impaired as in global aphasia.	Poor repetition.

TABLE 13.2 Commonly Used Standardized Language Tests for Aphasia Showing the Modalities Assessed

TEST	AUDITORY COMPREHENSION	ORAL EXPRESSION	READING COMPREHENSION	WRITTEN EXPRESSION
Western Aphasia Battery—Revised[1]	×	×	×	×
Boston Diagnostic Aphasia Examination—3rd edition[2]	×	×	×	×
Porch Index of Communicative Ability[3]	×	×	×	×
Communication Activities of Daily Living—2nd edition[4]	×	×	×	×
Boston Assessment of Severe Aphasia (BASA)[5]	×	×	×	×
Aphasia Diagnostic Profiles[6]	×	×	×	×
Psycholinguistic Assessments of Language Processing in Aphasia[7]	×	×	×	×
Comprehensive Aphasia Test[8]	×	×	×	×
Boston Naming Test[9]		×		
Revised Token Test[10]	×			
Reading Comprehension Battery for Aphasia—2nd edition[11]			×	
Discourse Comprehension Test[12]	×		×	

Sources:
[1]From Ref. (39). Kertesz A. *Western Aphasia Battery Revised*. Harcourt Assessment, Inc, San Antonio, TX: Harcourt Asessment Inc; 2007.
[2]From Ref. (46). Goodglass H, Kaplan E, Barresi B. *The Assessment of Aphasia and Related Disorders*. 3rd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2001.
[3]Porch BE. *Porch Index of Communicative Ability*. Palo Alto, CA: Consulting Psychologists Press; 1981.
[4]Holland AL, Frattali CM, Fromm D. *Communication Activities of Daily Living*. 2nd ed. Austin, TX: Pro-Ed; 1998.
[5]Helm-Estabrooks N, Ramsberger G, Nicholas M, Morgan A. *Boston Assessment of Severe Aphasia*. Austin, TX: Pro-Ed; 1989.
[6]Helm-Estabrooks N. *Aphasia Diagnostic Profiles*. Austin, TX: Pro-Ed; 1992.
[7]Kay J, Lesser R, Coltheart M. *PALPA: Psycholinguistic Assessments of Language Processing in Aphasia*. East Sussex, UK: Lawrence Erlbaum; 1992.
[8]Swinburn K, Porter G, Howard D. *The Comprehensive Aphasia Test*. Hove, UK: Psychology Press; 2005.
[9]Kaplan E, Goodglass H, Weintraub S. *Boston Naming Test*. Philadelphia, PA: Lea & Febiger; 2000.
[10]McNeil MR, Prescott TE. *Revised Token Test*. Baltimore, MD: University Park Press; 1978.
[11]LaPointe LL, Horner J. *Reading Comprehension Battery for Aphasia*. 2nd ed. Austin, TX: Pro-Ed; 1998.
[12]Brookshire RH, Nicholas LE. *The Discourse Comprehension Test*. Minneapolis, MN: BRK Publishers; 1993.

Even a major proponent of the classification system suggests that clinicians use the system cautiously, stating that syndromes are simply suggestive of a given behavior profile and should not be rigorously applied (33). He lists several limitations, which include the following:

- Syndromes must not be tied firmly to a given site of lesion. As previously described, current theory in aphasia rejects the notion of a one-to-one correspondence between specific linguistic structural elements and focal segments of the brain. Rather, one should understand that specific regions of the brain are an essential or critical element in a widely distributed neural network; it is not the case that a particular language skill that is now deficient resides in a particular part of the brain.
- Syndromes are not static—as a person recovers, he or she may evolve from one syndrome to another, even though the anatomical locus of the lesion does not change.
- Within a given syndrome, individuals with aphasia may exhibit a wide variety of severity and symptoms.
- Not all individuals with aphasia are classifiable. Approximately 80% of individuals with aphasia conform roughly to the aphasia syndrome and anatamoclinical scheme (32). Individual differences in brain structure, lesion size and location, and etiology, as well as factors such as age, handedness, prior brain damage, presence of seizures, depression, or other medical or psychiatric disorders, may all influence brain–behavior relations.

Finally, it should be noted that this connectionist classification scheme was developed to address the cortical aphasias, yet aphasia-producing lesions may not be limited to the cortex. Lesions to the thalamus and anterior and posterior capsular putamen may also result in an aphasia that is not classifiable using the scheme (29,44,45).

Despite these limitations and cautions, the most common tests of aphasia (Western Aphasia Battery and Boston

Diagnostic Aphasia Examination) (39,46) are based on this schema. Indeed, as Brookshire (41) observed, "the connectionist model is in many respects a fiction, but it remains a useful one" (p. 176).

Recovery and Prognosis

Individuals with aphasia and their family members frequently want an assessment of prognosis. For the clinician, reliable information regarding factors associated with both positive and negative recovery impacts prognostic determination, its application to family counseling, and clinical decision making, particularly in identifying candidates for treatment. Discussions about recovery and prognosis focus on three key interrelated questions: How much recovery can be expected? What is the timecourse of recovery? Will therapy have an impact on recovery? In addition, there are many different outcome areas that can be assessed, so another question relates to which particular factors are being referred to in the discussion on prognosis (e.g., improvements in specific language modalities, improvements in communication skills, and/or improvements in quality of life).

Factors Affecting Prognosis

Basso (47) has differentiated between neurologic and anagraphic factors, which may serve as indicators of prognosis. Neurologic factors are related to etiology, size and site of lesion, and severity and type of aphasia. In addition, through modern neuroimaging technologies, there has been an increased focus on pathophysiological indicators of recovery, the long-term cerebral changes related to resolving aphasia, and the neurophysiological consequences of therapeutic interventions. Anagraphic factors include personal characteristics such as age, sex, handedness, and health status.

Neurologic Factors

One of the difficulties encountered in research on aphasia recovery and prognosis is that many of these factors are interrelated. For example, the site of lesion determines to some extent the type of aphasia; the size of lesion and type of aphasia have some implications for severity; and the type of aphasia may not be independent of age. Consider, for example, the discussion on initial severity of aphasia, lesion size and location, and their impact on recovery. Some researchers have found that initial aphasia severity is the single most important factor for ultimate language function (48,49); others have found that lesion size exerts a negative influence on recovery (48,50–54). Although the negative effect of extent of lesion on initial severity of aphasia is unquestionable, once initial severity has been taken into account, the effect of lesion size on recovery may not be clear-cut (47).

In a series of studies that looked at location and extent of lesion on CT scans and the severity of impairment in different groups of aphasic individuals, Naeser and colleagues indicated that rather than total lesion size, it is the size of the lesion within specific areas that may affect recovery from aphasia (55–57). In their study of 10 patients with Wernicke's aphasia, there was no correlation between total temporoparietal lesion size and severity of auditory comprehension dysfunction (56). However, a correlation was found between the amount of temporal lobe damage within Wernicke's area and severity of auditory comprehension dysfunction. If damage was in half or less of Wernicke's area (defined as the posterior two-thirds of the superior temporal gyrus), patients exhibited good comprehension at 6 months after onset. If the lesion involved more than half of Wernicke's area, patients exhibited poor comprehension, even at 1 year after onset. Furthermore, anterior–inferior temporal lobe extension into the middle temporal gyrus area was associated with particularly poor recovery (56).

Similarly, Kertesz and colleagues correlated outcome measures of aphasia severity and comprehension with lesion extent in 22 patients with Wernicke's aphasia (54). Like Naeser et al., they found that the extent of involvement within specific structures, rather than overall lesion size, contributed to the prediction of language recovery (54,56). The angular gyrus and the anterior mid-temporal area were important for overall language recovery, whereas the extent of involvement of the angular gyrus contributed most significantly to recovery of auditory comprehension at 1 year.

Time Frame of Recovery

Expectations for recovery include not only the amount of recovery but also the time frame in which recovery can be expected. Historically, recovery was thought to be complete by 3 to 6 months after stroke. However, more recent research indicates that recovery from aphasia continues throughout the life of the person and that the benefits of rehabilitative intervention also continue throughout this entire period.

Hillis and Heidler have suggested that functional recovery from aphasia involves at least three overlapping stages, which extend over years (58). The acute stage, occurring in the first few days after stroke, involves the recovery of transiently impaired neural tissue in the ischemic penumbra, the area of the brain surrounding the core infarct. Although this area receives sufficient blood to survive, it is not enough to function. Restoration of function occurs only following increased blood flow to this area. The second stage of recovery begins within days of the stroke; continues for weeks, months, or possibly years after onset; and involves reorganization of structure/function relationships. When the reorganization is complete, further recovery (the third stage) depends on establishing new pathways for processing components that were "cut off" by the brain damage as well as learning compensatory strategies to facilitate more effective communication.

Neurophysiology of Recovery and Rehabilitation

Neuroimaging studies are increasingly being used to examine changes in brain activation patterns after left hemisphere stroke and aphasia. Despite a number of studies, much remains to be uncovered regarding the complex process of cortical reorganization of language-related brain regions

during recovery from aphasia and the effects of therapeutic interventions on brain systems involved in language processing.

A fascinating issue relates to the degree to which language improvement during recovery and rehabilitation is sustained by left hemisphere zones spared by the lesion, by recruitment of homologous right hemisphere regions, or both. Several of the earliest imaging studies in recovering aphasic patients have reported shifts in activation to the homologous right-side territories and have interpreted these as compensatory (59–63). However, a number of research findings and dynamic models of recovery have challenged this view. Some authors have suggested that right hemisphere activation during functional imaging indexes a maladaptive response reflecting loss of active transcallosal inhibition (64–66).

But the picture is much more complex than this. The apparent contributions of the left and right hemispheres depend on when they are measured, with early activation in the right hemisphere (67–70) remaining prominent over time only with the most severe left hemisphere injury (68,71–73). Further, the left and right hemispheres do not behave as unitary organs, with different parts of the hemispheres contributing differentially depending on individual characteristics. For example, one interesting patient showed benefit from inhibitory stimulation to the right inferior frontal gyrus, yet showed worsening aphasia following a subsequent right hemisphere infarction (74). It is important to reiterate that imaging studies will show different brain responses over time, reflecting brain remodeling and reorganization processes that eventually lead to regional contributions from a variety of areas in the left and right hemispheres (75–78). The net result of this process is a reorganized network that depends on individual patient characteristics, including size and location of initial infarction and premorbid neural status, reflecting adaptive capacities of perilesional tissue and of other ipsilesional and contralesional brain regions (79–81).

Studies that directly assess functional anatomical changes occurring with language therapy are emerging, but there remains no consensus. The earliest literature reported single cases or small numbers of cases (64,82–87) and focused more on issues of laterality than on complex patterns and time courses of recovery. This research suggested positive responses in the left hemisphere with speech and language treatment. Two of the studies found that post-therapy patterns were consistent with task-dependent activity in healthy adults (82,84), one found increased activity in the perilesional cortex (83), and one found that individual variability trumped these generalizations (87). Right hemisphere activations in a variety of areas were also reported (85–87).

More recent studies reporting biological changes with therapy in more than a few patients (88,89) have shown complex patterns of remodeling across individuals and have supported theories on the importance of the preserved left hemisphere in the very best recoverers.

Clearly, many questions remain regarding recovery and the effect of rehabilitation on patterns of language organization. Nevertheless, there is a long history of behavioral treatments for aphasia, which are presented in the following text with a discussion of treatment efficacy and outcomes.

Approaches to Aphasia Rehabilitation

Taxonomy of Language Remediation Approaches

There have been several attempts to categorize the numerous treatment techniques and procedures for language remediation in adults with aphasia. For example, a literature review of articles that were published in 5 major journals and that spanned approximately 20 years (1971–1991) identified 6 broad models of aphasia treatment, each of which is discussed in the following text (90). More recently, Basso (91) presented a general taxonomy of approaches to and theoretical underpinnings of aphasia rehabilitation, based on historical trends in the latter half of the 20th century. Interestingly, her taxonomy closely agrees with the categories identified previously (90). Yet any taxonomy is a simplification—it is not always clear where one approach ends and another begins, so some specific treatments may be consistent with more than one approach. For example, Horner and colleagues note that of the articles they reviewed, the majority (21.7%) used a hybrid or multitheoretic approach (90). Other language therapies may not fit into any of the approaches, particularly when therapies from different countries worldwide are considered (92). Nevertheless, the following six categories serve as an initial guide to the rich and varied treatments for aphasia. Selection of treatments occurs with consideration of patient-specific factors such as type, severity, and chronicity of the aphasia; the presence of associated impairments; and the patient's communication environment.

Stimulation–Facilitation Approach

The stimulation–facilitation approach is a name often used synonymously with that of Hildred Schuell, who proposed and supported this approach (93,94). It is based on the philosophy that in aphasia, language is not lost, but rather cannot be accessed. Aphasia is considered to be unidimensional in nature, so individuals with aphasia share many similarities in behavioral impairment and differ only in terms of severity. Therefore, regardless of the type of aphasia or site and size of the neurologic lesion, language rehabilitation can be essentially the same for all patients.

As the auditory modality is of prime importance in language processing and is also a key area of deficit in aphasia, treatment involves repetitive intensive auditory stimulation. The presentation of the auditory stimulation, which is designed to elicit a maximum number of responses, is sometimes paired with stimulation in other modalities. Error responses occur when stimulation is insufficient. Therefore, they are not corrected but are followed by additional stimulation, which if adequate, is likely to elicit the correct response. Although the assumptions underlying this approach have undergone serious debate, the stimulation method has been the predominant approach to treatment in the United States since the 1960s.

Modality Model Approach

In contrast to the premise that aphasia is unidimensional, proponents of the modality model view language as modality bound and aphasia as a modality-specific performance deficit involving one or more modalities. The goal of treatment is to remediate the specific input or output modalities, singly or in combination. One way that this can be accomplished is by systematically pairing weak and strong modalities to "de-block" impaired performance. This principle can be applied regardless of the specific modality that is being treated. For example, when confrontation naming is difficult, repetition may be used to help the patient produce the correct response; then, immediately after de-blocking has occurred through the use of repetition, the target response may be accessed in the previously inaccessible modality (i.e., confrontation naming) (95).

Luria's functional reorganization approach, which has widely influenced aphasia research and therapy, is consistent with the modality model. According to Luria, when brain tissue is destroyed, its original function cannot be restored to its previous form, but it can be performed by means of a partially new neural organization (96,97). Therapy therefore is directed toward reorganization and transfer of the function to other brain structures or functional systems. With intersystemic organization, new functional systems are created through the use of other undamaged links. With intrasystemic organization, the impaired function is carried out at a different level of the same functional system, either at a lower and more automatic level or at a higher and more voluntary level. Precise identification of which modalities are damaged and which are preserved makes it possible to develop and implement different training procedures.

Processing Approach

The processing approach is based on the cognitive neuropsychological models of normal language processes that have been developed for specific language tasks such as reading, spelling, naming, or sentence production (98). These information-processing models assume that a complex cognitive function consists of a system of distributed and interconnected modules or mental representations that allow processing of different types of information in cascade fashion. The representations and processes do not necessarily correspond to locations in the brain, but reflect functional components of a cognitive operation. Rehabilitation begins, for each individual patient, with identification of which cognitive processes and representations underlying the language task are impaired and which processes and representations are intact. For example, the task of reading words aloud involves the graphemic input lexicon, whereas repetition of words involves the phonological input lexicon. However, both tasks involve the semantic system and the phonological output lexicon. By comparing performance across tasks, inferences about the integrity of these cognitive processes can be made. Treatment then focuses on either the remediation of the impaired cognitive processes, compensation via the intact cognitive processes, or both. The primary contribution of the processing approach is that it guides the choice of interventions; however, it does not provide direct motivation for specific treatment strategies (98). There are many studies, mostly single case descriptions, in which cognitive analyses have been used to focus treatment (99); examples can be found in Hillis (2002).

Nondominant Hemisphere Approach

Several treatment approaches are based on the premise that the hemisphere that is nondominant for language has specific abilities, such as visual–spatial, affective–prosodic, and paralinguistic abilities, that can be used to facilitate communication. Melodic intonation therapy (MIT) is perhaps the best known of these treatment approaches (100–103). MIT is a hierarchically structured program that uses intonation and rhythm to increase the patient's ability to independently produce high-probability phrases and sentences. The steps of MIT range from intoning a melodic line with synchronous left-hand tapping to answering questions using drilled phrases and sentences. MIT may be most appropriate for those with large left hemisphere lesions whose recovery may depend more on the right than the left hemisphere (104); some limited evidence for its efficacy has recently emerged (105). Other remediation approaches that are consistent with the nondominant hemisphere mediation model utilize drawing as a communicative function (106,107) and encourage humor within the therapy session (108).

Linguistic Approach

The linguistic (neurolinguistic) approach is based on the principle that language has an internal organization that can be described by a specialized system of rules. In aphasia, there is disruption of lexical–semantic, syntactic, and/or phonologic performance. Treatment therefore focuses on restoring language performance using neurolinguistic principles that are specific for each linguistic impairment. For example, the sentence production program for aphasia systematically trains syntax using a story completion format (109). Selection of syntactic structures was based on a study of agrammatism that identified a hierarchy of difficulty across 14 grammatical constructions, with imperative intransitive statements being the easiest and future tense statements being the most difficult. Another sentence-production training approach, cuing verb treatments, is based on the notion that the verb is the central constituent in sentence structure (110). In this approach, verbs are presented as the central core of the simple active sentence; patients are trained to produce the verb and, in response to a "wh"-question cuing strategy, also produce specific sentence constituents (usually noun phrases) that are assigned to various thematic roles by the verb (e.g., agent, theme). A recent extension of this treatment is called Verb Network Strengthening Treatment (VNeST) (111,112). The basic task of VNeST is to generate agent and patient pairs to a target verb (e.g., chef/sugar, carpenter/lumber, surveyor/land for measure) with the intent of strengthening the connections between the verb and its thematic roles.

Based on aspects of formal linguistic theory and neurolinguistic research, and consistent with Chomsky's conceptual framework, Thompson and colleagues have developed a series of treatment strategies to improve sentence comprehension and production of complex sentences such as "wh"-questions and passives (113–115). Of particular clinical relevance is a finding that has been called the "complexity hypothesis" (116,117). The hypothesis suggests that there is more generalization of improvements from treated to untreated grammatical forms when treatment begins with more complex structures than when treatment is limited to simple forms. This contrasts with traditional treatment, which typically is hierarchically organized and starts at a simple level and gradually increases in level of difficulty.

A similar finding has been noted in the area of semantics. There is an extensive literature examining recovery of naming in patients with aphasia (118,119). One form of treatment, called semantic feature analysis, was developed to strengthen the semantic attributes or features of target words (120–124). The treatment involves repeated practice associating the target word with its various defining characteristics (e.g., *robin: has wings, has beak, lays eggs, flies, is small, builds nest, lives in trees, is a bird*). More recently, it has been demonstrated that when the treatment uses target words that are less typical of their category and therefore more complex (e.g., *penguin, ostrich are not typical of birds because they do not fly or live in trees*), generalization of treatment effects is greater than when typical targets are used (125–128). This hypothesis has been called the "semantic complexity hypothesis" and provides further support for the notion that treatment should not necessarily be provided in a hierarchical fashion from easy to more difficult (125–128).

Functional Communication Approach

In the functional communication or pragmatic approach, therapists are no longer interested only in the accuracy of the linguistic message, but rather focus on the patient's ability to communicate the intent of the message. Communication involves more than just speaking and understanding, but reflects the application of pragmatic rules and the ability to use language in a context. Therefore, treatment includes compensatory strategies for circumventing communication breakdown as well as strategies for communication breakdown repair. One of the best-known pragmatic approaches is PACE (Promoting Aphasic's Communicative Effectiveness) (129). In the PACE technique, four major treatment principles have been delineated in an attempt to incorporate rules of natural communication into semistructured treatment: the clinician and patient participate equally as senders and receivers of messages; the interaction incorporates the exchange of new information between clinician and patient; patients freely choose the channels through which they will communicate—words, gestures, drawing, or any other communication device; and the clinicians' feedback is based on the patient's success in communicating the message.

Other approaches such as practicing scripted conversations (130–134), ensuring a positive communication environment by training communication partners to use conversational supports (135), extending treatment into natural communication settings including aphasia communication groups (136), and removing environmental barriers to participation in community activities (137) may also be considered "functional" approaches. However, the term "social approach" may better describe some of these treatments, as they are *explicitly* designed to improve communication, life participation, and/or personal well-being (138–143).

Life Participation Approach to Aphasia

Recently, an umbrella philosophy called the life participation approach to aphasia (LPAA) has fueled even greater interest in the social approaches to the management of aphasia (139). The LPAA is a set of values that guides intervention, assessment, and research. It calls for a broadening and refocusing of clinical practice, suggesting that the focus of aphasia treatment should be on "re-engagement in life" for the person with aphasia.

The LPAA has applicability throughout and beyond the period of formal rehabilitation, beginning with initial assessment and intervention and continuing, after hospital discharge, until the person with aphasia no longer elects to have communication support. All those affected by aphasia are regarded as legitimate targets for intervention, including not only the person with aphasia but also family members, coworkers, and individuals in the community who may interact with the person with aphasia. According to the LPAA, treatment includes facilitating the achievement of life goals. Therefore, in addition to work on improving and/or compensating for the language impairment, clinicians should be prepared to work on anything in which aphasia is a barrier to life participation, even if the activity is not directly related to communication. This may include targeting environmental factors outside of the individual, as a highly supportive environment can lessen the consequences of aphasia on a person's life, whatever the language impairment (139).

Biological Approaches to Language Remediation

As we acquire new knowledge about aphasia and brain–behavior relations, additional approaches to treatment that are not easily categorized with the present taxonomy are emerging. For example, Small has advocated for a biological model of aphasia rehabilitation in which the goal of remediation is to alter brain anatomy and physiology so that language function can be restored (144,145). To effect the necessary neural changes, both novel biological treatments and speech–language treatment are necessary. The biological treatment stimulates or repairs the injured brain area, while the language treatments are provided to retrain the new circuitry and integrate it with the preserved, existing tissue.

Pharmacotherapy

Pharmacotherapy is the most frequently used biological therapy for aphasia. To date, the majority of studies have

TABLE 13.3 Drugs With Potentially Deleterious Effects on Stroke Recovery

- Benzodiazepines
- Clonidine
- Haloperidol
- Phenothiazines
- Phenytoin
- Prazosin

investigated the effects of four groups of neurotransmitters on language deficits in aphasia (146,147). These include the following: dopamine agonists such as bromocriptine (148–152); dextro-amphetamine and other agents that affect catecholamine systems (153,154); cholinergic medications such as donepezil (155,156) and galantamine (157), acetylcholinesterase inhibitors; and the nootropic agent, piracetam (158,159). A recent study evaluated the NMDA receptor antagonist memantine (160). Systematic reviews of this literature have concluded that efficacy of pharmacologic agents remains questionable, although some appear to have promise (146,147). However, the majority of the studies concerned the chronic stage of aphasia, and the authors suggest that the adjuvant pharmacologic treatment may best be applied before most neural reorganization has taken place. Treatments are notably ineffective (at worst) and less efficient (at best) when given alone than with associated speech language therapy (146). This finding resonates with Small's suggestion that pharmacologic treatment has promise but only when accompanied by concomitant language therapy (144,145,147).

Any discussion of aphasia and pharmacology must also consider the deleterious effects that some drugs may have on stroke recovery, including aphasia recovery. A retrospective study of medication use during aphasia rehabilitation indicated that more than 80% of all patients were taking some medicine at the time of their stroke and that 65% were taking multiple medications (161). Included in this list were such drugs as adrenergic blockers and benzodiazepines, which are known to impede stroke recovery in animal studies. Deleterious effects have been reported for neuroleptics (haloperidol), thiazides, and tricyclic antidepressant agents (161,162). Therefore, drugs that potentially interfere with catecholaminergic or GABAergic function or are thought to delay recovery by empirical study (i.e., the drugs in Table 13.3) should be avoided, if possible, during aphasia rehabilitation (43).

Cortical Stimulation

A relatively new area of investigation is the direct application of stimulation to the cerebral cortex to facilitate brain plasticity and enhance stroke recovery. There are several methods of delivering cortical brain stimulation transcranially—these include direct epidural cortical stimulation (163,164), repetitive transcranial magnetic stimulation (rTMS) (165–168), and transcranial direct current stimulation (tDCS) (169,170), each of which have been applied to the rehabilitation of language after stroke. Results suggest a potential role for cortical stimulation as an adjuvant strategy in aphasia rehabilitation.

There is only one study that assesses the safety and efficacy of direct epidural cortical stimulation in combination with intensive speech–language therapy on individuals with chronic aphasia (163,164). Eight participants received intensive behavioral therapy using a combination of articulation drills, oral reading, and conversational practice, delivered 3 hours daily for 6 weeks. Four of these participants also underwent fMRI-guided surgical implantation of an epidural stimulation device, which was activated for all therapy sessions. Behavioral data were collected before treatment, immediately after treatment, and at 6 and 12 weeks following the termination of therapy. Imaging data were collected before and after treatment. Results indicated that investigational subjects showed a mean aphasia quotient change of 8.0 points immediately after therapy at 6-week follow-up and 12.3 points at 12 weeks. The control group had smaller mean changes of 4.6, 5.5, and 3.6 points, respectively. Similar changes were noted on subjective caregiver ratings of the participants' language and communication skills, with larger changes being noted for the investigational group as compared to the control group at all time points. Functional imaging suggested increased consolidation of activity in interventional subjects. Therefore, though behavioral speech–language therapy improved the nonfluent aphasia, independent of cortical stimulation, the epidural stimulation of the ipsilesional premotor cortex may have augmented this effect. The largest effects between the groups were evident after completion of the therapy. The neural mechanisms underlying these effects were manifested in the brain by decreases in the volume of activity globally and in particular regions. Although the number of patients enrolled in this trial precludes strong conclusions, epidural stimulation could play an adjunctive role in the treatment of nonfluent aphasia.

Although further investigation of the effects of direct epidural cortical stimulation is warranted, the clinical applicability of this procedure may be limited by the invasiveness of the procedure, which requires neurosurgical implantation of the electrodes. A less invasive therapy for language remediation in aphasia is repetitive rTMS (165–168). Based on the premise that overactivity of the right hemisphere language homologues may be maladaptive and interfere with, rather than promote, aphasia recovery, rTMS was applied to the right hemisphere to reduce its cortical excitability. Preliminary results obtained in four individuals with chronic nonfluent aphasia indicated improved picture naming following 10 sessions of rTMS (165).

tDCS may also have potential for clinical use in view of its noninvasive application, ease of administration, and relatively low cost. tDCS is a method of delivering weak polarizing electrical currents to the cortex via two electrodes placed on the scalp: an active electrode placed on the site overlying the cortical target and a reference electrode usually placed over the contralateral supraorbital area. The nature of the

effect depends on the polarity of the current. Anodal tDCS has an excitatory effect believed to result from the partial depolarization of superficial cortical axons, whereas cathodal tDCS induces inhibition via presumed hyperpolarization. Studies on the efficacy of tDCS are emerging (169,170), and may, in the future, provide promise, especially when linked with intensive language treatment.

Treatment Intensity, Constraint-Induced Aphasia Therapy, and Computers

Regardless of the treatment approach, a critical question remains regarding how much treatment is optimal and at what frequency. The question of treatment intensity is of considerable importance in the light of recent work in neuroscience demonstrating that the neuroplasticity of the adult brain can be impacted by several experience-dependent principles, including intensity of training (171). In addition, a growing literature suggests that with intensive treatment, individuals with chronic aphasia continue to demonstrate language recovery for years after stroke. For example, Bhogal et al. (2003) conducted a literature review which suggests that intensive speech–language therapy delivered over a short period of time (average of 8.8 hours per week for 11.2 weeks) resulted in significant improvements, whereas lower-intensity therapy provided over a longer period of time (average of 2 hours per week over 22.9 weeks) did not result in positive change (172).

Pulvermuller, Meinzer, and their colleagues have spurred increased interest in treatment intensity with their studies of constraint-induced language therapy (CILT) for individuals with aphasia (173–177). With CILT (also called Intensive Language Action Therapy), verbal responses in an interactive communication context (e.g., requesting cards) are elicited through modeling and shaping. Importantly, responses are constrained to the verbal modality, that is, there is "forced use" of verbal productions, whereas use of other communication modalities is discouraged. In addition, CILT emphasizes the importance of massed practice, and treatment is typically provided on an intensive schedule, 3 hours per day for 2 weeks. Despite positive findings reported for CILT, it has been difficult to determine whether the treatment results emanate from the constrained forced language use, the intensity of the treatment schedule, or a combination of these two factors (178–179).

Nevertheless, it is generally agreed that intensity of speech–language therapy is an important component of aphasia intervention (179–181). However, providing intensive treatment to individuals in the early acute stage may not be feasible; patients may be too ill or may not have sufficient endurance to tolerate the prescribed treatment (182). For patients with chronic aphasia, treatment can be costly, and the current health care environment in the United States does not typically recognize its value. As a result, clinicians and researchers in the field are left searching for cost-effective ways to deliver aphasia treatment. One method of providing less costly but intensive treatment is via the computer.

A well-documented body of literature supports the positive effects of computerized treatment for aphasia (183–186). Although many earlier computer-based therapy programs relied on predefined exercises that were fairly inflexible, more recent programs have been designed to allow specifically for treatment that is interactive and individualized to clients' needs. Two examples of aphasia treatment software that have undergone extensive efficacy research are AphasiaScripts™ (130–133) and SentenceShaper (187). The AphasiaScripts™ software program uses an animated agent or virtual therapist that is programmed to produce natural speech with correct movements of the speech articulators. This virtual therapist serves as the conversational partner, whereas the person with aphasia repetitively practices prerecorded individualized conversational scripts with varying degrees of support and cues that are generated by the computer (130). Similarly, the SentenceShaper helps the person with aphasia practice self-generated short stories, but without the benefit of a virtual conversational partner (187).

As computer technology becomes more accessible and researchers and clinicians continue to explore the utilization and benefit of computerized treatments in clinical practice, computer treatment is becoming more commonplace. Nevertheless, computer therapy, even when practiced by individuals with aphasia independently in their homes, does not negate or diminish the importance of the experienced practitioner. The clinician plays a critical role in all aspects of treatment planning and development, whereas the computer provides the intensive, massed practice required for automatization of the learned narrative or conversational script—a laborious and time-consuming process when provided by a therapist.

Efficacy of Aphasia Treatment

Any discussion about language remediation in adults must also address the basic question of whether aphasia treatment works. One source of confusion surrounding this issue is the concept of remediation versus eradication. At present, there is no aphasia therapy that cures aphasia. Yet there is ample evidence that frequent sessions of aphasia therapy over a long period of time can lead to continued improvement.

To date, the historical record of clinical outcomes for treatments of aphasia is extensive (188). Over time, experimental methodologies in the field of aphasia have improved (e.g., measuring the change in communication behavior from pretest to posttest; controlling for time after onset; setting clear exclusion and inclusion criteria to establish homogeneous groups; introducing no-treatment control groups or using deferred treatment groups; random assignment; and controls on the type(s), amount, and duration of treatment), so that findings have become less ambiguous and support the conclusion that treatment for aphasia is both efficacious and effective (188). Although there are relatively few randomized clinical trials of aphasia treatment (189,190), more than 100 single-subject aphasia treatment studies have appeared in the literature. In addition, meta-analyses applied to the aphasia treatment literature have concluded

that aphasia treatment is effective (191–193). In two of these meta-analyses, based on 21 studies and 55 studies, respectively (191,192), it was also concluded that recovery of treated individuals was, on average, nearly twice as extensive as the recovery of untreated individuals when treatment was begun before 3 months after onset. Treatment also brought about appreciable gains when begun after 3 months after onset, and treatment brought about significant effects even in individuals with severe aphasia.

Treatment Outcomes

Returning to the question of what constitutes "outcome" in aphasia treatment, Kagan et al. (2008) have developed a framework that serves as a guide for categorizing different measures of outcome (194). Based on the World Health Organization's International Classification of Functioning, Disability and Health (ICF) (195), the Living with Aphasia: Framework for Outcome Measurement (A-FROM) model is pictured in Figure 13.2. The A-FROM framework consists of the following overlapping domains:

- *The participation domain*: This includes the life situations specific to an individual, such as life roles (e.g., mother, teacher); responsibilities (e.g., managing finances, performing a job); relationships (e.g., engaging in conversation, making friends); activities of choice (e.g., leisure and recreation, community participation); and tasks engaged in by an individual (e.g., writing letters, cashing a check—described as "Activities" in the ICF).

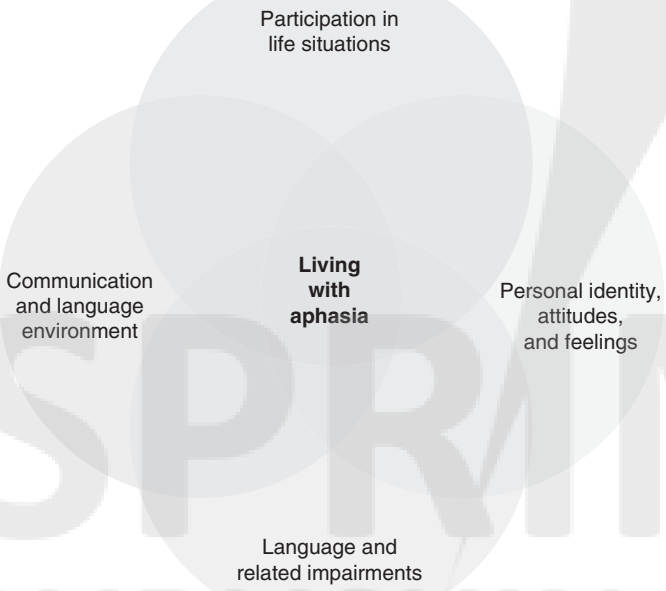

FIGURE 13.2 Living with aphasia: framework for outcome measurement (A-FROM).

Source: Reprinted with permission from the Aphasia Institute, Toronto, Canada.

- *Language and related impairments domain*: This is the correlate of the "Body Function" domain of the ICF and includes outcomes in the realm of language and cognitive processing, such as auditory comprehension (e.g., pointing to pictures named); reading (e.g., matching a written word to a picture); speaking (e.g., word finding, sentence formulation); and writing (e.g., writing the names of objects).
- *Communication and language environment domain*: This is the correlate of the ICF "Environmental Context" domain and includes aspects of external context that might facilitate or impede language, communication, or participation of people with aphasia, such as physical environment (e.g., signage, lighting, written supports); social environment (e.g., attitudes of people, skills of partners); and political environment (e.g., policies supporting participation).
- *Personal factors/identity domain*: This includes ICF factors such as age, gender, and culture, but expands the ICF domain to include internal factors that vary as a consequence of aphasia, such as confidence and personal identity.
- *Living with aphasia domain*: This is a dynamic interaction of four life domains, capturing elements of quality of life (how satisfied someone is with his or her life).

The A-FROM is not intended to be prescriptive in relation to aphasia intervention, but rather serves as a guide for selecting outcome domains across diverse aphasia interventions (194). The ultimate goal of any intervention is to make a difference to the everyday experiences of individuals with aphasia and their families, and there are multiple ways for clinicians to work toward accomplishing this (196). Thus, the A-FROM can also serve as a guide for the clinician to use when counseling patients and their families about the goals of rehabilitation and the specific focus of any one or more treatments within the context of the overriding goal of living successfully with aphasia. Although the A-FROM was developed to address specifically the outcomes of those with aphasia, its breadth makes it applicable to any type of communication disorder, including AOS and dysarthria, which are discussed in the next sections.

APRAXIA OF SPEECH

AOS is a disorder that is distinguishable at a theoretical level from both aphasia and dysarthria, but remains somewhat controversial at a more practical level. The main problem is that it still has an unclear neurologic and functional basis and has no universally agreed-upon definition (197).

Traditionally, AOS was defined as a disorder of motor programming, "an articulatory disorder resulting from impairment, due to brain damage, of the capacity to program the positioning of speech musculature for the volitional production of phonemes and the sequencing of muscle movements for the production of words" (198). More recently,

Van der Merwe (2009) has suggested that AOS is a disorder of motor *planning* rather than a disturbance in the *programming* of movements for speech. Difficulties arise at an earlier stage of speech processing in which the neural codes for specifying the spatial and temporal characteristics of the output are computed (199).

Neurologically, both hypotheses assume that specification and programming are mediated by the cortical association areas, including the lateral premotor cortex, the supplementary motor area, the prefrontal areas, and the posterior parietal areas. In contrast, some studies have observed AOS from isolated damage to the anterior portion of the insula, concluding that the insula must be damaged for AOS to occur (200,201). These findings are not without dispute, as other studies have demonstrated that AOS occurs in the absence of insular damage (202–204), and there may be alternative explanations for the data on the insula (205).

CHARACTERISTICS OF AOS

Despite the debate about AOS, there is general consensus that AOS is a disorder of articulation and prosody of speech. Numerous articulatory characteristics have been specified. For example, based on previous reports (198,206,207), Freed (2000) compiled a list of as many as 14 articulatory characteristics that occur most commonly (208). However, not all patients with AOS display all characteristics. Differences in the manifestation of AOS may be related to the possible existence of AOS subtypes, to various concomitant effects of a coexisting aphasia, to variability associated with AOS severity, or use of different compensatory strategies (8).

Nevertheless, there are some core symptoms of AOS that consistently form part of the diagnostic description, and these have been identified in a report by the Cochrane collaboration as follows (209):

- Effortful "groping" (that is trial-and-error attempts) at finding the correct articulatory positions for the target phonemes and therefore difficulty producing the correct sounds
- Inconsistent or variable errors (i.e., the same sounds are not always in error, and each attempt at a word could produce a different error)
- More consonant than vowel errors
- Articulatory errors that are characterized by perceived substitutions, distortions, omissions, and repetitions; phonemes and words often approximate the target; they sound similar but are not exactly the same as the target sound or word
- Difficulty in producing consonants that are adjacent to each other (e.g., *str*, *bl*, *kr*, *spl*) resulting in a tendency to insert additional vowels
- Awareness of errors

Prosodically, the rate of connected speech in AOS is usually slower than normal. Equal stress may be placed on the syllables in an utterance. Inappropriate pauses may occur at the start of a word or between syllables. These pauses may result from articulatory groping or because each syllable is being produced individually rather than being produced fluently by blending one syllable into another. The normal variations of pitch and loudness are restricted. In some cases, the altered prosody may lead to the perception of a foreign accent in monolingual speakers (210,211), although this may not be the only underlying mechanism of foreign accent syndrome (212). There are several explanations for the rate and prosodic abnormalities of AOS. They may be a fundamental feature of the disorder, a simple by-product of the articulation deficits, or they could reflect efforts at compensation for the articulation deficit.

An issue that is commonly discussed is whether AOS always co-occurs with Broca's aphasia or nonfluent aphasia, or whether it is isolable neurologically. Many of the articulatory and prosodic perceptual features of AOS have been confirmed by acoustic and physiologic studies (8). These studies also have provided data supporting the conclusion that many of the features of AOS reflect a phonetic disorder of motor planning and programming rather than deficits that are fundamentally linguistic in character (8,206).

In addition, Duffy (2013) asserts that most definitions of Broca's aphasia do not explicitly recognize the existence of a motor speech programming disorder, despite the description of poor "articulatory agility" and speech that is slow, labored or effortful, reduced in phrase length, and abnormal in prosody. Although these characteristics are consistent with those of AOS, individuals with Broca's aphasia also have grammatical and syntactical errors and problems with word retrieval, as well as problems with auditory comprehension, reading, and writing. Therefore, a reasonable conclusion is that patients with Broca's or nonfluent aphasia usually have AOS, but the aphasic components of Broca's aphasia include additional deficits that are outside of the definition of AOS (8).

Assessment of AOS

Most clinicians assess AOS with a comprehensive motor speech evaluation (8,208). This involves assessing muscle strength and tone and speed, range, and accuracy of movements during single and repetitive movements in both nonspeech and speech activities. It also includes specific tasks to assess phonation, articulation, resonance, prosody, and respiratory support for speech.

Tasks that require the patient to sequence speech sounds are particularly sensitive to the presence of AOS. These tasks include alternating motion rates (repetition of the same sound such as *pa*) and sequential motion rates (repetition of different sounds requiring multiple articulatory positions such as *pa-ta-ka*). Other sensitive tasks include repetition of words of increasing length (e.g., *fan*, *fancy*, *fantastic*), multisyllabic words with complex phoneme combinations, and phrases and sentences. In addition, connected speech is analyzed by asking patients to read paragraphs aloud and through spontaneous conversation.

Before making a diagnosis of AOS, it is important to rule out other conditions that may cause speech difficulties. For example, the muscle weakness and incoordination of a dysarthria can cause slow, labored, or awkward movements that result in a speech disorder. However, in AOS, the abnormal movements affecting speech are more obvious during voluntary movements. The patient may have no difficulty automatically saying *goodbye* when leaving the company of someone but may be unable to say *goodbye* out of context. Similarly, speech may sound quite good during production of automatic sequences such as counting, saying the days of the week, or reciting a familiar poem.

There are only a few published tests for AOS. These include the Apraxia Battery for Adults (213) and the Comprehensive Apraxia Test (214). Neither test provides data that discriminate impairments resulting from AOS, aphasia, or dysarthria. Therefore, the clinician must make the differential diagnosis based on observations of performance during the assessment tasks (8).

Treatment of AOS

Most treatments for AOS are behavioral, yet they are diverse in terms of their focus and theoretical underpinnings (215). Four general groups of treatments for AOS have been identified (216,217). Although these approaches are not mutually exclusive, and some treatments use a combination of techniques that cross one or more categories, the availability of a categorization scheme can be helpful for treatment planning. Importantly, almost all approaches for which there is some evidence of efficacy incorporate principles of motor learning (8).

The most common group of treatments for AOS target improved positioning and movements of the articulators and have been referred to as *articulatory kinematic* treatments (216). In general, these treatments tend to be time-intensive, repetitive, and highly structured, progressing from simple to complex verbal productions of targeted phonemes, words, and phrases. Emphasis is placed on self-monitoring and self-correction, with feedback from the clinician helping to facilitate this.

Several specific strategies are incorporated, to various degrees, into these types of treatments. During imitation, the patient simply watches and listens as the clinician provides a model that the patient then attempts to reproduce. A variation of imitation is called "integral stimulation" in which the patient is instructed to "watch me, listen to me, and say it with me" while the clinician exaggerates the presentation of the stimulus to make it as salient as possible (218,219). Another strategy is phonetic derivation, the progressive approximation or shaping of the positioning and movement of the articulators using sounds and movements that the patient can already make to teach the placement and movement of sounds that he or she cannot make. For example, patients may be instructed to put their lips together and blow to assist with the production of *p* and *b* sounds, thereby using a nonspeech posture to help produce the target speech sounds.

Phonetic placement techniques make use of explicit verbal, written, and graphic descriptions of how a sound is made in combination with physical manipulation of the articulators. An example of a program that includes direct instruction for speech production is PROMPT (Prompts for Restructuring Oral Muscular Phonetic Targets) (220). In PROMPT, the clinician provides a complex combination of auditory, visual, tactile, and kinesthetic cues to the face and neck to represent the various positions of the articulators during speech and to signify various aspects of speech production, including relative timing of speech segments.

Instrumental biofeedback such as electromagnetic articulography (EMA) has been used to provide visual feedback about articulatory movements during treatment. Kinematic and auditory perceptual data have revealed improvement in the accuracy and generalization of effects for at least some speakers and some treated sounds (221,222).

Darley et al. (1975) have emphasized the use of phonemic drills involving repeated production, as many as 10 to 20 times, of the same consonant–vowel combinations. Careful selection of the target sounds is essential (198). The drills begin with just a single vowel, and consonants are slowly added. The first consonant is typically the *m*, which is highly visible and often the easiest to produce. The position of the vowel in the word is alternated between the initial position (*ma*), the final position (*am*), and then the medial position (*ama*). Different combinations of consonant–vowel syllables that gradually increase in complexity and length are practiced before moving to real words, two-word combinations, and phrases. Similar drills have been described by Dabul and Bollier (1976), who set the criteria for each target combination of 60 one-syllable repetitions or 20 two-syllable repetitions in 15 seconds before moving to combinations at the next level of difficulty (223). Another theoretically motivated treatment approach, called Speech Motor Learning, also utilizes syllable drills (224).

Although treatment may begin at the level of the individual phoneme or speech sound, especially for more severe cases, there is general agreement that, as much as possible, target stimuli should be made up of functional words that are immediately useful to the patient (209,218). To promote generalization of sound production to words, the key word technique involves practicing the target sounds in a core vocabulary, and then expanding the limited number of words into a larger set.

Sound Production Treatment (SPT) is an articulatory-kinematic treatment that has received more extensive and systematic study than any other specific treatment for AOS (8). In SPT, movement patterns for sounds are practiced and refined by using syllables and words with minimally different contrasts (e.g., fan/van, bye/pie). Stimuli are determined by the patient's unique error patterns. Little clinical assistance is given initially but when errors occur, modeling-repetition, integral stimulation, articulatory placement cueing, and verbal feedback are provided (219,225–227).

A second group of treatments addresses speech rate and the rhythmic, temporal, or prosodic aspects of speech

production (228,229). In these techniques, an external source of control is applied to the speaker's productions, such as finger counting, hand tapping, and/or a metronome. Some studies have also used computer-generated controls of rate and rhythm (230,231). The underlying premise of these treatments is that AOS is characterized by disruptions in the timing of speech production, although the mechanism responsible for behavioral change is not well understood. Some techniques have also incorporated speech prolongation and reduced rate as part of the rhythm control. The additional slowing of speech production may provide extra time for motor planning and/or programming, as well as for processing of sensory feedback.

A third group of treatments reflects the concept of *intersystemic facilitation/reorganization*. These approaches are based on the premise of using relatively intact systems or modalities to facilitate speech production. Gestural reorganization has been studied most frequently, with the gestures serving as a relatively intact nonverbal ability that helps to reorganize speech. In most studies, the gestures are paired with verbalizations during treatment (232). The use of singing in the treatment of AOS may also be considered a form of intersystemic facilitation/reorganization (233).

The final approach to working with AOS involves the use of *alternative and/or augmentative communication* (AAC) methods to substitute for or supplement verbal communication. Selection of the AAC approach should be highly individualized and may include one or more of the following: picture and word communication books; writing or drawing; gestures; alphabet supplementation; voice output aids; and informed communication partners. Goals may vary from instruction of a consistent "yes/no" response to conversational practice and role playing in simulated situations (234,235).

As Peach (2004) points out, however, few treatments have been reported where the individual had a pure AOS (236). Usually, patients tend to have a coexisting/accompanying aphasia. Therefore, selection of treatments must consider the severity of the accompanying aphasia. There are a few treatment programs that have addressed aspects of both the AOS and the aphasia, including MIT and conversational scripting (237) discussed previously, as well as a technique called oral reading for language in aphasia (ORLA) (238). ORLA combines integral stimulation of sentences, multimodality-paced choral reading, and rhythmic pointing and has been used successfully with individuals with nonfluent aphasia and AOS (238).

Efficacy of Treatments for AOS

Several recent reviews of treatments for AOS are available (197,209,216,217). A Cochrane review of interventions for AOS following stroke did not identify any trials that matched the search criteria of randomized controlled trials of nondrug interventions for adults with AOS in which the primary outcome was functional speech at 6-month follow-up (209). Therefore, the authors concluded that rehabilitation approaches for AOS following stroke "have yet to be supported or refuted by randomized trials" (209).

In contrast to the Cochrane group, a systematic review of the evidence for treatment of AOS was conducted by a committee of the Academy of Neurologic Communication Disorders and Sciences (ANCDS) using search criteria of "providing data pertinent to the effects of treatment with at least one person with AOS" (216,217). From a total of 59 data-based treatment reports that met these criteria, the committee concluded that, taken as a whole, individuals with AOS "show gains in measured performance as a result of treatment," even when the AOS is chronic. They acknowledge that study quality was generally weak, with methodological issues relating to insufficient description of the subjects and their AOS, trial design that often lacked experimental control, inclusion of small numbers of subjects, and outcome measures that were not always reliable and valid (239). Still, a growing body of evidence is available to support the articulatory kinematic treatments, and evidence for the other types of treatments for AOS is "promising, but limited" (217).

In conclusion, AOS is a condition with a range of severities and manifestations. Although future research continues to address the question of treatment efficacy, clinicians working with individuals with AOS have a repertoire of different approaches from which to choose and adapt to the unique characteristics and needs of their patients.

DYSARTHRIA

Dysarthria is a collective term for the group of speech disorders that result from paralysis, weakness, or incoordination of the speech musculature following damage to the central or peripheral nervous system (198,240,241). The definition of dysarthria includes disturbances of any of the basic components underlying speech production (i.e., respiration, phonation, articulation, resonance, and prosody).

Classifying the Dysarthrias

In clinical practice, the most common approach used to classify the dysarthrias is the perceptual method. Its premise is that each type of dysarthria sounds different and that these perceptual differences can be tied to specific underlying neuropathologies (198,240,241). Based on cluster analysis of listener judgments of speech dimensions, six distinctive types of dysarthria—flaccid, spastic, ataxic, hypokinetic, hyperkinetic, and mixed—were identified initially (240,241). A seventh dysarthria type, unilateral upper motor neuron (UUMN) dysarthria (206), was later recognized and subsequently described by Duffy (1995). Examples of the perceptual dimensions used to characterize the different dysarthrias are listed in Table 13.4 (242).

Although theoretically a stroke could cause damage to the central and peripheral nervous system resulting in any type of dysarthria, vascular incidents within the central nervous system typically affect certain cortical areas, the cerebellum, or

TABLE 13.4 Sample Speech Dimensions and Characteristics Rated in the Perceptual Method of Classifying Dysarthria

SPEECH DIMENSIONS	SAMPLE CHARACTERISTICS
Pitch characteristics	Pitch level (decreased, increased), pitch breaks, monopitch, tremor
Loudness	Overall loudness (decreased), monoloudness, excess loudness variation, alternating loudness
Vocal quality	Harsh, hoarse (wet), breathiness (continuous), breathiness (transient), strained/strangled, voice stoppages, hypernasality, hyponasality, nasal emission
Ventilation	Audible inspiration, forced inspiration-expiration, grunt at end of expiration
Prosody	Rate (fast, slow), phrases (short), increased rate in segments of speech, inappropriate silences, short rushes of speech, excess and equal stress
Articulation	Imprecise consonants, distorted vowels, irregular articulatory breakdown
Overall	Intelligibility, bizarreness

Source: Reprinted with permission from Hammen VL. Motor speech problems associated with stroke: the dysarthrias. *Top Stroke Rehabil*. 1994;1(2):68.

the brainstem. Therefore, the most common dysarthrias following a stroke are UUMN dysarthria, spastic, ataxic, flaccid, and mixed dysarthrias. Each of these dysarthrias is discussed with an emphasis on the characteristic perceptual features of the associated disordered speech. However, a summative narrative review of the characteristics of dysarthria after stroke indicated that regardless of stroke location, imprecise articulation and slow speaking rate are consistent features, whereas voice disturbances, especially harshness, and reduced prosodic variation are also common (243).

UUMN Dysarthria

UUMN dysarthria, as its name implies, is caused by unilateral cortical damage involving the upper motor neurons. As a result, there is damage to the lower face, with weakness of the lips and tongue on the opposite side from the lesion. Movements, therefore, are slow and reduced in range of motion, with the main perceptual characteristic of UUMN dysarthria being imprecise consonant production. However, intelligibility of speech is usually only mildly affected. In some patients, the resultant dysarthria is transient. In others, the effects of the dysarthria can be persistent so that referral to speech therapy is appropriate (8,206).

Effects of UUMN damage on other structures of speech production (velum, pharynx, larynx) are less well understood. Because the upper motor neurons on the unaffected side provide sufficient innervation to the cranial nerves serving the two sides of these structures, they should not be affected. However, there is some individual variability in anatomy that could alter this, and a harsh vocal quality and hypernasality have been noted in some patients.

Spastic Dysarthria

Spastic dysarthria occurs from a single stroke in the brainstem or from more than one lesion that causes bilateral upper motor neuron damage affecting both the pyramidal and extrapyramidal systems. The symptoms reflect the combined effects of both systems on the speech muscles. Weakness and spasticity result in slow movement and reduced range and force. The weakness and slowness are most evident in movements of the tongue and lips, leading to imprecise consonant production, vowel distortions, and a slow rate of speech. The effect of spasticity on the velum causes incomplete velopharyngeal closure and hypernasality. Spasticity in the laryngeal muscles results in hyperadduction of the vocal folds, which is perceived as a harsh and strained–strangled vocal quality. Because of difficulty forcing subglottic air through hyperadducted vocal folds, the person may speak in short phrases in conversational speech. In addition, the frequent inhalations of air interrupt the normal rhythm of speech. Prosodically, a low pitch as well as monopitch and monoloudness may be present. Spastic dysarthria may be associated with pseudobulbar affect in which uncontrollable laughing or crying accompanies the damage to the upper motor neurons of the brain stem.

Flaccid Dysarthria

Flaccid dysarthria results from injury to the lower motor neurons in one or more of the cranial or spinal nerves. It reflects problems in the nuclei, axons, or neuromuscular junctions that make up the motor units of the final common pathway. Weakness, hypotonia, and diminished reflexes are the primary characteristics, and atrophy, fasciculations, and fibrillations commonly accompany them.

The effects of flaccid dysarthria on respiration, phonation, articulation, resonance, and prosody vary depending on which cranial nerves are affected. The cranial nerves of speech production are the trigeminal nerve (V), facial nerve (VII), glossopharyngeal nerve (IX), vagus nerve (X), accessory nerve (XI), and hypoglossal nerve (XII). Damage to the facial and hypoglossal nerves most often causes imprecise consonant production, ranging in severity from only mild distortions to

complete unintelligibility. Bilateral facial nerve involvement can affect production of bilabial (*p*, *b*, *m*) and labiodental (*f*, *v*) phonemes, as well as consonants and vowels that require lip rounding. Bilateral damage to the hypoglossal nerve likely results in misarticulation of phonemes requiring tongue elevation (e.g., *l*, *r*). Damage to the trigeminal nerve can also affect articulation because of difficulty elevating the jaw sufficiently to bring the articulators into contact with each other.

Hypernasality is one of the most noticeable signs of flaccid dysarthria, although it is not unique to that condition. Nasal emission (escape of air through the nasal cavity) may also occur because of incomplete velopharyngeal closure. At the laryngeal level, damage to the recurrent branch of the vagus nerve that provides innervation to almost all of the intrinsic muscles of the larynx leads to incomplete adduction of the vocal folds during phonation and a resulting breathy voice quality.

The spinal nerves are also important because they innervate the muscles of respiration. If the cervical and thoracic spinal nerves responsible for innervating the diaphragm and the intercostal muscles are damaged, then decreased inhalation or impaired control of exhalation during speech leads to reduced subglottic air pressure for speech and, therefore, reduced loudness, shortened phrase lengths, and a strained vocal quality.

Ataxic Dysarthria

Ataxic dysarthria is associated with cerebellar damage or damage to the neural pathways that connect the cerebellum to other parts of the central nervous system. Cerebellar damage disrupts the timing, force, range, and direction of movements needed to maintain normal articulation. Articulation deficits are a major problem, with imprecise consonant articulation being the most prevalent speech error. Often the articulation errors are inconsistent, varying from utterance to utterance and giving the speech the characteristic described as irregular articulatory breakdowns.

Prosodic errors also are prominent in ataxic dysarthria. Many speakers tend to put equal stress on syllables or words that would normally have varied stress patterns. They also tend to put excessive stress on syllables or words that are not normally stressed to any degree, giving the impression that each syllable or word is produced separately. In addition, ataxic speech is characterized by prolonged phonemes and prolonged intervals between phonemes, contributing to an overall slow rate of speech.

Cerebellar damage may cause tremors that affect various body parts, and when the laryngeal or respiratory muscles are involved, the result can be a voice tremor. Cerebellar damage can also cause uncoordinated movements in the respiratory muscles. Exaggerated movements of the respiratory muscles can lead to excessive loudness variations during many speech tasks, including conversation.

Mixed Dysarthrias

When neurologic damage extends into two or more parts of the motor system, the resulting dysarthria is called a mixed dysarthria. For example, a flaccid–ataxic mixed dysarthria results from involvement of both the lower motor neurons and the cerebellum. A flaccid–spastic mixed dysarthria may result from a brainstem stroke in which the lower and upper motor neurons are in close proximity to each other. The speech characteristics of a mixed dysarthria reflect a combination of the characteristics found in the single or pure dysarthrias, with the location and extent of the neurologic damage determining which characteristics are likely to appear. Thus, the relative prominence of each dysarthria type can vary from patient to patient. For example, in one individual with a flaccid–spastic dysarthria, the flaccid component (e.g., nasal emission) may be much more evident than the spastic component (e.g., strained–strangled voice quality), whereas the opposite may be apparent in another individual.

Assessment of Dysarthria

Most clinicians assess dysarthria with a comprehensive motor speech evaluation that is similar to the assessment described previously for AOS (8,208). The motor speech examination includes tasks designed to describe the speech characteristics and the underlying neuromuscular features that influence speech production. Speech characteristics include those at the levels of respiration, phonation, articulation, resonance, and prosody, whereas the "salient" features of neuromuscular function include muscle strength, speed, range, accuracy, steadiness, and tone (8).

The oral mechanism (lips, tongue, jaw, velum, pharynx, larynx) is examined at rest and during nonspeech activities to provide confirmatory evidence and information about the size, strength, range, tone, steadiness, speed, and accuracy of orofacial structures and movements. Speech tasks include vowel prolongation during which pitch, loudness, voice quality, and duration are observed. Alternating motion rates for assessing the speed and regularity of rapid repetitive articulatory movements and sequential motion rates for assessing the ability to move quickly from one articulatory position to another are also included in the motor speech assessment.

Contextual speech, such as reading a paragraph aloud, retelling a story, or responding in conversation, shows how well all the components of speech are integrated. Judgments of speech intelligibility are also made. These may include estimates by the clinician or formal assessment with standard intelligibility tests such as the Frenchay Dysarthria Assessment (244) and the Assessment of Intelligibility of Dysarthric Speech (245).

Many acoustic and physiologic tests are available to study motor speech disorders, and they have the potential to quantify and explain clinical perceptual observations and to increase our understanding of the pathophysiologic underpinnings of dysarthric speech (8). However, they are not yet standard practice, and their use is limited primarily to the research laboratory.

Treatment of Dysarthria

The impact of stroke-related dysarthria transcends the physiological impairment (246). Therefore, a successful management program should address both the impairment and the activity/participation limitations imposed by the impairment. Treatment techniques for the impairment focus on improving the physiologic support for speech, including respiration, phonation, articulation, and resonance, with an emphasis on muscle tone, strength, movement precision, and coordination. Treatment techniques at the level of activity and participation may include modifying speech through compensatory speaking strategies, developing alternative and augmentative means of communication, and controlling the environment and communicative interactions to maximize communication.

Body positioning can influence respiratory support for speech (247,248). Therefore, postural adjustments, particularly for patients in wheelchairs, may be a simple way to improve respiratory drive for speech. However, improvements in respiratory support are ideally targeted during actual speech production. Some patients may simply need to practice inhaling more deeply or using more force when exhaling during speech. When the number of words produced on a single exhalation of air is limited, chunking utterances into short syntactic units with normal pauses within and between sentences may facilitate production.

For work at the phonological level, effort closure techniques are exercises that help the vocal folds adduct by providing overall increased muscle contractions in the torso and neck regions (247,248). Examples of effort closure techniques include pushing or pulling with both hands against the bottom of one's chair or clasping one's hands together and squeezing as hard as possible. Such exercises may improve vocal fold strength, resulting in increased loudness and reduced breathy voice quality (247). In contrast, hyperadduction of the vocal folds is treated with various tension-reducing strategies emphasizing easy onset of phonation such as "yawn-sigh," "chewing," or "chanting" techniques. Various forms of muscle relaxation exercises of the head and neck areas, enhanced with biofeedback, have also been noted in the literature (247).

Consultation with medical staff outside the usual rehabilitation team may be indicated for some patients. For example, if vocal folds are not functioning adequately, an otolaryngologist may determine if injectible substances or thyroplasty surgery might improve laryngeal functioning. When a patient has velopharyngeal weakness, a prosthodontist may fit a prosthetic device such as a palatal lift.

Many clinicians incorporate oral strengthening exercises for muscle weakness of the tongue, lips, and jaw into their treatment program. These oral exercises take the form of moving the articulators in various directions against some sort of resistance, followed by attempts to hold them in their position of maximum range. Strengthening exercises for the velum include various blowing and sucking tasks (249). The value of these strengthening exercises for muscle weakness is controversial, and to date, there are no definitive research studies to support their use in the recovery of speech production.

Strategies to improve intelligibility of speech focus on increasing the precision of articulation, controlling the rate of speech, and improving prosody so that communication sounds more natural. Direct instruction on the correct placement of the articulators during production of a specific sound helps the patient understand how to produce the sound correctly as well as the cause of the sound errors, thereby preventing errors from occurring.

Overarticulation or exaggeration of consonants helps the patient to better articulate words, in particular those sounds that are in the middle or at the ends of words. Minimal contrast drills with words that vary by only one vowel or consonant are also helpful. The differences between the words may be in the voicing (*park/bark*), the manner of production (*dime/mime*), or the place of production (*sea/she*) (8). Rate control can be accomplished by reciting words and syllables to a metronome or by finger or hand tapping to set the pace of appropriate syllable production (250). Slowing the speaking rate is often helpful because the patient may have more time to achieve articulatory placements. When speakers pause more often to slow down their rate, the listener is also given more time to process what is being said. Problems with intonation, stress, and rhythm contribute to the unnaturalness of speech. Treatment may include pitch range exercise or contrastive stress drills in which words, phrases, and sentences are practiced with different stress patterns each time.

Environmental modification may involve altering the number of listeners, the amount of noise, and the distance between the speaker and listener and improving eye contact. Modifications may also include informing new listeners about speech disorders and how best to communicate and strategies for repairing breakdowns in communication (e.g., repeating utterances, rephrasing, spelling, writing, and answering clarifying questions).

If a speaker remains unable to communicate satisfactorily using speech, augmentative or alternative communication modes should be considered (251). Selection of one or more systems depends on factors such as the motor, sensory, cognitive, and linguistic abilities of the patient. AAC devices may range from simple picture boards or spelling boards to portable amplification systems to high-tech electronic devices.

Efficacy of Dysarthria Treatment

A series of recent systematic reviews has addressed the efficacy of techniques for the management of dysarthria. These reviews have included behavioral procedures for managing respiratory and phonatory dysfunction (248) and velopharyngeal dysfunction (249); behavioral techniques for the treatment of loudness, rate, and prosody (250); and speech supplementation techniques (e.g., indicating the first letter or the topic of the sentences) for those with severe dysarthria (251). Although

results from the majority of the studies indicated positive outcomes, many of the studies included very small numbers of subjects, and few of the studies were specific to patients with stroke. More recently, a growing number of studies have investigated behavioral interventions specifically targeting stroke-related dysarthria and the results have been positive (252–256).

Despite these findings, a Cochrane review of speech and language therapy for dysarthria caused by nonprogressive brain damage (stroke) did not identify any randomized controlled trials that met their standards of inclusion (257). The review concluded that "there is no evidence of the quality required to support or refute the effectiveness of speech and language therapy interventions for dysarthrias following nonprogressive brain damage." Nevertheless, as noted by Yorkston, Spenser, and Duffy (2003), "treatments for which there is evidence of effectiveness do not necessarily represent the most appropriate or the most effective treatments that are available; they only represent the treatments for which evidence about treatment effects have been acquired." They further note that there are many techniques and treatments for which there is expert opinion about effectiveness or lack thereof (248).

Future research demonstrating the efficacy and effectiveness of the various treatment approaches for dysarthria using rigorous scientific methodologies is critical. A focus on more homogeneous groups of individuals based on etiology may serve to expand our knowledge base of dysarthria resulting specifically from stroke. An essential question is whether the potential facilitation of speech relearning could have a significant effect on reducing functional limitations and improving quality of life for people with dysarthria. Hopefully, further research will provide clarification and lead to more effective treatments for individuals with dysarthria.

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14

Dysphagia

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EPIDEMIOLOGY

Swallowing dysfunction, or dysphagia, is common after stroke. The true incidence of dysphagia after acute stroke is unclear, but estimates range from 20% to 90%, largely dependent on timing and method of ascertainment (1). Conservative estimates of the true incidence report that nearly 50% of acute stroke survivors experience dysphagia within the first few days after stroke (2–4). Dysphagia is associated with development of pneumonia, dehydration, and malnutrition; increased length of stay; and mortality after stroke (5–8). Dysphagia has traditionally been associated with brainstem and bilateral cerebral infarctions (1,9), but in recent years it has been shown to occur in isolated cerebral infarctions as well. The incidence may be as high as 25% for left hemisphere and 15% for right hemisphere lesions (6,10).

Aspiration Pneumonia

Aspiration, the passage of food or other foreign material through the vocal folds, is common in stroke survivors with dysphagia. The risk of aspiration pneumonia is increased threefold in stroke survivors with dysphagia and between 11- and 20-fold in patients with aspiration confirmed by videofluorography (3,11). Aspiration can sometimes be detected by clinical examination, but silent aspiration, that is, aspiration without cough, occurs in up to two-thirds of stroke survivors (12). Although aspiration on videofluorography is associated with an increased risk of pneumonia, the risk of dehydration and death is similar to the risk of other dysphagic stroke survivors (13). The material aspirated is also an important consideration. The effects of the aspirated material depend largely on the amount, bacterial load, acid content, and physical characteristics (14,15).

Aspiration of gastric material usually leads to chemical pneumonia, with bacterial infection occurring as a complication 2 to 3 days after injury in cases where the pH of the gastric content is higher due to antacids, proton pump inhibitors, or H2-receptor blockers (15). Aspiration of material with a pH greater than 2.5 causes severe lung injury with parenchymal inflammation, which can lead to adult respiratory distress syndrome (16). Gastric colonization with gram negative bacteria has been documented in patients receiving enteral feeding, placing them at risk for combined chemical and bacterial pneumonia after aspiration of gastric contents (17).

Bacterial pneumonia is predominantly related to aspiration of oral flora and upper airway colonization (14,15); thus, multiple organisms can be isolated (18). Good oral care can reduce the risk of pneumonia by reducing the bacterial load (19).

Malnutrition

Malnutrition in stroke survivors has been reported in 8% to 34% cases (20,21). Malnutrition has also been associated with poor outcomes after stroke, including longer lengths of stay and increased number of complications such as pressure ulcers, falls, tachycardia, and infections (22). Details on nutrition and nutritional interventions after stroke are detailed in Chapter 34.

Recovery of Swallow Function After Stroke

Swallowing dysfunction generally resolves for about half of stroke survivors within 7 days, and only 11% to 13% have persistent swallowing dysfunction after 6 months (23,24). Prognosis is dependent on many factors related to medical status, dysphagia, and rehabilitation potential. Severity of stroke, recurrent stroke, low serum albumin levels, dependence on tube feedings, need for ultra-thickened liquids, and aspiration documented on a videofluorographic swallowing study (VFSS) have been linked to poor outcomes (25,26). Advanced age, impaired cognition, and dependence on a wheelchair are also linked to poor outcomes (27). The best outcomes occur when individuals receive early assessment and treatment of dysphagia with a structured, interdisciplinary team approach.

SWALLOWING PHYSIOLOGY

The process of swallowing, or deglutition, is a series of complex volitional and reflexive movements with two critical biomechanical functions:

1. The food passage propelling the food bolus carried from the oral cavity to the stomach
2. Airway protection insulating the nasal passages, larynx, and lower respiratory tract from the pharynx during food passage

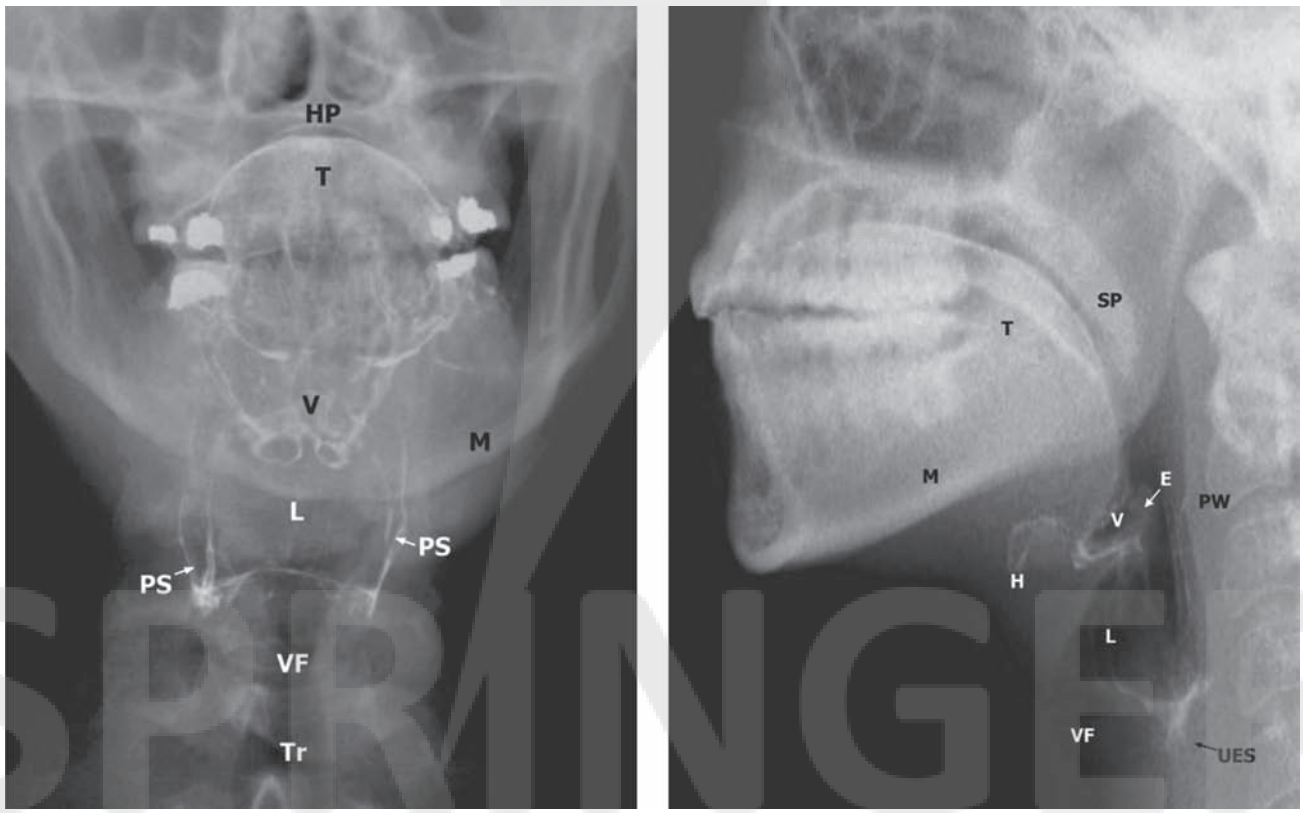
The main anatomical structures involved include the oral cavity, pharynx, larynx, and esophagus (Figure 14.1).

Swallowing Stages

The swallowing process is classically divided into four stages according to the location of the bolus (28). After ingestion, food is prepared for propulsion to the pharynx (oral preparatory stage). The tongue pushes the bolus through the fauces and into the pharynx (oral propulsive stage). Stereotyped movements of pharyngeal structures move the bolus from the pharynx to the esophagus through the upper esophageal sphincter (UES) (pharyngeal stage). Finally, peristalsis and gravity carry the bolus down the esophagus and through the lower esophageal sphincter (LES) to the stomach (esophageal stage). According to the traditional model of swallowing, the oral preparatory stage is initiated voluntarily, but once oral propulsion starts, the rest of the process follows immediately. The total duration of food transit to the esophagus occurs in less than one second in normal adults.

Oral Stage: Differences Between Drinking and Eating

Although the general sequence of an oral swallow is the same for liquid and solid boluses, there are differences relative to preparation and timing. Once ingested, liquids are collected by the tongue and maintained between the tongue's dorsal surface and hard palate surrounded by the upper dental arch until the oral propulsive stage is started (Figure 14.2). Liquids are prevented from leaking into the oropharynx before the swallow initiation by a seal created by the soft



A B

FIGURE 14.1 Videofluorographic image, lateral and AP views. (A) Postero-anterior projection in a videofluorographic image. (B) Lateral projection in a videofluorographic image.

Abbreviations: E, epiglottis; H, hyoid bone; HP, hard palate; L, laryngeal vestibule; M, mandible; PW, posterior pharyngeal wall; PS, pyriform sinus; SP, soft palate; T, tongue; TC, thyroid cartilage; Tr, trachea; UES, upper esophageal sphincter; V, valleculae; VF, vocal folds.

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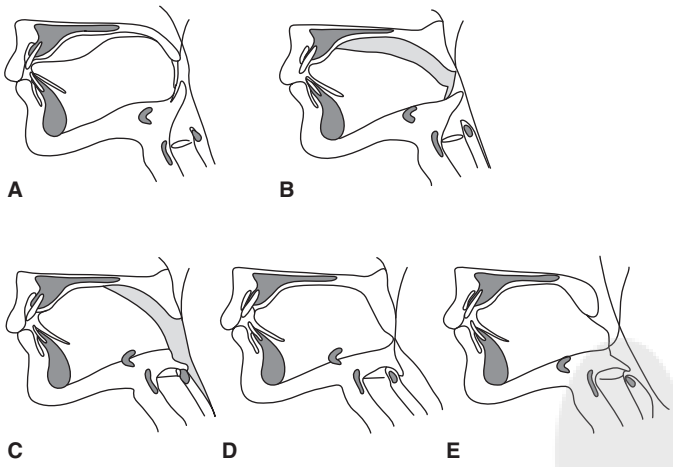

FIGURE 14.2 Normal swallowing of a liquid bolus. These drawings are based on an actual videofluorographic sequence recorded in the lateral projection. (A) The bolus is held between the anterior surface of the tongue and hard palate, in a ready-to-swallow position. The tongue presses against the palate both in front of and behind the bolus to prevent spillage. (B) The bolus is propelled from the oral cavity to the pharynx through the fauces. The anterior tongue pushes the bolus against the hard palate just behind the upper incisor. The posterior tongue drops away from the palate. (C) The soft palate elevates, closing off the nasopharynx. The area of the tongue–palate contact spreads posteriorly, squeezing the bolus backward to the pharynx. The larynx elevates, and the epiglottis tilts downward. (D) The upper esophageal sphincter opens. The tongue base retracts to contact the pharyngeal wall, which contracts around the bolus, starting superiorly and then progressing downward toward the esophagus. (E) The soft palate descends, and the larynx and pharynx reopen. The upper esophageal sphincter returns to its usual closed state after the bolus passes.

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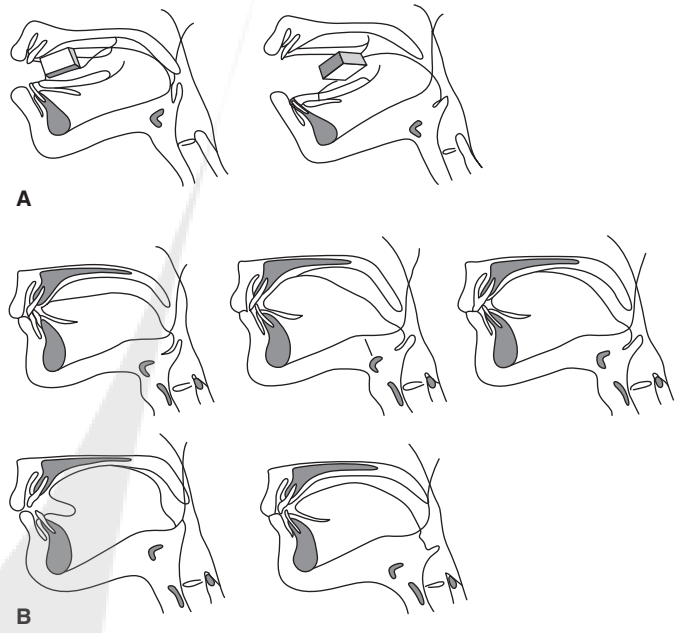

FIGURE 14.3 Mechanisms of food transport in a normal subject eating solid food. (A) Stage I transport: The tongue carries the bite of food back to the postcanine region and then rotates to place it on the occlusal surfaces. (B) Stage II transport: The tongue squeezes the bolus backward along the palate, through the fauces, and into the pharynx.

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palate and dorsal tongue contact. Although this posterior oral seal is usually effective in young, healthy individuals, it is often incomplete, and some liquid may enter the pharynx before the onset of oral propulsion. In contrast to single liquid boluses, during continuous drinking, for example, as seen during drinking with a straw, the bolus often advances to the level of the valleculae prior to swallow initiation (29).

The oral propulsive stage starts when the tip of the tongue makes contact with the hard palate just behind the upper anterior teeth. The tongue surface moves upward and the tongue–palate contact area expands posteriorly, squeezing the bolus into the pharynx.

Eating solid food is quite different from drinking liquid because the food requires significant processing before it is ready to be swallowed (30,31). The process model, a recent development in understanding the physiology of swallowing, incorporates critical aspects of mastication and oral food transport (31,32). When solid food is placed in the mouth, the tongue shifts backward and then rotates its surface to one side. This movement pulls the food back to the molar region and places it on the occlusal surfaces of the postcanine teeth during stage I transport (Figure 14.3A). Then food particles are reduced in size by mastication and softened with saliva until the consistency of the food is optimized for the swallow (food processing). The movements of the jaw, tongue, cheek, soft palate, and hyoid are rhythmical and linked to each other, spatially and temporally, during food processing (33–36). Processed food particles are placed on the dorsal tongue surface and squeezed back to the pharynx during stage II transport (Figure 14.3B), with a mechanism that is nearly identical to that indicated for the oral propulsive stage described earlier. Stage II transport occurs intermittently during food processing cycles so that a food bolus forms in the oropharynx and gradually accumulates for several seconds before the pharyngeal swallow. When sufficient food has accumulated, the pharyngeal stage of swallowing is initiated.

Pharyngeal Stage

The location of the bolus at the initiation of pharyngeal swallowing differs between drinking and eating. The bolus is usually maintained in the mouth during discrete liquid swallows, but it can be in the oropharynx during sequential

swallows or with solid food (29–31,37). The leading edge of the bolus is often in the hypopharynx at swallow onset when eating food with mixed consistencies (liquids and solids) (38).

The pharyngeal stage is a rapid sequence of overlapping and nearly synchronous events (39–42) (Figure 14.2C–D):

1. The soft palate elevates and contacts the lateral and posterior wall of the pharynx, closing the nasopharynx.
2. The base (pharyngeal surface) of the tongue retracts, pushing the bolus posteriorly and downward. The pharyngeal wall contracts around the tongue, both from the back and from the sides, squeezing the bolus. The pharyngeal contraction is sequential, beginning at the top of the pharynx and proceeding downward (43). The pharynx also shortens vertically, reducing its volume (44).
3. The hyoid bone and larynx are pulled upward and forward by contraction of the suprahyoid muscles and thyrohyoid muscle. The anterior and superior movements of these structures are critical for airway protection and opening of the UES (45).
4. Prior to UES opening, the vocal folds close to seal the glottis (46–48). The arytenoid cartilages tilt forward to contact the base of the epiglottis. The anterior and superior movements of the hyoid and larynx tuck the larynx under the base of the tongue and fold the epiglottis backward to seal the laryngeal vestibule. The downward bolus movement and tongue base retraction also helps epiglottal tilt (49). To prevent inhalation of food, breathing ceases briefly during swallowing (deglutitive apnea) for approximately 0.4 to 1.0 seconds (50,51). Breathing resumes in the expiratory phase.
5. Opening of the UES is essential for the bolus to reach the esophagus. The UES is held closed at rest by tonic contraction of the cricopharyngeus muscle (45,52). Muscles just above and below the cricopharyngeus may also assist in UES closure. During a swallow, these muscles relax, and the UES opens. Three important factors contribute to this opening:
   - The active relaxation of the cricopharyngeus muscle
   - Contraction of the suprahyoid muscles that move the hyoid bone and larynx forward, effectively pulling the sphincter open (45)
   - The pressure of the descending bolus (53) pushes the UES outward, assisting in its opening

Esophageal Stage

The bolus transit mechanism in the esophagus is different from that of the pharynx. The cervical esophagus (upper one-third) is composed mainly of striated muscle, but the thoracic esophagus (lower two-thirds) is smooth muscle. Peristalsis is controlled by autonomic nerves. Once the bolus passes the UES and enters the esophagus, a peristaltic wave carries the bolus down to the stomach. Gravity assists peristalsis in the upright position. The LES contracts tonically between swallows to prevent gastroesophageal reflux, and relaxes to allow bolus passage into the stomach.

NEURAL CONTROL OF SWALLOWING

Swallowing is a complex process that involves sequential muscle contraction and inhibition of more than 30 muscles (54). The major muscles involved in swallowing and their innervation are detailed in Table 14.1. Similar to respiratory control, swallowing functions are controlled primarily by centers in the brainstem. Although the main center controlling swallowing is in the brainstem, the cerebral cortex and other supratentorial structures also have a role in swallowing control.

Brainstem: Central Pattern Generator

The swallowing central pattern generator (CPG) generates the sequential pattern of motor activities required for a swallow. The pattern for muscle contraction and inhibition is dependent on three distinct components:

1. The afferent input to the CPG in the brainstem (sensory and supramedullary)
2. The efferent output that provides innervation to the swallowing muscles
3. The interneuronal network that integrates afferent and efferent input in the CPG (55)

TABLE 14.1 Innervation of Major Muscles Related to Swallowing

CRANIAL NERVE	MUSCLES
Trigeminal nerve (V)	Masticatory muscles Mylohyoid Tensor veli palatine Anterior belly of digastrics
Facial nerve (VII)	Facial muscle Stylohyoid Posterior belly of digastrics
Glossopharyngeal nerve (IX)	Stylopharyngeus
Vagus nerve (X)	Levator veli palatine Palatopharyngeous Salpingopharyngeous Intrinsic laryngeal muscles Cricopharyngeus Pharyngeal constrictors
Hypoglossal nerve (XII)	Intrinsic tongue muscles Hyoglossus Geniohyoid Genioglossus Styloglossus Thyrohyoid

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The CPG is located within the nucleus tractus solitarius (NTS) and the reticular formation surrounding both the NTS and above the nucleus ambiguus (NA) in the rostral and ventrolateral medulla (55,56). The CPG is organized into two main regions with distinct functions:

1. The dorsal group involved in triggering, shaping, and timing of the sequential swallowing pattern
2. The ventral group that distributes the swallowing drive to the various pools of motor neurons involved in swallowing (56)

Sensory (afferent) input from the mechanoreceptors, chemoreceptors, and thermoreceptors in the oral cavity, pharynx, and larynx to the CPG has been implicated in swallowing initiation, facilitation, and airway protection (1,57–61). General sensory neurons from the oral cavity synapse in the trigeminal sensory nuclei, whereas those from the pharynx and larynx travel in branches of cranial nerves IX, X, and XI and synapse in the NTS (62).

The ventral CPG premotor neurons have connections with the trigeminal (V), facial (VII), hypoglossal (XII) motor neurons, and the NA (IX and X) that innervate the swallowing muscles (56). The output from the CPG can be modified by sensory feedback. Motor timing varies with bolus characteristics and other variables (63).

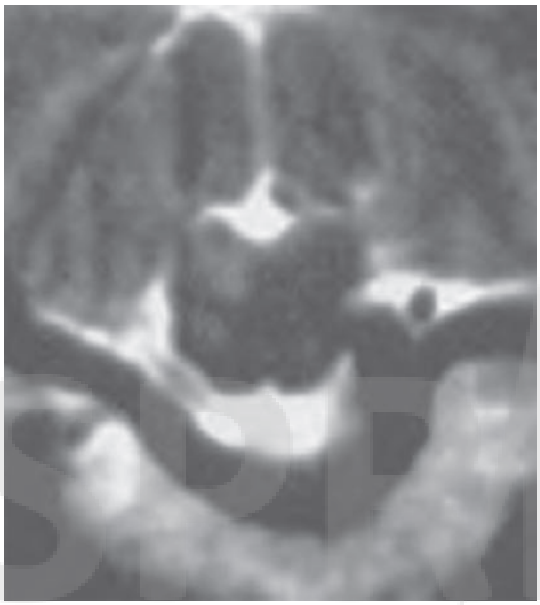
Wallenberg Syndrome: Disruption of the Swallowing Central Pattern Generator

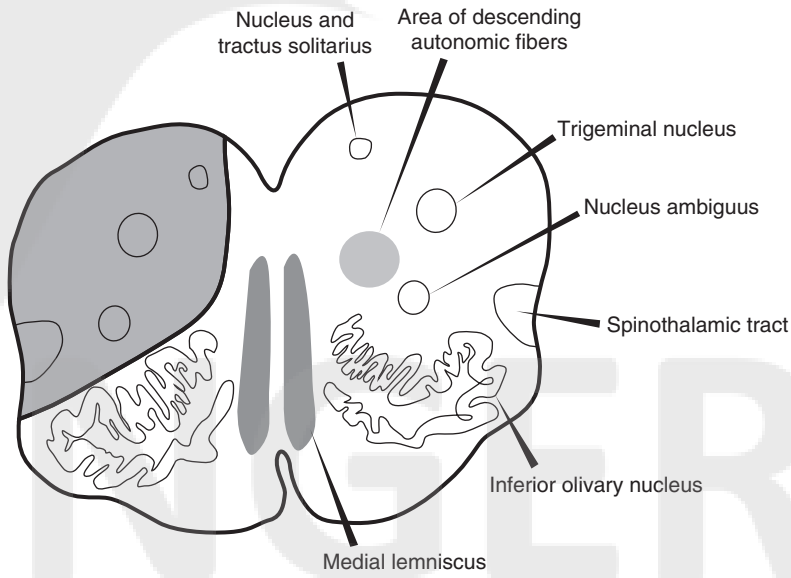
Disruption of the swallow CPG can result in a severe and long-standing dysphagia associated with aspiration (57,64). Wallenberg, or lateral medullary, syndrome results from occlusion of the vertebral, posterior inferior cerebellar, or medullary perforator arteries. Lateral medullary infarction (LMI) can affect the NTS, NA, and motor nuclei of the cranial nerves involved in swallowing (Figure 14.4). Involvement of the NA produces weakness or paralysis of the ipsilateral muscles of the pharynx, larynx, and soft palate. Involvement of the NTS can hamper initiation and coordination of the pharyngeal swallow.

Electrophysiological evidence suggests that, in LMI, the swallowing function is affected bilaterally, indicating an acute disconnection syndrome to the contralateral swallowing centers (57). The mechanism for recovery of swallowing after LMI is poorly understood.

Supramedullary Control of Swallowing

Although the swallowing CPG is located in the brainstem, mounting evidence suggests that several supratentorial structures, most prominently the cerebral cortex, have an essential role in the regulation of swallowing (65–67). Voluntary





A B

FIGURE 14.4 Lateral medullary syndrome, axial cut through the rostral medulla. (A) MRI (B) Diagram. Lateral medullary syndrome causes dysphagia by affecting the NTS and NA. Other deficits include—Contralateral loss of pain and temperature: Involvement of the spinothalamic tract. Ipsilateral loss of pain and temperature sensation on the face: Involvement of the descending nucleus and tract of V. Ipsilateral Horner's syndrome (ptosis, meiosis, and anhidrosis): Involvement of descending autonomic fibers. Ipsilateral ataxia: Involvement of the inferior cerebellar peduncle (restiform body).

initiation of swallowing requires integrity of the motor areas of the cerebral cortex (59). Studies using positron emission tomography (PET) have identified multiple, asymmetric loci associated with swallowing, including the right orbitofrontal cortex, left mesial premotor cortex and cingulate, right caudolateral sensorimotor cortex, right anterior insula, bilateral medial cerebellum, and bilateral temporopolar cortices (68). The strongest activation has been seen in the sensorimotor cortices, insula, and cerebellum. Swallowing is represented asymmetrically in the cortex, and there is no clear right or left laterality (69). Studies in stroke survivors have shown that the size of the swallowing area in the unaffected cortex determines the presence or absence of dysphagia (70). The cortical representation of swallowing within the motor and premotor cortex has been shown to be bilateral but markedly asymmetric (71). Using this theoretical framework, one would expect individuals with strokes of the hemisphere with higher swallowing representation to have a predisposition to dysphagia.

Although mechanisms of recovery of the swallowing function remain unclear, studies using transcranial magnetic stimulation suggest that recovery of the swallowing function after a cortical stroke is associated with compensatory cortical reorganization in the undamaged hemisphere (72). In spite of the obvious contributions of the cerebral cortex, insula, cerebellum, and others to the normal swallowing mechanism, it is still unclear how these areas are integrated with the brainstem to produce functional and voluntary swallowing. It is also unclear why recovery does not occur in some cases of unilateral supratentorial stroke.

Suprabulbar Palsy: Disruption of the Corticobulbar System

Disruption of the corticobulbar system may result in suprabulbar palsy (SBP). SBP, or pseudobulbar palsy, is a clinical syndrome characterized by dysphagia, dysarthria, dysphonia, impairment of voluntary movements of tongue and facial muscles, and emotional lability. The most common cause of SBP is multiple bilateral lacunar infarcts, but it is also associated with amyotrophic lateral sclerosis (ALS), Parkinson's disease, and multiple sclerosis. Swallowing difficulties in these patients are common and range from mild, subclinical findings to severe dysphagia precluding oral feeding.

Studies in SBP patients suggest that the basal ganglia and associated neural pathways play a role in the pathogenesis of dysphagia after stroke and that progressive involvement of the excitatory and inhibitory corticobulbar fibers is responsible for the difficulties that SBP patients experience (73). The swallowing problems in SBP cases are primarily difficulties in triggering a swallow and a dysfunctional cricopharyngeal sphincter that is hyperactive and uncoordinated (73). Slowing of oropharyngeal swallowing and saliva accumulation in the mouth was also associated with extrapyramidal dysfunction.

SWALLOWING IN THE ELDERLY

Because stroke occurs often in the elderly, it is important to consider specific deficits that might be present prior to a cerebrovascular event that can impact dysphagia outcomes after a stroke.

Dentition generally worsens with age. This is further worsened by the development of oral infections, such as periodontal disease or dental caries. With aging, masticatory muscles weaken, masticatory forces decrease, and speed of jaw motion slows. These factors result in increased mastication time and reduced efficiency (74). Despite the increase in mastication time, the bolus size at the time of swallow onset is larger in the elderly than in the young, primarily because of the decrease in masticatory function. Strength of labial closure and tongue–palate pressure also decreases. Although saliva secretion is stable with aging, disease, atrophy of the salivary glands, or medication side effects can cause xerostomia, or dry mouth, in elderly individuals (75,76).

The duration of transit from the oral cavity to the pharynx increases with age (53). The time interval from arrival of the bolus at the pharynx until onset of laryngeal elevation is also extended. Because of this time interval increase, laryngeal penetration is more frequent in the elderly, but aspiration is not (77–79).

Aging also affects UES function. Decreased UES compliance and reduced hyolaryngeal elevation reduce UES opening, resulting in increased hypopharyngeal intrabolus pressure during transsphincteric flow (53). The interval from the onset of the oral stage to the UES opening is delayed in the elderly, but the intervals from the onset of pharyngeal stage or from the onset of glottal closure until UES relaxation are not affected by age (53,61). Aging lowers resting pressure and shortens the length of the UES, but no significant effect is seen on the LES (80).

Aging increases the duration of swallow apnea, but it does not change the typical resumption of breathing in the expiratory phase after a swallow (40,81,82).

Dysphagia Rehabilitation

Rehabilitation of dysphagia includes improving overall function, increasing swallowing function by correcting underlying physiologic abnormalities, using compensation for unsafe or inefficient swallowing, and preventing complications such as aspiration pneumonia and malnutrition.

Abnormal Swallowing After Stroke

The specific dysphagia symptoms following stroke depend on the site of the lesion and differ in severity between individuals with the same site of lesion. Deficits may be unilateral or bilateral and may affect sensory and/or motor components of the swallow. Labial weakness can result in an inability to competently ingest a bolus from a utensil and in difficulty containing the bolus in the mouth. Lingual and buccal weakness may result in inadequate bolus formation

and propulsion, leading to ineffective oral clearance and piecemeal swallowing. Impaired mandibular and tongue movements result in ineffective mastication of solid foods. Sensory deficits may result in pocketing of oral residue into one or both cheeks or retention of food on the lips and tongue after swallowing.

Pharyngeal dysfunction can result in delayed swallow initiation, ineffective bolus propulsion, and retention of food after swallowing. Velopharyngeal inadequacy can cause nasal regurgitation. Impaired laryngeal elevation, vocal cord dysfunction, or epiglottic inversion result in ineffective airway protection. This places individuals at risk for laryngeal penetration (food material entering the larynx above the level of the vocal cords) or aspiration (food material passing through the vocal cords). An ineffective cough, caused by vocal cord dysmotility, weakness of expiratory muscles, or impaired coordination of glottal adduction with expiration, hampers clearance of aspirated material. Laryngeal sensory impairments can result in silent aspiration, in which there is lack of cough response to aspiration. Impaired opening of the UES can result in pharyngeal food retention, placing individuals at risk for aspiration after the swallow. Esophageal dysmotility leads to ineffective esophageal clearance and reflux. Esophageal dysfunction typically is not a problem after stroke, but should be considered, as it may coexist with oral and pharyngeal impairments.

The presence of a tracheostomy tube presents additional challenges. A tracheostomy tube is associated with altered laryngopharyngeal aerodynamics, eliminating the normal post-swallow expiration through the pharynx, reducing laryngeal sensation, and limiting ability to effectively cough and clear aspirated material.

Evaluation of Dysphagia

Early assessment and management of dysphagia reduce pneumonia rates and length of stay, and improve overall outcome from stroke (83–85). An interdisciplinary team's involvement in the dysphagia evaluation process is crucial to address the complex needs of the dysphagic individual. This team should include a physician, speech–language pathologist, dietician, occupational therapist, nurse, and other subspecialties as needed. Speech–language pathologists have substantial training in evaluation and treatment of dysphagia and should be consulted whenever a problem with oral or pharyngeal swallowing is suspected.

Comprehensive assessment of swallow functioning after stroke begins with a thorough medical history. Specific lesion localization may be useful in predicting presence and severity of dysphagia, as a large percentage of brainstem lesions, especially lateral medullary infarcts, result in severe dysphagia (10). However, dysphagia can also be present in cases with no brainstem involvement, particularly in cases of multiple or bilateral cerebral infarction. Medical history and current medical status, including cardiac, pulmonary, neurologic, and nutritional information, must be considered. Medications, such as barbiturates, benzodiazepines, antihistamines, or antidepressants, may negatively affect physical or neurologic function and limit an individual's participation in the rehabilitation process. A clear description of dysphagia-related symptoms, such as choking or coughing with food or liquids, vomiting, or the sensation of food stuck in the throat, provides information regarding possible deficits and indicates the need for further evaluation. The sensation of food sticking in the throat or chest is an important symptom of dysphagia. The sensation of food sticking in the throat has poor localizing value, as it may be seen in cases of esophageal as well as pharyngeal dysphagia. The sensation of food sticking in the chest, in contrast, is generally associated with esophageal problems.

Dysphagia Screening

Given the high prevalence of dysphagia and its complications, a swallowing screening examination should be completed as part of every stroke survivor's initial assessment. Elements commonly evaluated on bedside screening are described in Table 14.2. Dysphagia screening is part of the practice guidelines for adult stroke rehabilitation care (86). The goals of swallowing screening examination are to identify possible signs of dysphagia and aspiration and identify patients in need of further evaluation. The water swallow test is commonly used as a screening tool. The patient continuously drinks a predetermined amount of water, usually three or four ounces, and clinicians observe for signs of aspiration or dysphagia (87–89). Other screening tests include items from history as well (90). This screening is usually performed by trained medical personnel. Results of this screening must be interpreted with caution, as they have limited predictive ability, cannot detect silent aspiration, cannot determine safety with other forms of food/liquids, and cannot provide information regarding the mechanism of dysphagia. It is essential to have a high index of suspicion to improve sensitivity of screening. Several validated tools

TABLE 14.2 Elements Commonly Evaluated on Bedside Screening

General assessment
1. History of dysphagia or enteral feeding
2. Conciousness level: Altered alertness or arousal
3. Postural control
4. Difficulty managing oral secretions
5. Weak voluntary cough
Swallow challenge (One teaspoon of water followed by three ounces of water)
1. No laryngeal elevation
2. Coughing
3. Choking
4. Wet or "gurgly" vocal quality

are available in the literature, all with strengths and shortcomings that should be taken into account when choosing a screening tool for a particular setting.

Physical Examination

A physical examination of the upper aerodigestive tract, including cranial nerve testing, should be performed to assess structure and function. Symmetry, strength, and range of motion of the facial and oral muscles are examined in isolated and purposeful movements. Sensation to facial, lingual, labial, and palatal stimulation is assessed. Drooling and secretion management should be noted, as they are associated with the ability to manage food and liquid boluses. Hearing and vision skills should be screened as well. Symmetry and strength of movement of the velopharynx is demonstrated through vocalization and by eliciting a gag reflex. The presence or absence of a gag reflex should not be used as a predictor of safety in swallowing. Some normal individuals have an absent gag reflex; individuals with severe dysphagia can have intact gag reflexes (91).

The larynx is manually palpated for abnormalities at rest and during a volitional swallow of saliva (Figure 14.5). Laryngeal function is assessed further by eliciting a volitional cough and assessing vocal quality. Ventilatory control is observed at rest, during speech, and through sustained phonation. Cognition and communication skills, including orientation, attention, memory, and insight, should be examined, as impairments in cognition can negatively impact outcomes (92,93).

Clinical Swallow Evaluation

If the presence of dysphagia is suggested by the screening examination or the patient complains of symptoms associated with swallowing dysfunction, that individual should be referred for a complete clinical swallow evaluation (CSE).

FIGURE 14.5 Palpation of the larynx. Each finger is used to palpate a different structure: middle finger, hyoid bone; fourth finger, top of thyroid cartilage; fifth finger, cricothyroid notch.

The clinical (or bedside) swallow evaluation examines an individual's potential risk for dysphagia and aspiration with various food and liquid consistencies and is usually performed by a speech–language pathologist. Findings are used to guide decision making on further instrumental examinations, safe means of alimentation, and an appropriate treatment plan. During a CSE, clinicians complete a thorough oral, pharyngeal, and laryngeal motor and sensory assessment. Liquids and solid foods are presented. Oral function is observed for ability to manage substances with adequate lip, tongue, and jaw control and movement. This includes adequate mastication and maneuvering of liquid and solid boluses and ability to propel boluses into the pharynx without oral residual. The timing and strength of the pharyngeal swallow is assessed through palpation of the tongue base, hyoid, and larynx. Clinicians look for signs of overt aspiration before, during, or after the swallow occurs. Although silent aspiration cannot be reliably detected during a bedside examination, several clinical signs are associated with risk of aspiration. These include dysphonia, dysarthria, weak cough, abnormal laryngeal elevation, impaired control of secretions, cough after swallow, and voice change after swallow (94–97).

Clinical tools provide additional information and assist in making judgments during the CSE. Using cervical auscultation with a stethoscope, clinicians may listen to the sounds of swallowing for coordination, timing, and pre- and postswallow breath sounds. Clear classifications of the sounds heard and their physiological implications have yet to be described (98,99). Decline in pulse oximetry during swallowing has been explored as a tool to predict aspiration; however, evidence has been contradictory (100,101).

Checklists have been suggested as tools to help guide assessment. One formal CSE tool is the Mann Assessment of Swallowing Ability (MASA), a standardized swallowing test that uses a checklist to place individuals in categories that describe their risk of dysphagia and aspiration (102).

The CSE relies on indirect information to make judgments regarding swallow abnormalities. Although clinician judgments regarding the presence of abnormal oral and pharyngeal function have reasonable reliability, they are not perfect, and they may fail to identify some patients with dysphagia and aspiration. In addition, the presence or absence of aspiration, the timing and cause of aspiration, and the effectiveness of compensatory maneuvers cannot be reliably determined with a CSE (28,88,100). Instrumental examination of swallowing is essential to the comprehensive assessment of patients with clinical signs of dysphagia or at high risk of silent aspiration.

Instrumental Assessment Tools

Videofluorographic Swallowing Studies

The VFSS is the gold standard in swallowing assessment. This procedure is typically performed by a speech–language pathologist along with a radiologist or

TABLE 14.3 Penetration-Aspiration Scale

ASPIRATION RISK	SCORE	CLASSIFICATION	DESCRIPTION
No risk	1	Normal	No airway invasion
	2	Mild	Bolus enters into airway, remains above the vocal folds with clearing
Risk of aspiration	3	Moderate	Bolus enters into airway, remains above the vocal folds without clearing
	4	Moderate	Bolus contacts vocal folds with airway clearing
	5	Moderate	Bolus contacts vocal folds without airway clearing
Positive aspiration	6	Severe	Bolus enters trachea; clears into the larynx or out of the airway
	7	Severe	Bolus enters trachea; not cleared despite attempts
	8	Severe	Bolus enters trachea; no attempt is made to clear

Source: From Ref. (104). Rosenbek JC, Robbins JA, Roecker EB, et al. A penetration-aspiration scale. *Dysphagia*. 1996;11:93–98.

physiatrist. During a VFSS, the patient ingests liquids and solids with barium or other radiopaque contrast while motion radiographic images are produced and recorded. The purpose of this test is to identify the structural or functional abnormalities related to swallowing and to identify circumstances for safe swallowing (103). Clinicians make observations of structure and function that cannot be made during a CSE. These include oral bolus control and propulsion, pharyngeal transport, timing and coordination of the swallow, presence and depth of laryngeal penetration or aspiration, and possible causes of aspiration or laryngeal penetration. In this context, *laryngeal penetration* is defined as contrast entering the larynx but not passing through the vocal folds. *Aspiration* is defined as contrast passing through the larynx and vocal folds. The penetration-aspiration scale (104) is a semiquantitative tool for describing the degree or severity of laryngeal penetration and aspiration (Table 14.3). However, it is not typically used in clinical practice.

Use of standardized VFSS procedure improves its reliability and clinical utility (Table 14.4) (105). Images of the swallow should be obtained in both the lateral and anteroposterior views to determine laterality of swallow dysfunction. Observations are made regarding motions of the tongue, jaw, soft palate, epiglottis, hyoid bone, larynx, pharyngeal walls, and UES. Additional observations are made regarding timing and extent of bolus flow, including timing of swallow, retention of contrast after swallowing, and the presence of penetration or aspiration. Performing and interpreting a VFSS require analysis of the mechanism of swallowing dysfunction. This analysis will suggest opportunities for treatment. The VFSS also provides opportunity to test compensatory maneuvers such as modifications of posture or bolus characteristics that may improve the safety and efficiency of swallowing.

Radiation exposure limits the duration of the VFSS, so the VFSS is brief and provides only a window into the swallow function. However, the radiation dose and relative risk of radiation-related complications are low (106).

TABLE 14.4 Videofluorographic Swallow Study Protocol

Lateral projection, patient sitting upright in usual position of comfort
Speech sample ("candy, candy") to visualize velar motion
Command swallow: 5 mL of thin liquid from a spoon
Drink thin liquid from a cup (patient controls rate and volume)
Command swallow: 5 mL nectar-thick liquid from a spoon
Drink nectar-thick liquid from a cup (patient controls rate and volume)
Eat 1 tsp pudding from spoon
Eat 1 tsp soft food (e.g., chicken salad sandwich spread) from a spoon
Eat shortbread cookie (e.g., ½ of a Lorna Doone)
Compensatory techniques as appropriate
Other food consistencies as indicated

Anteroposterior (AP) projection, sitting upright (neck slightly extended if safe)
Phonation of "e" (as in "he") several times in succession to visualize motion of vocal folds and arytenoids
Command swallow: thin or nectar-thick liquid, 5 or 10 mL
Compensatory techniques or other foods as appropriate
Additional swallows as needed for imaging the esophagus

Source: From Ref. (105). Palmer JB, Kuhlemeier KV, Tippett DC, Lynch C. A protocol for the videofluorographic swallowing study. *Dysphagia*. 1993;8:209–214

Fiberoptic Endoscopic Evaluation of Swallowing

The fiberoptic endoscopic evaluation of swallowing (FEES) is a bedside procedure in which a nasally inserted flexible endoscope is used to directly view the nasopharynx and larynx during swallowing (Figure 14.6). During this procedure, individuals swallow various consistencies of food and liquids dyed for visualization.

The FEES is a useful procedure for evaluating the laryngeal and pharyngeal anatomy and assessing vocal cord function (107,108), and it is highly sensitive for detecting silent aspiration (109). However, the pharynx is not directly visible during a swallow because its closure produces a white-out

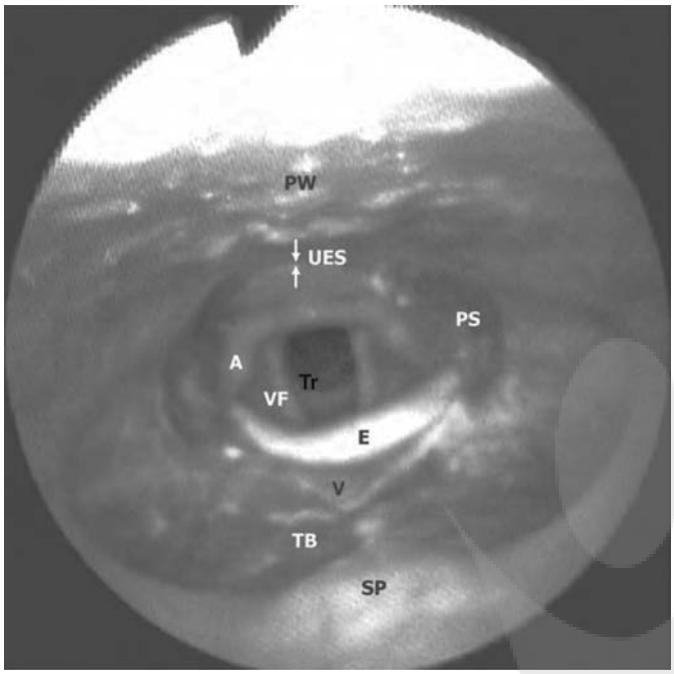


FIGURE 14.6 Fiberoptic endoscopic image of the pharynx.

Abbreviations: A, arytenoid; E, epiglottis; PS, pyriform sinus; PW, posterior pharyngeal wall; SP, soft palate; TB, tongue base; Tr, trachea; UES, upper esophageal sphincter; V, valleculae; VF, vocal folds.

Source: Modified from Jeffrey B. Palmer, Cathy A. Pelletier, Koichiro Matsuo. Rehabilitation of patients with swallowing disorders. In: Randall L. Braddom, ed. *Physical Medicine and Rehabilitation* (3rd ed., p. 608). © 2007, with permission from Elsevier.

effect on the image. The FEES is ideal for cases where radiation exposure is a concern. Its portability makes it a valuable tool for critical care patients or patients who are unable to tolerate transportation to a radiology suite. Disadvantages of the FEES procedure include the inability to:

- Observe a swallow directly
- Observe critical pharyngeal swallow events
- Observe the oral and esophageal stages of swallowing

The inability to evaluate tongue base retraction, pharyngeal constriction, epiglottic tilt, and UES opening limit the utility of FEES for analyzing swallow mechanics and pathophysiology.

Other Tools

Other instrumental tools can be useful in further assessing swallowing. Esophagoscopy is useful in assessing anatomical abnormalities of the esophagus. Functional or physiological disorders are better assessed with radiologic studies. Manometry measures pressure in the pharynx and in the esophagus during swallowing. It is primarily used to analyze motor disorders of the esophagus. Electromyography (EMG) is useful in diagnosing dysphagia in motor unit disorders and as a biofeedback tool in dysphagia therapy. It provides little information regarding the mechanism of swallowing, so it cannot be a guide for rehabilitation. Ultrasound may be used in the diagnosis of oral dysfunction, but it does not provide information on pharyngeal or esophageal function.

Treatment of Dysphagia After Stroke

The primary treatment principles in dysphagia management are amelioration of the underlying disease process, prevention of complications, compensation for an unsafe swallow, improvement of swallowing via therapy, and use of environmental modifications. A basic tenet of dysphagia rehabilitation is that the best exercise for swallowing is swallowing. This means it is important to determine the circumstances for safe swallowing before initiating a swallowing therapy program. Successful management of dysphagia requires adherence to these principles. As with evaluation, therapeutic management of the dysphagic stroke survivor requires an interdisciplinary approach.

Prior to initiation of dysphagia therapy, the stroke survivor must be stabilized medically. This includes preventing recurrent stroke, minimizing or preventing complications, and ensuring proper management of general health functions (110). Depending on the clinical presentation, a period where the patient receives no oral feeding might be indicated. Recent studies have demonstrated no difference in outcomes when comparing early tube feedings and avoidance of it (111,112). In addition to inability to safely take oral nutrition due to dysphagia, nutritional intake may be reduced by poor appetite caused by depression and medication effects, lack of dentures, cognitive levels, or impaired arm function. Nutritional status should be closely monitored by following body weight and blood chemistries (113). Intravenous fluids may be required to improve fluid intake. Some individuals may be able to tolerate supplemental water and ice chips despite dysphagia. Allowing water intake as part of the therapeutic diet may increase compliance with dietary recommendations and overall satisfaction (114), but it may lead to aspiration. Dysphagia management teams need to carefully consider an individual's risk of developing pneumonia, taking into account CSE and instrumental assessment results prior to allowing water in patients who aspirate.

Swallowing therapy is associated with successful outcomes, including return to oral feeding (115). Therapeutic programs must be individualized to the physiological and behavioral needs of the individual. A number of therapy techniques can be utilized to compensate for oral and pharyngeal control deficits and reduce the occurrence of penetration and aspiration. Environmental modifications should be employed, including reduction of distractions, proper seating and positioning, modifying bolus volume and rate, use of straws, and use of adaptive equipment.

Direct Swallowing Therapy Techniques

Direct swallowing therapy focuses on diet modification and behavioral compensations to improve swallowing efficiency and safety while allowing for oral nutrition. The

therapy plan is individualized and based on the mechanism of swallowing dysfunction in the particular individual with dysphagia. A VFSS is necessary to determine the circumstances for safe swallowing for a dysphagic stroke survivor and should be performed prior to initiating direct swallowing therapy.

Regular solid foods may be too difficult to effectively masticate and manipulate. Solid foods can be mechanically altered to make them softer, reduce particle size, or simplify consistencies to assist in mastication and food transport. Liquid viscosities can be altered to compensate for specific deficits. Thin liquids are generally the most difficult liquid consistency to tolerate for most dysphagic stroke survivors because they are difficult to control and may be aspirated before or during the swallow. Use of various levels of thickened liquids provides better oral and pharyngeal control and timing and may prevent aspiration. For other individuals, thin liquids are better tolerated because the major issue is lack of propulsive force or poor opening of the UES. Patients with these deficits may retain liquids in the pharynx and aspirate after swallowing. The National Dysphagia Diet, published by the American Dietetic Association, provides labels and descriptions of frequently used levels of food and liquid consistencies (Table 14.5) (116). Given the variety of swallowing in pathophysiology, these descriptions are not comprehensive, and clinicians must individualize diets based on specific findings in clinical and instrumental exams.

Altered bolus presentations—liquids by teaspoon, elimination of straws, decreased volume—can reduce aspiration risk and improve bolus transport in some patients. These strategies must be tested during the VFSS to determine their effectiveness and safety before their use in therapeutic diets. In addition to diet modifications, postural maneuvers are frequently utilized to facilitate safe and efficient swallowing. These postures are not effective for all dysphagic individuals and can be dangerous if utilized inappropriately. Careful clinical examination and testing during instrumental assessment ensure their appropriate use.

The chin tuck maneuver reduces laryngeal penetration and aspiration by improving laryngeal closure and preventing posterior loss of control of the bolus (28,117,118). This is accomplished by reducing the laryngohyoid distance and the hyoid-mandibular distance. The chin tuck maneuver also weakens pharyngeal contractions and can cause aspiration in patients with weakened pharyngeal muscles and tongue base retraction (37,119).

Rotation of the head to the affected (weak) side is useful in individuals with unilateral pharyngeal weakness and impaired UES opening. This maneuver alters the bolus pathway and propels the bolus through the pharynx on the unaffected side. Head rotation also aids in UES dynamics and pharyngeal clearance (120). Tilting the head away from the weak side can also divert the bolus through the stronger side of the pharynx.

Use of neck extension posture can be beneficial for individuals with impaired anteroposterior oral propulsion. Extending the neck provides gravity assist for the bolus to move through the oral cavity. Caution should be used when attempting this technique if pharyngeal control is impaired, as it may cause aspiration. A reclining position can be useful in individuals who retain food in the pharynx after the swallow and experience overflow aspiration. The reclining posture elevates the laryngeal aditus (entry) relative to the hypopharynx, inhibiting overflow aspiration.

Two related behavioral techniques can be used to reduce aspiration. The supraglottic swallow technique involves holding the breath before and during swallowing and coughing after swallow. This produces closure of the larynx prior to swallowing to prevent aspiration. In the super-supraglottic swallow, the breath holding is combined with valsalva maneuver, which closes the laryngeal vestibule in addition to adducting the vocal folds (121).

Several compensatory techniques can improve pharyngeal clearance. The effortful swallow technique is used to compensate for impaired pharyngeal constriction. Individuals are instructed to swallow hard. This technique assists pharyngeal clearance by increasing tongue base retraction (122).

TABLE 14.5 National Dysphagia Diet

NDD SOLIDS	DESCRIPTION
Level 1	Dysphagia—Pureed (homogenous, very cohesive, pudding-like, requiring very little chewing ability)
Level 2	Dysphagia—Mechanical altered (cohesive, moist, semi-solid foods, requiring some chewing)
Level 3	Dysphagia—Advanced (soft foods that require more chewing ability) (all foods allowed)
Regular	
NDD liquids	**Description in centipoise (cP)**
Thin	1–50 cP (liquid viscosity similar to water[a])
Nectar	51–350 cP (liquid viscosity similar to cream soup)
Honey-like	351–1, 1,750 cP (liquid viscosity similar to honey or molasses)
Spoon-thick	Greater than 1,750 cP (liquid viscosity similar to ketchup)

[a]Water has a viscosity of 1 centipoise at 20°C (68°F).

When food is retained in the pharynx after a swallow, a subsequent liquid swallow can be used to clear residue. If residue occurs consistently, it may be useful to alternate solids and liquids. The double-swallow technique uses a volitional swallow to assist in clearing pharyngeal residue. In the case of severe retention after swallowing, individuals often require three or more volitional swallows. The Mendelsohn maneuver increases the extent and duration of the UES opening by voluntarily prolonging contraction of the suprahyoid muscles (123). This can improve pharyngeal clearance.

Intraoral prostheses can be beneficial in selected individuals with decreased lingual and palatal strength and range of motion (124). Palatal augmentation assists individuals with oral stage transfer deficits. A device is fitted to improve contact of the tongue with the hard palate. Apalatal lift prosthesis elevates the palate to compensate for velopharyngeal insufficiency. Use of a one-way speaking valve for individuals with tracheostomy restores expiratory airflow after the swallow, allowing for coughing and clearing the airway.

Oral sensory stimulation involves use of altered temperature and taste to improve timing of the pharyngeal swallow. This technique is based on the premise that oral afferent information assists in swallowing initiation. Presentation of a sour bolus improves onset of oral swallow, reduces pharyngeal delay time, and improves swallow efficiency (125). Presentation of larger bolus volumes acts similarly by increasing swallow response time. Stimulation of the faucial arches with a chilled laryngeal mirror improves the swallow initiation when provided immediately before the swallow (126).

Neuromuscular electrical stimulation (NMES) is another modality used for the treatment of oropharyngeal dysphagia. The first device designed solely to provide NMES for swallowing therapy was approved by U.S. FDA in 2002 (VitalStim®, EMPI, Danbury, CT). A similar device was approved in 2011 (eSwallow™ Dysphagia therapy unit, eSwallow USA, Scottsboro, AL). Tetanic stimulation is delivered via surface electrodes overlying the submental and anterior neck muscles, and individuals are asked to swallow (127). It is suggested that NMES contracts the muscles used for swallowing and improves the swallow function (128). Although this technique is increasing in popularity among clinicians, its effects on swallow biomechanics are not well understood. Initial evidence indicates that NMES can stimulate only superficial muscles and not the pharyngeal muscles. The purpose of stimulation, at least in part, is to increase laryngeal elevation. There is evidence, however, that it can promote laryngeal descent in some cases (129–131). A study in chronic poststroke dysphagia suggested that sensory-only electrical stimulation reduces episodes of penetration or aspiration (130). NMES may instead be useful as a resistance exercise in individuals with reduced laryngeal elevation (130,132).

Long-term outcome studies using NMES are emerging in the literature. Unfortunately, heterogeneity in patient populations, outcome measures, and small sample size limits the comparability and conclusions of the various studies (133). The largest controlled study in the literature (99 subjects) compared surface electrical stimulation to thermal tactile stimulation in stroke survivors (134). The study reports that both interventions were effective in improving swallowing function but that the proportion of patients with sustained 2-year improvement was higher in the electrical stimulation group when compared to the thermal-tactile stimulation group. Unfortunately, lack of randomization and standardization of time poststroke (to account for spontaneous recovery) confound the results. Further research into the immediate and long-term outcomes of NMES treatment is necessary to determine its role in dysphagia treatment.

Indirect Swallowing Therapy Techniques

Indirect therapy involves the use of exercise to improve flexibility, strength, and coordination of the oral, pharyngeal, and respiratory muscles for swallowing. Common indirect therapy techniques are summarized in Table 14.6.

Oral exercises are designed to target motions used in the oral stages of swallowing. Oral control exercises include rapid lingual lateralization, rotary lingual movements, suck-and-swallow movements to assist in posterior bolus propulsion, simulated chewing via lateralization of gauze or sponges to improve bolus manipulation, and simulated labial seal to reduce labial leakage.

Oral muscles can be strengthened with resistance exercise. Lingual muscles are strengthened by pushing the tongue against a tongue blade, pushing the tongue into a cheek, and pulling the tongue posteriorly while being held anteriorly. Devices are being used to supplement lingual strengthening exercises. The Iowa Oral Performance Instrument (IOPI) is a handheld device that uses a plastic bulb positioned between the tongue and the soft palate to measure tongue pressure. Pressure is measured in kPa and displayed in the device and a series of lights change color from red to green with increasing pressure, providing the patient with biofeedback (135). The Madison Oral Strengthening Therapeutic (MOST®) device incorporates five air-filled sensors in a custom-molded mouthpiece attached to a laptop computer to accomplish the same goal (136). The Madison Oral-Lever Resistance Exercise (MORE®) device, currently in development, is intended for over-the-counter use by patients who need to perform independent exercises to increase or maintain tongue strength (137).

Labial muscles are strengthened by maintaining closure on a moving tongue blade and squeezing lips closed to resistance. Mandibular strengthening is achieved by opening and closing the jaw to resistance. Oral flexibility is improved through lateral, anterior, and rotary stretching of the tongue; protrusion and retraction of the lips; and mandibular opening and closure.

Pharyngeal exercises are designed to improve the range of motion and strength of the tongue base, pharyngeal muscles, and laryngeal muscles. Lingual protrusion and retraction improves tongue base contact with the pharyngeal wall. The Masako tongue-holding maneuver increases strength and

TABLE 14.6 Common Indirect Therapy Techniques With Brief Descriptions

THERAPY TECHNIQUES	BRIEF DESCRIPTION
Oral cavity	
Oral motor control exercises (jaw, tongue, lip)	Jaw opening and closing Tongue rotation, lateralization, protrusion, retraction Lip protrusion, lateralization, opening/closing Stretching and increasing range of motion
Relaxation and ROM (jaw, tongue, lip)	Opening/closing the jaw against resistance
Resistance exercise (jaw, tongue, lip)	Pushing the tongue against resistance
Pharynx	
Laryngeal elevation exercise	Volitional laryngeal elevation by saying a high-pitched "ee"
Vocal cord adduction exercise	Pushing wall or table, uttering "ah" simultaneously
Masako maneuver	Swallowing with the tongue tip held anteriorly outside the mouth
Sensory stimulation	Tactile stimulation of the faucial arches with cold or sour stimuli
UES opening	
Shaker exercise	Active head raising (neck flexion) in the supine position
UES dilatation	Expansion of a balloon catheter in the UES

Abbreviation: ROM, range of motion.

duration of tongue base contact with the pharyngeal wall. In this technique, the tongue tip is held anteriorly outside of the mouth while swallowing (138). Shaker exercises strengthen the anterior submental muscles, improving the UES opening during the swallow and thereby reducing food retention in the pharynx (139,140). In this exercise, the patient lies supine and lifts the head against resistance of gravity, flexing the neck, and looking at the toes (Figure 14.7). The patient lifts the head three times for 1 minute each and then performs 30 consecutive head lifts without holding. The patient holds the mouth closed during this exercise to focus resistance on the submental muscles.

Laryngeal muscles are stimulated through sustained elevation exercises. Maintaining a high-pitch sound (e.g., "ee"), performing effortful swallows, and using the Mendelsohn maneuver can improve laryngeal elevation during swallowing. Hard glottal attacks (forceful volitional closure of the vocal cords) and pushing-pulling exercises (phonation while pulling or pushing an object like a chair) improve vocal cord adduction to strengthen the cough response and vocal cord closure during swallowing.

EMG biofeedback is an adjunct therapy that allows individuals to visualize the force of muscle contraction. By increasing awareness of muscle activity, individuals are often able to effect greater control of those muscles (141). EMG can be used to record submental and infrahyoid activity during swallowing therapy, assisting the patient in contracting those muscles. EMG may be beneficial in training effortful swallows, sustained pharyngeal contraction, lip closure, and tongue mobility (142). Laryngoscopy can provide visual feedback when teaching a patient to perform laryngeal exercises. It provides direct visualization of the vocal cords and larynx, and it can be useful in completing vocal cord adduction exercises and learning breath control techniques such as the supraglottic swallow.

Pharyngeal Bypass

When safe alimentation is not possible, pharyngeal bypass measures may be employed, eliminating the need for oropharyngeal swallowing and providing nutrition and hydration. Short-term feeding—that is, less than 30 days—can be accomplished via nasogastric (NG) tubes. NG tubes have risks, and they can result in numerous complications, including reflux aspiration, improper positioning, dislodgement, and ulceration of pharyngeal and esophageal tissue. Long-term feeding options include percutaneous gastrostomy (PEG) tubes and percutaneous jejunostomy (PEJ) tubes. Although use of a PEG tube does not prevent aspiration pneumonia in acute stroke (143,144), there is a reduction in the number of aspiration cases when compared to continued oral feeding (145). Aspiration and pneumonia from PEG tubes can be minimized through measures such as head elevation, good hygiene with bag and line handling, continuous drip feeding (as opposed to bolus feeding), and consistent monitoring for gastric residue (146). PEJ tubes are indicated for individuals with chronic aspiration of tube feedings or impaired gastric motility (147). PEG tubes can provide uninterrupted feeding, which is not possible with NG feeding, resulting in improved nutrition (148). Many

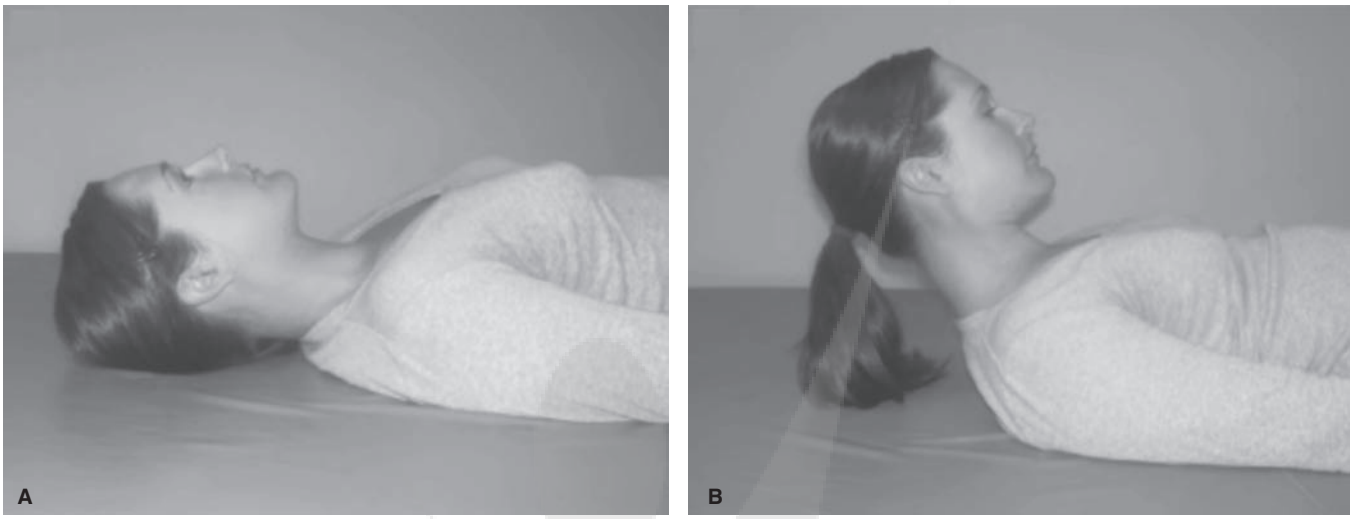


FIGURE 14.7 Shaker exercises. (A) The patient is instructed to lie flat on his or her back on the floor or bed. (B) Patient holds the head off the floor or bed, looking at his or her feet, for 1 minute without raising the shoulders from the floor or bed. The second part of the exercise involves the same movement (without sustaining the head lift) for 30 repetitions.

individuals who return to oral nutrition after stroke benefit from PEG use to allow exercise and therapeutic oral feeding to continue (149). As with any surgery, infection is a risk with insertion and use of PEG or PEJ tubes.

Surgical and Pharmacological Management

Surgical options for dysphagia are rarely used in the United States. One exception to this is dilatation of the esophagus or UES, which is performed in the case of stricture, web, or stenosis. Cricopharyngeal myotomy is a surgical procedure that disrupts the cricopharyngeus muscle to reduce UES pressure and improve bolus flow from the pharynx to the esophagus. Laryngeal diversion procedures are performed in cases of severe intractable aspiration caused by dysphagia (150,151). The larynx is separated from the upper airway, and a permanent tracheostomy is performed (152). Although laryngeal diversion eliminates aspiration, significant consequences include loss or reduction of upper airway functions like phonation, cough, or smell as well as potential for persistent pharyngeal dysphagia.

There are no specific pharmacological treatments for oral or pharyngeal dysphagia, but some symptoms may be managed with medication. Anticholinergic medications can reduce salivary flow in individuals with sialorrhea and chronic aspiration of oral secretions (153). Botulinum toxin injections have been used in cases of oromandibular or lingual dystonia, trismus, cricopharyngeal dysfunction, and sialorrhea. Botulinum toxin injections carry some risk of exacerbating dysphagia.

Additional Considerations

Oral care is an often overlooked, but critical, concept in dysphagia management. Proper oral care (including tooth

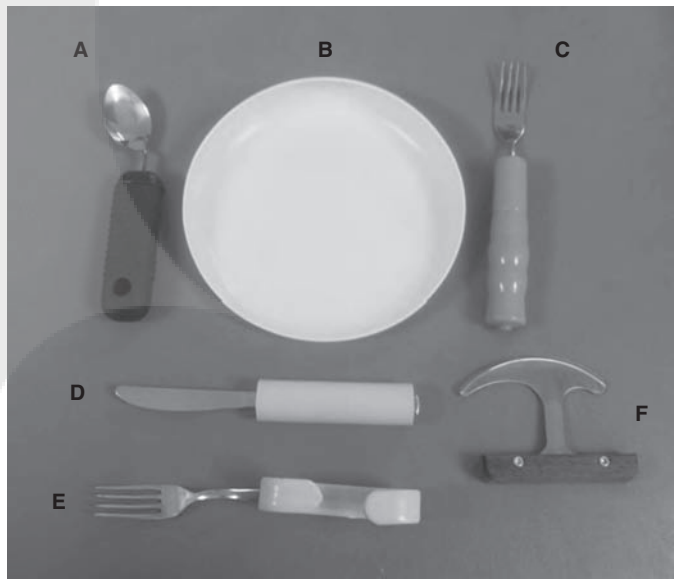


FIGURE 14.8 Assistive devices used for feeding. (A) Wide grip, weighted utensils. These utensils have soft-ribbed handles and bendable shafts. They are weighted to help keep hands steady. The extra handle weight provides help for individuals with limited hand control. The shaft can be bent for either right- or left-handed use. (B) Tapered front scoop dish. Nonskid feet keep the plate from sliding. Curved edge simplifies scooping food. Specially suited for individuals who have limited flexibility, motor coordination, or feed using one hand (e.g., one who had a hemiparetic stroke). (C) Universal grip aid. These aids can be used with conventional flatware, and provide better grip by increasing friction and handle size. (D) Foam grip aid. Increases handle size, providing a large, more comfortable grip and better control of the utensil. (E) Universal feeding cuff. For individuals with little to no grip. Securely attaches the utensil to the hand for feeding. (F) Rocking "T" knife. For individuals with a weak grasp. Cuts food with a rocking motion. Wooden handle fits the hand and safety edge reduces risk of injury.

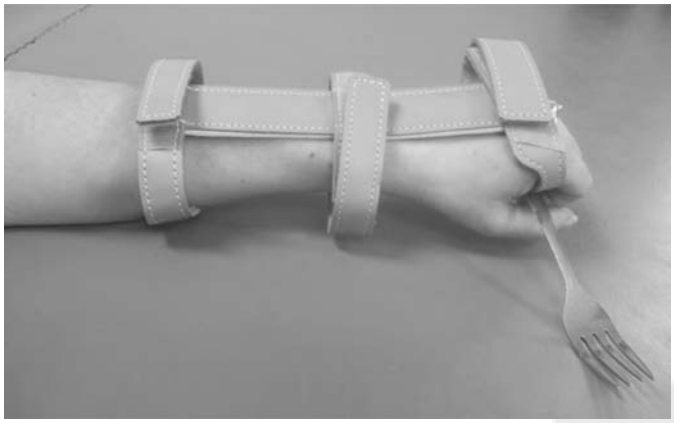


FIGURE 14.9 Wrist support with universal cuff. Allows self-feeding for individuals with weak grip and weak wrist or wrist drop.

brushing, flossing, and rinsing) before and after meals reduces the bacterial load in the mouth, thereby reducing the risk of developing aspiration pneumonia (19). Proper positioning is important in dysphagia management (154). Individuals should be seated upright during and after meals to maximize effectiveness of rehabilitation techniques and reduce the risk of gastroesophageal reflux with subsequent aspiration. Adaptive equipment is used by individuals with motor disabilities in order to improve self-feeding. Some examples of adaptive equipment are shown in Figures 14.8 and 14.9.

CONCLUSION

Although dysphagia after stroke has been associated with increased incidence of complications, morbidity, and mortality, early identification of feeding difficulties can affect long-term outcomes and improve quality of life. Early assessment and treatment are vital to preventing complications during the acute phase and allow normal recovery of the swallowing function. For those individuals whose swallowing function does not recover spontaneously, sophisticated therapeutic options that can be tailored to address individual needs are available. Current research in the field is focusing on standardization of screening, bedside, and instrumental assessments and identification of new therapeutic interventions that are tailored to the specific brain-based deficits.

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15

Right Hemispheric Neurobehavioral Syndromes

Joanne A. Byars and Kenneth M. Heilman

RIGHT HEMISPHERIC NEUROBEHAVIORAL SYNDROMES

This chapter provides an overview of some of the major neurobehavioral syndromes associated with right hemisphere strokes. The most common and disabling disorders associated with isolated right hemisphere injury fall into three principal domains: the neglect syndrome; emotional disorders, including disorders of emotional communication and emotional experience; and visuospatial disorders. We review the most common components of these major right hemisphere neurobehavioral syndromes. We omit some of the less common neurobehavioral disorders that can arise from right hemisphere disease—including some forms of amusia, identity disorders such as prosopagnosia, delusional misidentifications such as Capgras and reduplicative para-amnesia, disorders of automatic speech, and auditory agnosia for familiar voices. Patients with right hemispheric injury can also develop changes in mood and affect, such as inappropriate jocularity, emotional flattening, euphoria, and depression. Chapter 31 reviews these mood disturbances, so we do not discuss them here.

NEGLECT AND RELATED DISORDERS

Definitions

Neglect consists of the failure to report, respond, or orient to meaningful or novel stimuli presented in a portion of space, in spite of adequate elementary motor and sensory function (1).

Neglect, a common and severely disabling neurobehavioral disorder, most commonly arises from discrete lesions of the right hemisphere, such as cerebral infarctions and hemorrhages. However, tumors, trauma, and degenerative diseases involving the right hemisphere may also cause neglect. Of all the behavioral disorders caused by focal hemispheric brain damage, neglect (diagnosed at the time of an acute injury) carries the poorest prognosis for independent living, even worse than the prognosis for global aphasia.

Neglect syndromes may present a variety of clinical features. Table 15.1 characterizes the different dimensions that may distinguish various types of neglect and the modes by which they manifest involvement.

We discuss next the signs and symptoms associated with the different forms of this disorder, the means by which clinicians can test for neglect and related disorders, and the management and treatment of these disorders. We also briefly review the pathophysiology of neglect.

Clinical Syndromes, Signs, and Testing

Sensory Inattention

Unawareness. Selective unawareness constitutes the most profound form of sensory inattention. Sensory inattention is often classified by its modality (tactile, visual, or auditory) and its distribution (hemispatial or personal). Ipsilesional attentional bias and inability to disengage from stimuli in ipsilesional space may accompany contralesional sensory inattention.

To clinically test for inattention, the examiner presents the patient with stimuli (visual, tactile, and auditory) or no stimuli, alternating to either the ipsilesional or contralesional sides of the body in random order. With each presentation of a stimulus or nonstimulus, the examiner says, "Now!" Attention allows a person to determine whether something is present or not present; thus, patients may make errors by failing to recognize the absence of stimuli, as well as failing to recognize stimuli that do occur. The patient then tells the examiner if the stimulus occurred on the right, left, or not at all. If the patient makes more errors on one than the other side (e.g., more contralesional than ipsilesional errors), it constitutes evidence of unilateral sensory inattention.

When a patient consistently fails to detect contralesional stimuli, the question arises whether he or she may have a primary sensory defect rather than inattention, as these two disorders may initially resemble each other. However, several maneuvers may help dissociate inattention from a primary sensory defect caused by deafferentation. In the tactile modality, sometimes moving the patient's left hand from contralesional to ipsilesional hemispace may allow the person to detect tactile stimulation applied to the hand. Cold water caloric stimulation can also help differentiate hemianesthesia (such as from thalamic lesions) from inattention: if a patient has left-sided inattention, cold water caloric stimulation of the left ear will allow

TABLE 15.1 Forms of Neglect

		MODES OF INVOLVEMENT					
DIMENSIONS OF NEGLECT	Input/output	Afferent: attentional (sensory) neglect			Efferent: intentional (motor) neglect		
	Sensorimotor modality	Visual	Auditory	Tactile	Limb movement		Eye gaze
	Domain	Spatial		Personal		Representational	
	Temporal distribution	Occurs with single unilateral stimulus/movement			Only occurs with bilateral simultaneous stimuli/movements		
	Spatial distribution	Frame of reference			Location		
		Viewer-centered	Environment-centered	Object-centered	Horizontal (left vs. right; ipsilesional vs. contralesional)	Vertical (up vs. down)	Radial (proximal vs. distal)

this person to feel the tactile stimulus, but it will not help overcome a true sensory loss (2). In the visual modality, inattention may be viewer-centered hemispatial, whereas a true hemianopia is hemiretinal (Figure 15.1). Thus, the patients with visual inattention who cannot detect visual stimuli (for example, the examiner's moving fingers) in contralesional hemispace might detect these stimuli if their eyes are deviated to the ipsilesional side (such that the contralesional retinal field now falls in the ipsilesional hemispace) (3). If a patient has a true hemianopia, the defect will be retinotopic, and they will remain unable to see stimuli presented to the contralesional visual field even when their eyes deviate to the ipsilesional hemispace. Hemispheric lesions do not cause contralesional hemispatial deafness, so if a patient fails to detect auditory stimuli (e.g., snapping fingers or speech) presented on one side of space, he or she has inattention. Even a premorbid unilateral hearing loss could not account for this hemispatial unawareness. Psychophysiologic techniques such as evoked potentials also may help demonstrate that a defect is inattention rather than deafferentation, and structural imaging may clarify whether or not the lesion injures afferent pathways.

Sensory Extinction to Simultaneous Stimulation (Extinction). Many patients who initially experience unawareness of stimuli may recover and regain the ability to detect isolated stimuli, but when receiving bilateral simultaneous stimulation, they fail to detect the contralesional stimulus—a phenomenon known as *extinction* (1). Many patients never demonstrate inattention to unilateral stimuli, but they still might demonstrate sensory extinction. Extinction may occur in visual, tactile, and auditory modalities. Extinction most often involves a failure to appreciate a contralesional stimulus when both sides of the body receive simultaneous stimulation; however, when two stimuli are given on one side of the body, extinction may also cause the stimulus closest to the contralesional position to go undetected (Figure 15.2) (4).

Action-Intentional (Motor) Neglect

Motor Neglect. Motor neglect—or action-intentional neglect—can occur in several forms, distinguished by the means of testing and the behavior demonstrated by the patient.

Motor neglect, or limb akinesia, can resemble a hemiplegia, but brain imaging and transcranial magnetic stimulation will reveal an intact corticospinal motor system (5). Unlike patients with true hemiplegia, who will attempt to move their weak limbs, these patients often do not appear to be attempting to move. Some patients have hemispatial akinesia, in which they experience contralesional limb akinesia only when the limb is on the contralesional side of the body, but they can use the limb when it is brought over to the ipsilesional side. Other patients have difficulty moving their heads, eyes, or even arms in a contralesional direction, a disorder known as *directional akinesia*. Some patients can move their eyes, heads, or arms in both directions, but at rest they deviate their eyes, arms, or heads to the ipsilesional side. These findings constitute intentional directional bias. The term "gaze palsy"—sometimes used to describe the ocular manifestation of this bias—represents a misnomer, as these patients do not have paralysis or weakness. This gaze preference may be related to inattention of one side of space, a directional akinesia of eye movements, or both.

Hypokinesia is a milder form of intentional neglect in which patients can move their limbs, head, and eyes, but experience a delay in initiating these movements (1). Measuring reaction times effectively tests for hypokinesia. Hypokinesia can occur in specific limbs (limb hypokinesia), in a specific hemispace (hemispatial akinesia), and in a specific direction (directional hypokinesia). Directional akinesia and hemispatial hypokinesia can be observed during eye and head movements.

Motor impersistence is the inability to sustain a movement or posture (1). When testing for motor impersistence, the examiner asks the patient to maintain a posture for a given period of time. Motor impersistence, like hypokinesia, may involve the limbs, eyes, or head, and can occur in a particular hemispace or direction.

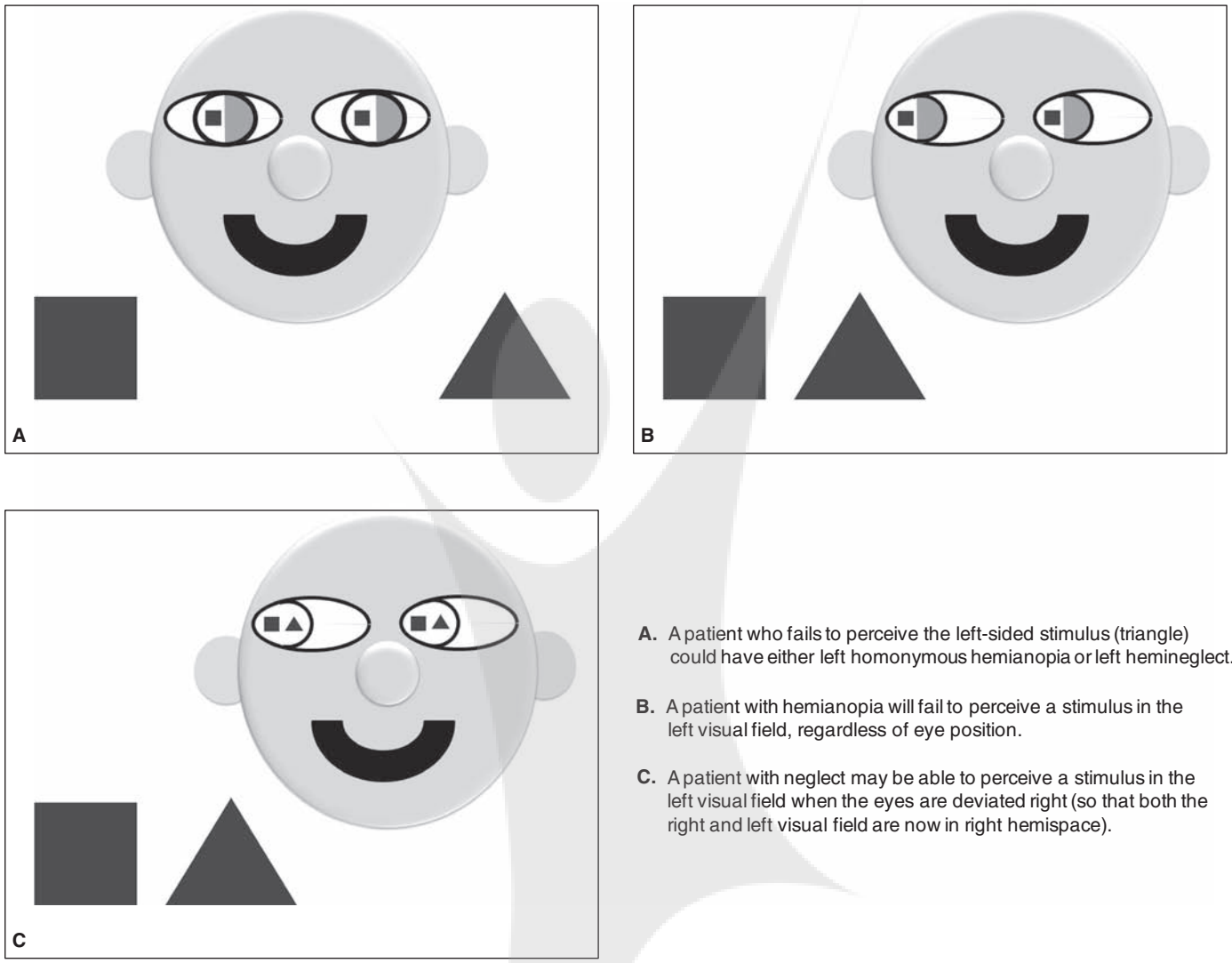


FIGURE 15.1 Hemianopia versus hemineglect.

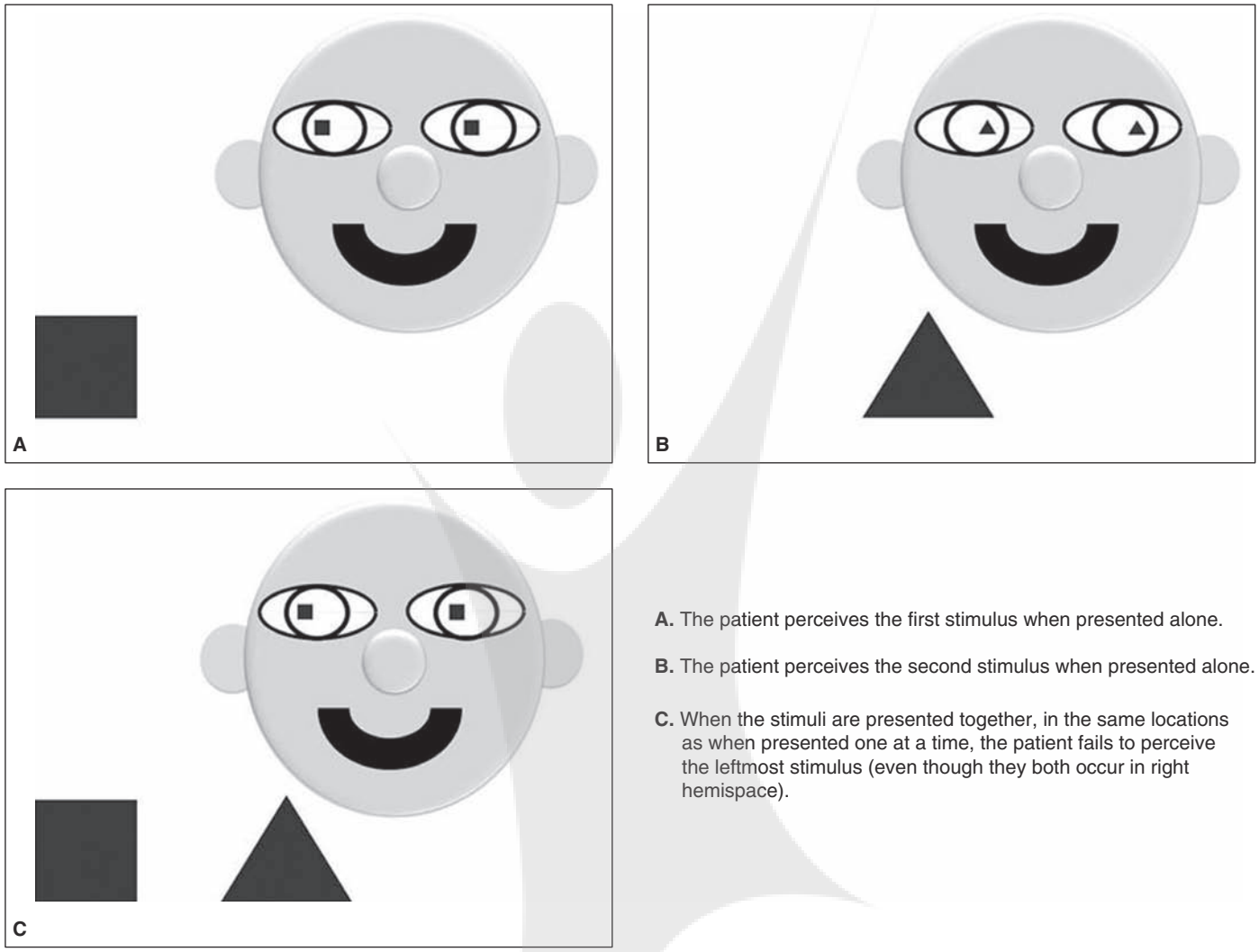
Hypometria is when a patient makes abnormally small movements with the limbs, eyes, or head (1). Premature discontinuation of movement owing to impersistence can reduce movement amplitude and thus give rise to hypometria. However, other factors such as perceptual disorders, inattention, and abnormal spatial representations can also induce hypometria.

Motor Extinction. Some patients who can move the contralesional limb alone have difficulty initiating movement of this limb simultaneously with the ipsilesional limb, a phenomenon known as *motor extinction* (1). To test for motor extinction, the examiner first establishes whether the patient can move each forelimb independently. Then the patient closes his or her eyes and puts his or her hands on his or her lap; the examiner randomly touches the right, left, or both hands, asking the patient to lift the stimulated hand. To distinguish sensory extinction from motor extinction, the examiner should also test for sensory extinction by asking the patient to tell the examiner which hand(s) the examiner touched. Patients with motor extinction will detect the bilateral stimulation but move only one hand.

Some patients may have hypokinetic extinction. Unlike those with akinetic motor extinction, these patients do move both hands when touched bilaterally but have a delay in initiating movement of their contralesional hand, which causes this hand to move slower than the ipsilesional hand and slower than when moving the contralesional hand alone.

Spatial Neglect

Contralesional Spatial Neglect. Spatial neglect, which is a failure to be aware of or interact with stimuli in a portion of space, can occur in all three dimensions of space: horizontal (right/left), vertical (up/down), and radial (near/far), as well as in combinations of these dimensions (1). Spatial neglect can also take place in near (peripersonal) or far (extrapersonal) space or both (1). Therefore, tests for spatial neglect should assess all these dimensions. However, in this discussion, we focus



A. The patient perceives the first stimulus when presented alone.

B. The patient perceives the second stimulus when presented alone.

C. When the stimuli are presented together, in the same locations as when presented one at a time, the patient fails to perceive the leftmost stimulus (even though they both occur in right hemispace).

FIGURE 15.2 Extinction with two unilateral simultaneous stimuli.

primarily on horizontal spatial neglect. Three bedside tests can screen patients for spatial neglect: line bisection, target cancellation, and drawing. Each of these tests, in part, assesses a different aspect of spatial neglect; therefore, though some patients may show impairment on all these tests, others may show impairment on only one or two of these tests.

In the line bisection task, the examiner presents the patient with a line and asks him or her to mark the midpoint of the line. Longer lines have a greater sensitivity for the detection of neglect than do shorter lines. Typically, when patients with contralesional spatial neglect attempt to bisect long lines, they deviate their bisection mark toward the injured hemisphere. However, with very short lines, patients may err by placing their mark on the portion of the line in contralesional hemispace, a phenomenon called the *crossover effect*. Placing the entire line in the portion of space on the side opposite the injured hemisphere (rather than in ipsilateral hemispace) increases the likelihood of detecting neglect.

In the cancellation test, a sheet of paper with many targets (such as randomly placed, small, line segments) is placed before the patient, and the patient is asked to mark out all the targets. Patients with neglect will often fail to cancel targets positioned in the contralesional hemispace. Increasing the number of targets, asking the patient to selectively cancel target stimuli intermixed with foils, and using foils similar to the targets (for example, target Ts in a background of Ls) can all improve the sensitivity of the task.

In addition to occurring in the three dimensions of space, spatial neglect can take place within three different reference frames: viewer-centered, object-centered, and environment-centered. To distinguish between viewer-centered and object-centered neglect, the examiner can ask the patient to copy some simple objects, such as a house with tree on one side and a bush on the other side. If a patient with neglect fails to draw the object on the contralesional side of the paper, the patient most likely has viewer-centered neglect. However, if the patient attempts to draw all three objects but only draws one side of these objects, then the patient has object-centered neglect (Figure 15.3). Asking patients to perform line bisection tasks while upright

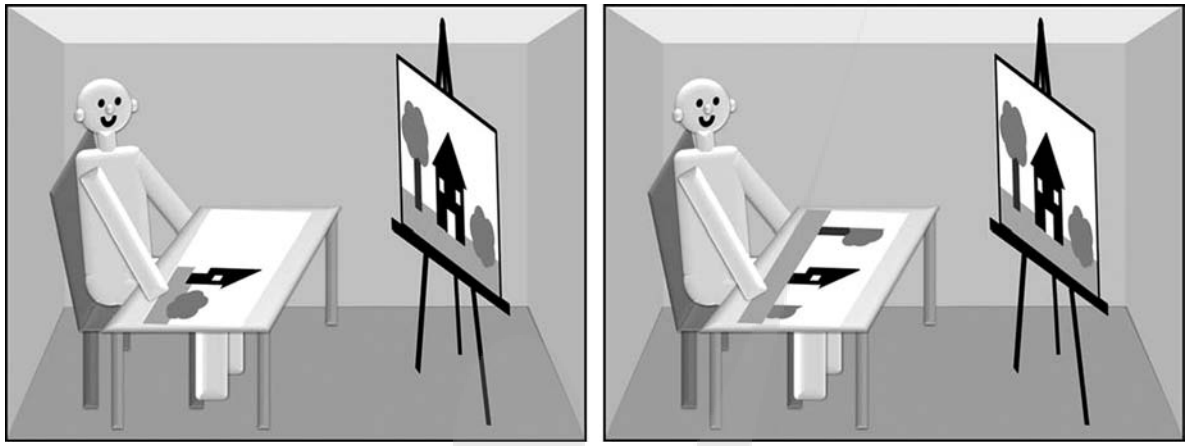


FIGURE 15.3 Horizontal neglect: viewer-centered (A) versus object-centered (B).

and lying flat on their side can evaluate for environment-centered neglect; all lines remain horizontal with respect to the environment, regardless of the patients' position (such that the lines are parallel to the patient's vertical body axis at times and parallel to the patient's horizontal body axis at others). If a patient deviates in the same direction on line bisection when lying down and sitting up and performs accurately on radial line bisection, then that individual has environment-centered neglect (Figure 15.4).

In addition to demonstrating contralesional spatial neglect with the line bisection, cancellation, and drawing tasks, patients with neglect might also show impairment when reading and writing, failing to read or write a part of a sentence or a part of a word.

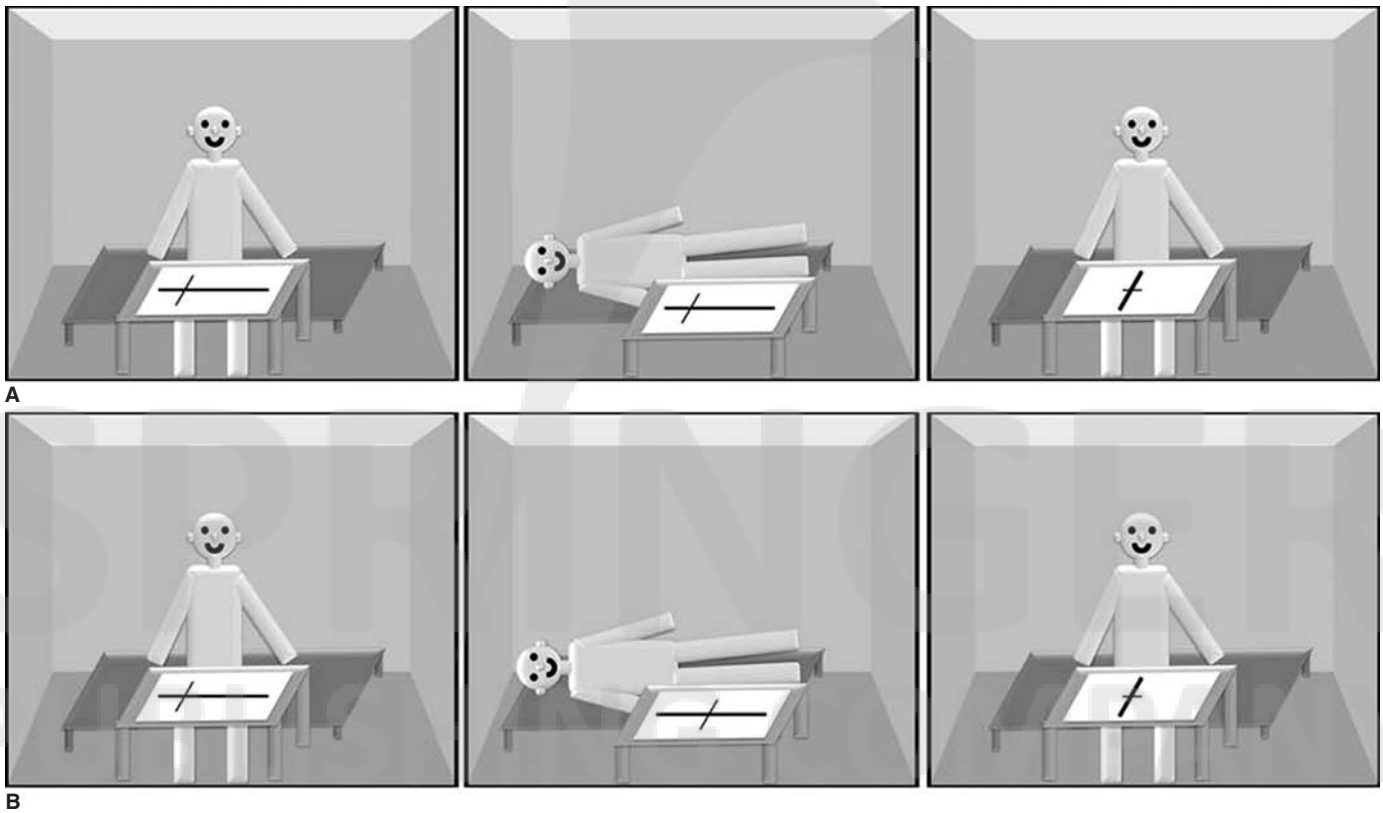


FIGURE 15.4 Horizontal neglect: environment-centered (A) versus viewer-centered (B).

Ipsilesional Neglect. When performing a task such as line bisection, patients with neglect will mostly exhibit contralesional neglect, deviating to the side of hemispheric injury (6). Some patients, however, will deviate atypically, in the opposite direction (for instance, deviating to the left following a right hemisphere lesion), a finding called *ipsile-sional neglect*. Unlike the crossover effect mentioned earlier, ipsilesional neglect can occur even when using long lines.

Attentional Versus Intentional Spatial Neglect. Disturbances of attention may account for the failure of many patients with neglect to correctly perform tasks such as line bisection or cancellation. This attentional disturbance might alter performance on these tasks by several means. Normally, awareness depends on attention: when we are inattentive to something, either that item does not reach our awareness, or we do not maintain awareness of it. If we are not aware of an item or part of an item, we do not interact with it. Patients with spatial neglect might be unaware of a segment of a line (generally the left side) and only bisect the portion of which they are aware, thus deviating to one side. Similarly, they might be unaware of cancellation targets on one side of a paper and thus fail to cancel these targets.

People can vary the degree of attention they allocate to an object or part of an object, and objects or parts of objects that receive more attention appear to have a greater magnitude than those that receive less. For example, we pay more attention when we first drive down a new road than when we return, which causes the road to appear longer when going than when returning. Thus, when patients with spatial neglect view a line, the segment of the line to which they are inattentive (typically, the contralesional side) might appear shorter than its actual size, and the segment to which they strongly attend will appear longer. This attentional asymmetry induces a misperception, and patients deviate their attempted bisection toward the segment that appears longer. To determine the size of a line or to find all the targets, a person has to be able to move his or her attention. If a person has a strong attentional bias toward an object or a part of space, he or she might have difficulty disengaging his or her attention and moving attention to other parts of space. Patients with neglect often have problems disengaging their attention from a portion of space (usually, ipsilesional space) and thus neglect the opposite portion of space (usually, contralesional space).

In addition to correctly allocating attention, to correctly bisect a line, cancel targets, or copy a picture, individuals must move their eyes and arms to different parts of space. Some patients, as mentioned earlier, might have types of motor neglect where they fail to explore with their eyes or move their arms into a part of space (e.g., the contralesional left space).

To dissociate attentional from intentional hemispatial neglect, the clinician can use a variety of techniques, including video cameras with an image reversal system and a monitor, strings and pulleys, and mirrors. All of these techniques can dissociate the direction of action (e.g., leftward) from the direction of sensory feedback (e.g., rightward). If reversed feedback causes a patient to change the side of his or her bias—for example, from a right-sided bias on the line bisection in the direct condition to a leftward bias on the reversed feedback condition—then this patient has primarily an attentional neglect. However, if the bias does not change in the reverse condition, the patient has a primarily intentional spatial neglect.

Asomatognosia and Personal Neglect

Patients with personal neglect may fail to groom or even dress one side of their bodies. Patients with asomatognosia do not recognize that parts of their body belong to them (7). To test for asomatognosia, the examiner can take a portion of the body contralateral to the hemispheric injury and bring it into ipsilateral hemispace and visual field. To make certain that the patient sees this part of his or her body, the examiner can write a number on it. The examiner then asks the patient to read the number on this body part. If the patient can recognize this number, the examiner can then ask the patient who this body part belongs to. If the patient denies that this body part belongs to him or her, the patient has asomatognosia. To test for personal neglect more formally, the examiner can perform a type of cancellation task where the examiner puts little pieces of sticky paper on different portions of the patient's body and asks the patient to remove all the pieces of paper. The examiner can also perform a type of line bisection task, placing a large horizontal line before the patient and asking the patient to point to the position on the line directly across from the middle of his or her chest, right shoulder, and left shoulder. Patients with personal neglect will often shift their midline and contralesional shoulder to the ipsilesional side. Patients with asomatognosia and personal neglect might also have lost or degraded their mental representations of their own bodies. Some of these patients will also demonstrate allesthesia and allokinesia. When touched on the contralesional side of their body, patients with allesthesia claim that they were touched on the ipsilesional side. When asked to move the contralesional side of their body, patients with allokinesia move the ipsilesional side.

Representational/Imagery Neglect

Representational or imagery neglect causes patients to neglect one side of their mental picture of a place or object (8). Imagery neglect may be spatial or personal. When patients with retrograde imagery neglect are asked to recall details of a scene with which they were familiar before the onset of their illness, they might only report those details that are ipsilateral to their lesion. This disorder can also be anterograde: for instance, a patient with a stroke may view a scene in which he or she can recognize all the objects; but when attempting to recall the scene after an interval, he or she may only report those parts of the scene ipsilateral to the hemispheric injury. Patients may also fail at performing a

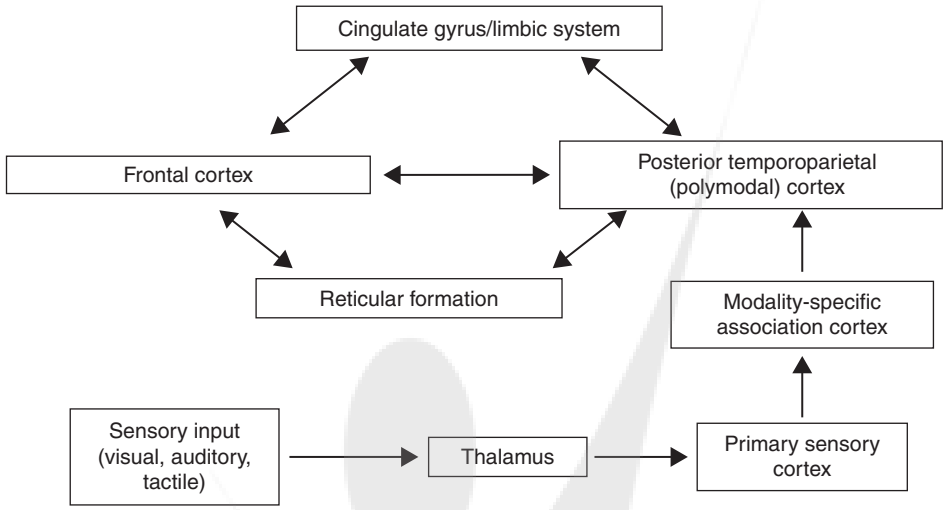


FIGURE 15.5 Simplified schematic diagram of attentional systems. Lesions interrupting these networks can produce attentional neglect.

task where they are required to imagine a contralesional part of their body (4).

Anosognosia and Anosodiaphoria

Patients with neglect can be unaware of their illness and disability (7). For example, many patients with neglect also have weakness of their contralesional arm. However, when asked about weakness, such patients may explicitly deny their hemiparesis. They might also deny sensory loss or hemianopia. Anosognosia most often presents during the acute phase of illness. After being repeatedly told that they have a disability, most patients with anosognosia will usually acknowledge their illness, but they may exhibit anosodiaphoria, appearing unconcerned or even joking about their disabilities.

Pathophysiology of Neglect

Attention

In 1949, Morrizzi and Magoun established the critical role of the reticular activating system (RAS) in mediating arousal (9). When an organism encounters a novel or significant stimulus, it becomes behaviorally and electrophysiologically aroused. An organism that cannot become aroused cannot normally attend. Therefore, arousal constitutes a critical element in the systems that mediate attention. The mesencephalic reticular formation and portions of the thalamus mediate arousal, and unilateral injury to either of these structures can produce neglect.

Attention must also be selective, and Sokolov posited that the cortex selects which stimuli to attend to (10). The human brain can only process a limited number of stimuli, and sensory input into the brain often exceeds its processing capacity. To decide where and what to attend to, the regions of the brain that make these computations must get information about long-term goals, emotions, and needs. Because each parietal lobe is a convergence area that receives input from the lateral frontal lobe (which subserves long-term, prospective, goal-oriented behavior) and the medial frontal lobe/cingulate gyrus (a region highly interconnected with other portions of the limbic system important in mediating behaviors induced by biological needs and emotions), as well as information from sensory processing systems that indicate the type of stimulus (what) and its spatial position (where), the temporoparietal cortex can compute where and to what stimuli a person's attention should be directed (1).

In humans, attentional neglect most commonly follows right hemisphere lesions that involve the posterior superior temporal lobe and the adjacent inferior parietal lobe (1). This temporoparietal region receives afferent (input) information from the cortical visual, auditory, and tactile association areas and sends projections to the RAS. However, lesions in other areas, such as the lateral frontal lobe and the medial frontal lobe, may also induce neglect in humans, presumably owing to disruption of critical attentional networks (1). Figure 15.5 illustrates the neural networks involved in attention.

Imagery

The posterior superior temporal and inferior parietal cortices share strong reciprocal relations with the hippocampus. Damasio posited that the hippocampus participates in retroactivation of sensory association areas (11). Therefore, lesions of the posterior temporal–inferior parietal region might interfere with retroactivation and induce the imagery and representational defects described by Bisiach and Luzzatti (12).

Action-Intention

As mentioned earlier, *attention* is the process by which the brain triages incoming stimuli according to its importance to a person's long-term goals as well as his or her immediate needs and drives. In addition to the limited input processing capacity, the brain also has a limited ability to prepare and control motor actions directed to the environment. "Selective intention" denotes the process by which the brain triages environmentally directed actions. A complete failure of this action-intentional system induces a total inability to initiate movements, termed *akinesia*. Milder defects in the action-intentional systems may induce hypokinesia (delay in implementing an action), abulia (reduced number of self-initiated actions), or motor impersistence (failure to continue action until successful completion of a task). All these action-intentional deficits can involve different body parts and can be directional or hemispatial.

Deciding whether to act and where to act requires knowledge of long-term goals (mediated by the prefrontal lobes), knowledge of drives, needs, and emotions (mediated by the limbic system), and cognitive knowledge of how to act (mediated by temporoparietal regions). Just as the RAS regulates the cortical arousal required for attentional processing, the basal ganglia–dopaminergic system plays a parallel role in the action-intentional system (Figure 15.5). Thus, unilateral injury to the frontal lobe–basal ganglia system or dopaminergic system will produce forms of unilateral or asymmetrical action-intentional neglect. The basal ganglia receive glutaminergic (excitatory) projections from the premotor cortices of the lateral and medial frontal lobes, so damage to any of these regions can also induce action-intentional neglect (1). Figure 15.6 illustrates the neural networks involved in action-intention.

Although both sensory-attentional and action-intentional neglect can develop from damage to either the temporal–parietal or frontal lobes (both lateral and medial), in general, injury to the frontal lobes typically induces primarily action-intentional neglect and injury to the parietal lobes induces sensory-attentional neglect (1). However, for a person to successfully interact with the environment, the intentional and attentional systems must interact, a process facilitated by strong connections between the frontal and parietal lobes.

Right–Left Asymmetries of Attentional and Intentional Neglect

Although either right or left hemisphere lesions may produce neglect, in humans neglect is more common and severe with right than left hemisphere lesions. These asymmetries of neglect appear to arise from asymmetrical attentional and intentional representations of the body and space. Electrophysiological and functional imaging studies suggest that, whereas the left hemisphere attends primarily to the right side or in a rightward direction, the right hemisphere can attend to both sides or in both directions (13). Similarly, whereas the left hemisphere can prepare for right-sided or rightward actions, the right hemisphere can help prepare for actions on both sides or in both directions.

Treatment of Neglect

Treatment of Underlying Diseases

Although ischemic and hemorrhagic stroke represent the most common causes of neglect, any disease that injures

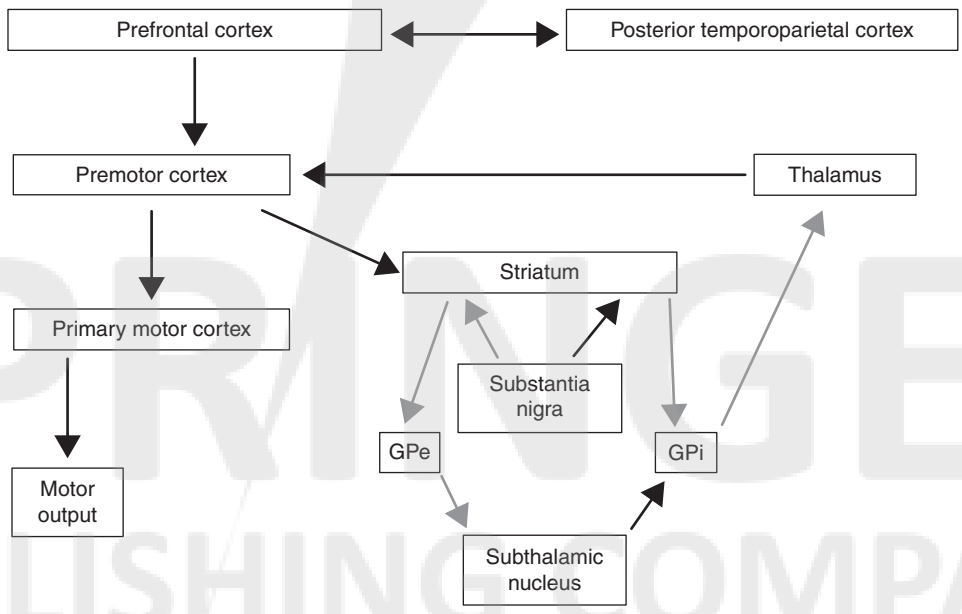


FIGURE 15.6 Simplified schematic diagram of intentional systems. Lesions interrupting these networks can produce neglect. Lesions interrupting these networks can produce intentional neglect. Black arrows: excitatory; gray arrows: inhibitory.

Abbreviations: GPe, globus pallidus externa; GPi, globus pallidus interna.

or destroys networks important in mediating attention and intention can also induce neglect. Therefore, clinicians always need to evaluate patients to learn the cause of the neglect, so that when possible, they can treat the underlying disease and attempt to prevent additional brain injury.

Pharmacologic Treatments

Experiments in animals demonstrated that unilaterally damaging the dopaminergic system by injury (such as by MPTP) or interruption (such as by hydroxydopamine) can produce neglect (14,15); based on these findings, some investigators have examined whether increasing dopaminergic tone may treat neglect. In the largest study of dopamine therapy for neglect to date, a 16-patient double-blind randomized placebo-controlled trial, the dopamine agonist rotigotine appeared to improve neglect on neuropsychological tests (16). However, case reports have described patients treated with dopaminergic agents whose neglect did not improve, or even worsened, with this treatment (17).

One open-label study of the cholinesterase inhibitor rivastigmine (given at a relatively low dose over a short period of time) suggested that this drug may potentially accelerate improvement from neglect, without necessarily affecting the final outcome, as a nontreated group showed similar—though slower—improvement (18). However, these benefits only manifested on neuropsychological tests for neglect, not in activities of daily living (ADLs).

Based on the evidence thus far, we recommend that clinicians considering the use of medications for neglect carefully assess their patients before and after the initiation of treatment to ensure that they really improve. In addition, because many patients spontaneously improve with time, clinicians should perform periodic medication withdrawal with before-and-after testing to make sure that the medication, in fact, caused the improvement.

Neurostimulation

Therapies such as repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS) can activate or inhibit cortical electrical activity; these effects may potentially persist beyond the duration of the stimulus by influencing brain plasticity (19). Recently, investigators have examined whether these therapies could help ameliorate neglect, possibly by reducing the ipsilesional attentional bias.

A double-blind placebo-controlled randomized trial found that rTMS improved both performance on neuropsychological tests for neglect and ADLs; these improvements persisted at least three weeks after finishing the rTMS treatment (20). Although no studies have examined long-term effects of tDCS, double-blind placebo-controlled randomized trials of tDCS indicate that it can reduce neglect on neuropsychological tests administered immediately after treatment (21–23). Further studies may help clarify the optimal role of neurostimulation therapies in neglect rehabilitation.

Behavioral Treatments

"Bottom–Up" Interventions. As many patients with neglect have anosognosia for their deficits, many investigators have tried to develop treatments for neglect that can train patients to automatically attend to contralesional hemispace without having to consciously remember to do so each time; these treatments constitute the "bottom–up" approach, as opposed to "top–down" strategies focusing on conscious efforts (24). These "bottom–up" interventions include prism adaptation, optokinetic stimulation, cold caloric vestibular stimulation, neck stimulation, and monocular eye patching (24)

In prism interventions, patients with left-sided neglect receive training in interacting with environmental stimuli while wearing Fresnel prism lenses that shift the environment to the right. Thus, when patients point to objects they see, they initially overshoot and point to the right of the true location; however, with feedback, they learn to shift their interactions toward their left to reach the target. After removing the prisms, patients experience an aftereffect in which they continue to overcompensate to the left. Although the exact mechanisms by which prisms may treat neglect remain incompletely understood, the leftward bias they produce may contribute to the long-term potentiation of the network directing attention and action-intention to contralesional space (25).

Two randomized controlled trials of prisms have shown that prism interventions can improve neglect not only on neuropsychological tests but also in ADLs, with benefit persisting up to three months after concluding treatment (26,27). In addition, other uncontrolled studies of patients with neglect found similar sustained improvements, lasting up to two years following prism interventions (28–31). One randomized controlled trial of prisms found no improvements, but the prism glasses used only shifted the environment by 6 degrees, whereas the studies that showed improvement used stronger prisms that shifted the visual perception of the environment by 10 degrees or more (25,32). Taken together, the evidence suggests that prisms can be an effective intervention for neglect, with gains sustained well past the conclusion of treatment; however, a dose effect may exist, requiring an adequate number of prism intervention sessions (10–20 sessions) with adequate prism strength (10 degrees) to optimize benefits (25).

Optokinetic stimulation (tracking images moving to the left) and cold caloric stimulation (cold water injected in the left ear) induce a smooth pursuit eye movement to the left (33,34). When healthy individuals attend to and watch an object moving to the left, they make leftward pursuit movements with their eyes, suggesting that perhaps these movements upregulate the systems involved in allocating attention to the contralesional hemispace (33,34). In controlled trials, optokinetic stimulation reduced both auditory and visual neglect on neuropsychological testing, with benefits lasting up to two months after the intervention (33,35–37). A controlled trial of contralesional cold caloric stimulation found that it improved neglect on neuropsychological testing as well as postural control, with effects lasting for at least one hour following treatment, a much longer benefit than the few

seconds described in prior reports (34,38). Cold calorics may reduce attentional neglect more than intentional neglect (39). Vibrating or electrically stimulating the left neck muscles or the left hand can also improve neglect on neuropsychological tests, with benefits lasting for one week in the case of electrical stimulation of the neck (37,40,41). One study found that a vestibular rehabilitation program consisting of specific head movements improved neuropsychological measures of neglect, balance, and ADLs during the period in which patients participated in the intervention (42).

Monocular eye patching derives from the work of Sprague, who produced neglect (asymmetrical exploration and orienting) in animals by ablating a posterior portion of the neocortex, then subsequently reduced this orienting asymmetry by ablating the superior colliculus on the opposite side of the animals' brains (43). In mammals, the retina (both temporal and nasal) in each eye projects more strongly to the contralateral than ipsilateral colliculus. Posner and Rafal suggested that decreasing the visual input into the colliculus of the nonlesioned hemisphere could reduce unilateral spatial neglect (44). Patching the eye ipsilateral to the lesioned hemisphere might reduce the activation of the contralateral colliculus, and this decrease in activation may achieve effects similar to collicular ablasion; the colliculus might influence posterior neocortical activation, and a reduction of cortical activation of the intact hemisphere might potentially reduce the ipsilesional attentional bias. One study did demonstrate a reduction of left-sided neglect with a right eye patch (45); however, Barrett et al. reported a patient with left-sided neglect whose problem worsened with patching the right eye, for unknown reasons (46).

"Top–Down" Training. Operant training techniques can help train patients with neglect to use self-cueing (e.g., "look left") to explore and scan contralesional hemispace (47). One randomized controlled trial found that visual scanning training improved neglect on neuropsychological tests and improved ADLs, with benefits still present, albeit diminished, three months after concluding the intervention (48). Another randomized controlled trial of strategy training found that performance on an untrained task also improved immediately after the intervention (49). However, other studies have found that training often fails to generalize to other tasks, including ADLs and instrumental activities (50–52). Many patients with neglect also have anosognosia for their deficits and may not remember to consciously deploy these training strategies, which may limit the usefulness of these techniques (53).

Salience and Arousal. Although neglect represents an involuntary phenomenon, measures that increase the salience of the neglected space may improve the performance of individuals with neglect. A randomized controlled trial found that rewarding neglect patients for detecting targets improved performance both overall and on targets in the neglected hemispace, compared to when no rewards were given (54). However, two out of the ten patients studied did not show improvement in the reward condition; lesion analysis revealed that, unlike the eight patients whose performance improved, these individuals had strokes involving the right striatum (54). These results suggest that a dopamine-mediated effect on attention and salience could potentially contribute to the efficacy of reward on improved performance (54).

Providing spatially inattentive patients with appropriate attentional cues may also encourage them to attend to contralesional hemispace. Novel stimuli command attention, and novel visual, auditory, and tactile cues presented in contralesional hemispace can help patients direct their attention toward the formerly neglected side (55,56). Self-initiated motor cues may also help: when patients with neglect from a right hemisphere lesion use their left hand to perform tests of visuospatial neglect (such as line bisection and cancellation tasks), they show less neglect than when using their right hand (57). Although many patients with neglect have hemiplegia, any attempted movement of the left arm—even movements unrelated to the task under study, or when the arm remains out of view—can improve performance (58).

Some recent studies have examined whether training to improve attention and alertness in general can help improve neglect. Trials of both visual and auditory sustained attention training improved performance on visuospatial tests of neglect, suggesting that optimization of supramodal attentional mechanisms may transiently ameliorate neglect; however, this improvement was not sustained on later retesting (59,60).

Forced Use. Interventions that force patients with neglect to use the neglected side of the body and to interact with neglected hemispace may help lessen the signs of neglect. Multiple studies have shown that poststroke hemiparesis can improve with forced use or constraint-induced therapy, a technique in which the therapist places the less affected hand in a mitt and intensively trains the paretic upper extremity using an array of behaviorally reinforced tasks (61); as patients with neglect may have limb akinesia (limb motor neglect), which resembles hemiparesis, forced use therapy may help them as well. One recent randomized controlled trial found that constraint-induced therapy of the left arm lessened neglect behaviors in ADLs (62).

Patients with neglect often demonstrate a directional akinesia of their eyes, failing to move their eyes in a contralesional direction and failing to explore contralesional visual hemispace. When patients with neglect wear glasses in which an opaque material covers the ipsilesional half of each lens, this may force them to learn to move their eyes in a contralesional direction to see. One randomized controlled trial in patients with neglect compared the effects of occupational therapy done with the right hemifield patched to standard occupational therapy; the patched group did better on neuropsychological tests for neglect when tested shortly after the intervention, but the groups did not differ on ADLs (63).

Environmental modifications that require patients with neglect to attend to the contralesional space may also act as a form of forced-use therapy. One randomized controlled trial found that for patients with neglect who used a wheelchair, placing the wheelchair control joystick on the left led to significantly more accuracy while driving the wheelchair than when the control joystick was placed on the right; putting the joystick on the left may have acted as a spatial cue, forcing patients to attend more to the contralesional side (64).

Optimization of Standard Rehabilitation Therapies

Neglect can substantially interfere with participation in physical therapy and occupational therapy targeting other neurological deficits, such as hemiparesis and difficulty in walking. However, some simple modifications of standard rehabilitation therapies may help patients with neglect participate more fully. In the acute poststroke period, having family members participate in the rehabilitation program with patients with neglect may improve outcomes on both neuropsychological measures and ADLs (65). Patients with neglect from acute stroke generally experience longer hospital stays than those without neglect; however, when patients undergo very early mobilization (beginning within the first 24 hours after stroke), length of stay does not differ between patients with and without neglect (66). It remains unknown at this point, though, whether shortening hospital stays through early mobilization improves the long-term outcome for patients with neglect.

Combinations of Interventions

The various treatments for neglect described earlier may differentially affect the various neural mechanisms believed to underlie the neglect syndrome. Thus, combinations of treatments may potentially offer synergistic benefits (24). However, not all studies combining treatments have found an additive benefit, and in some cases the combination may be less effective than the treatments in isolation, particularly if combining treatments prevents results in an inadequate amount of time with each different intervention (24,62,67).

Management of the Environment and Safety Considerations

The sensory-attentional and action-intentional disorders associated with neglect dramatically reduce a person's capacity to successfully interact with his or her environment. To reduce disability and keep the patient and others safe, patients with these disorders must have their environment altered to reduce the risk of injury and to increase the possibility for successful interaction with environmental stimuli. Patients with even the mildest forms of neglect should not drive vehicles or use machinery with the potential to injure themselves or others.

Neglect more often occurs in reference to the patients' body (egocentric neglect) rather than to the objects in the environment (allocentric neglect). Thus, many patients can be positioned and the environment arranged such that environmental stimuli take place on the ipsilesional side of the patient's body. The historical case of President Woodrow Wilson offers a dramatic example of how optimizing the spatial arrangement of a neglect patient's environment may significantly improve performance. Following Wilson's large right hemisphere stroke and left hemiparesis, many members of Congress were worried that his medical condition would make him incapable of governing the country, so they dispatched some senators to visit him. However, before they came, Wilson's wife, who was doing much of the governing, placed him so that his left side was against a wall and his right side faced the senators. After their visit, the senate delegation claimed that Wilson was fit to govern (68). In contrast, if a patient's environment never requires him or her to attend to or act in contralesional hemispace, this could possibly impede recovery.

Appropriate temporal structuring of activities may also help optimize functioning. Because patients with neglect have a reduced attentional capacity and have difficulty dealing with more than one stimulus, reducing competing or distracting stimuli may improve performance. In addition, because patients with neglect also have a reduction of sustained attention and vigilance, the most important stimuli or actions should take place first.

EMOTIONAL COMMUNICATION DISORDERS

Changes in emotional communication can result from injury to the right hemisphere and include modality-specific subtypes (visual/facial and auditory/prosody) as well as afferent (receptive) and efferent (expressive) subtypes.

Receptive Disorders

Emotional Faces

To interpret the emotional aspects of a given situation, as well as to successfully communicate with others, we must correctly perceive and comprehend visual stimuli such as facial expressions, gestures, and scenes.

When patients with right versus left hemisphere lesions were asked to name the emotion being expressed by faces, as well as to discriminate whether two faces displayed the same or different emotional expressions, right hemisphere-damaged individuals showed a specific impairment in emotion processing, not attributable to facial identity discrimination or other visuospatial disorders (69). Investigators from other laboratories have also reported that patients with right hemisphere stroke experience more impairment than their left hemisphere counterparts in recognizing or categorizing facial emotions (70–72). In general, these defects in identifying facial affect do not depend on emotional valence, as patients with right hemisphere damage have trouble recognizing both positive (happy) and negative (sad or angry) emotional expressions.

Based on stimulation studies of patients with epilepsy, Fried et al. found that inducing dysfunction of the posterior portion of the superior temporal gyrus by focal electrical

stimulation caused patients to become impaired in comprehending and discriminating emotional facial expressions (73). As patients with damage to this area fail at both naming emotional faces as well as discriminating between the same and different emotional expressions, these patients might have an iconic representational deficit. When patients with these face comprehension deficits encountered sentences that either describe emotional expressions or emotion-invoking stories, they showed deficits in comprehending the emotions associated with expressions but not stories, suggesting that they had degradation of emotional expressive representations (74). In addition, Bowers et al. demonstrated that the patients with right hemisphere damage had deficits of facial emotional imagery, but not object imagery, providing evidence that these representations are, at least in part, iconic (75). However, other studies also suggest that the discrimination of emotional faces might depend on motor-imitation or movement mirroring (76).

Affective Prosody

When people with a meaningful relationship talk to each other about a disagreement, one of the partners frequently says to the other, "It's not what you said, but how you said it." This expression indicates that speech might carry more than one message. In addition to communicating a propositional message—which requires lexical, syntactic, and phonemic encoding and decoding—speech may simultaneously communicate a message by the use of prosody. Prosody—expressed by making changes in pitch, tempo, amplitude, and rhythm—frequently conveys an emotional message, though it may also express linguistic content (e.g., in English, rising intonation often denotes a question).

Since Paul Broca's reports of right-handed patients who develop aphasia from left hemisphere strokes, numerous studies have repeatedly demonstrated that in more than 95% of right-handed people, the left hemisphere mediates propositional language. Hughlings Jackson, however, described a patient with nonfluent aphasia who remained capable of expressing emotional speech prosody and posited that the uninjured right hemisphere might mediate this skill (7,77). The first systematic studies of emotional prosody, conducted by Heilman et al. (78) and Tucker et al. (79), indicated that when compared to patients with aphasia from left hemisphere injury, those with right hemisphere injury frequently showed impairment at comprehending and expressing emotional speech prosody. Although Ross reported similar findings (80), not all investigators found differences between right and left hemisphere-damaged patients. Further evidence for the dominant role of the right hemisphere in comprehending affective intonations comes from studies that demonstrate preserved abilities in patients with left hemisphere lesions. Patients with global aphasia who have destroyed their entire left perisylvian speech cortex and patients with pure word deafness (normal speech output and reading, but impaired speech comprehension and repetition) induced by injury to the left auditory cortex, comprehend speech very poorly but may have no difficulty recognizing emotional intonations of speech (81,82). Tucker et al. attempted to determine whether patients with right hemisphere disease could discriminate between affective intonations of speech without having to verbally classify or denote these intonations and found that patients with right hemisphere disease performed more poorly on this task than patients with left hemisphere disease (79).

The defect underlying the impaired comprehension of emotional prosody remains incompletely understood; however, we suspect that the right hemisphere contains the auditory representations of the prototypical emotional prosodies, and degradation of these representations or an inability to access them could impair both comprehension and discrimination of emotional prosody.

In normal conversation and experimental tasks, emotional prosody generally exists superimposed on propositional speech, raising the possibility that after right hemisphere damage, the intact left hemisphere fails to comprehend emotional prosody as it devotes its resources to processing the propositional semantic message. When right and left hemisphere-damaged individuals underwent an emotional prosody task that varied in the degree of conflict between the emotional message conveyed by the prosody and that conveyed by the propositional content, the right hemisphere-damaged group experienced more disruption when the propositional and prosodic emotional messages conflicted strongly than when they conflicted less (83). However, in a subsequent experiment, when the propositional semantic message was deleted by filtering the speech, the patients with right hemisphere damage still showed more impairment than those with left-sided lesions; these findings suggest that, though the left hemisphere is capable of some processing of emotional prosodic information, the right hemisphere is dominant, and distraction by propositional content cannot fully account for the prosody deficits that follow right hemisphere injury (83).

Visual and Auditory Verbal Processes

The comprehension of spoken and written words by patients with aphasia from left hemisphere-damaged patients improves when emotional words or phrases are used (84), suggesting that the right hemisphere has a lexical–semantic system that can process emotional words better than non-emotional words. However, increased arousal, which typically accompanies emotional stimuli, may instead represent the critical factor. Support for a right hemisphere emotion-based lexical–semantic system comes from the work of Borod and coworkers, who tested patients on emotional and non-emotional sentence and word discrimination tests and found that right hemisphere damage produced more impairment than left hemisphere damage on the emotional discrimination tests (85). Other studies, however, suggest that lesions of the right hemisphere do not specifically disrupt lexical semantic knowledge about emotions or emotional situations (86). Patients with right hemisphere lesions appear to have intact conceptual knowledge about emotions that are communicated verbally, as long as this communication does not involve verbal descriptions of nonverbal affect signals (74).

Expressive Defects

Speech and Writing

We demonstrated that many patients with right hemisphere disease cannot express affective speech prosody (expressive affective aprosodia) (79). Typically, these patients speak in a flat monotone and often verbally denote their emotions through the propositional content of their speech. Ross and Mesulam described two patients who could not express affectively intoned speech but who could comprehend affective speech prosody (87). Ross postulated that right hemisphere lesions may disrupt the comprehension, repetition, or production of affective speech in the same manner that left hemisphere lesions disrupt propositional speech (80).

The evidence suggests that patients with right hemisphere dysfunction can still express emotions using propositional speech or writing, although Bloom et al. reported that right hemisphere-damaged patients used fewer words when denoting emotions in their spontaneous speech (88). However, this finding might be related to other factors such as the decreased arousal associated with right hemisphere injury, rather than a true lexical–semantic deficit.

Facial Expressions

Buck and Duffy reported that patients with right hemisphere damage express fewer facial emotions than patients with left hemisphere damage (89). Multiple other studies have replicated these findings, and these patients show similar deficits in more naturalistic settings outside the laboratory (86). By contrast, studies using the facial action coding system have not found differences in facial emotion expressiveness between patients with right and left hemisphere damage (90,91). The reason for this discrepancy remains unclear; however, the observation that normal people express emotions more intensely on the left side of the face supports the postulate of right hemisphere dominance (92).

Treatment

Rosenbek and associates demonstrated that both imitative treatment and cognitive–linguistic treatments might help patients with expressive aprosodia (93). However, no well-controlled studies have examined the treatment of comprehension disorders of aprosodia or of disorders of facial emotional communication.

VISUOSPATIAL FUNCTIONS

Angle and Face Matching

Based on observations of patients with discrete lesions and corpus callosum disconnection, neuropsychologists have proposed functional hemispheric asymmetries, including left hemisphere dominance for mediating speech and language and right hemisphere dominance for visuospatial functions. However, Trojano tested patients with brain lesions using many tests of visuospatial ability, including mental rotation and the copying portions of the Rey Complex Figure Test, and did not find significant differences between those with right and left hemisphere injuries (94).

Only two well-known visuospatial tests—the Judgment of Line Orientation (JOLO) and the face-matching test—clearly differentiate between right and left hemisphere damage (95). On the JOLO, patients see a series of pages displaying two line segments drawn at different angles from each other and subsequently perform a recognition test, selecting the angle on a protractor-like display (95). On the face-matching test, patients attempt to match photographs of faces of unfamiliar people; the photographs are taken from different perspectives so that patients cannot correctly perform this task by simply making same–different decisions (95). On these two tests, patients with left hemisphere injuries perform normally and those with right hemisphere injuries show significant impairments.

These findings suggest that the right hemisphere may perform some specific visuospatial functions distinct from those represented in the left hemisphere or bilaterally. With regard to intrahemispheric localization, some investigators have hypothesized that injury to the posterior portions of the right hemisphere's cerebral cortex, including the parietal lobes, induces visuospatial dysfunction (96).

Constructional Apraxia

Constructional apraxia, or an impaired ability to copy and make drawings, may occur after either left or right hemisphere injury; however, patterns of errors may differ depending on the laterality of the lesion (97). Patients with left hemisphere lesions appear to have problems with planning and organizing their drawing; therefore, their productions become simplified and impoverished. For example, when attempting to draw a three-dimensional cube, patients with left hemisphere damage might draw several attached rectangles. In contrast, patients with right hemisphere lesions have problems in correctly producing the spatial relationships between the components of the drawing. When attempting to draw a cube, patients with right hemisphere damage will have problems displaying the correct angles between the lines that form the cube. Patients with right hemisphere damage also frequently demonstrate elements of spatial neglect and thus might fail to copy or draw the left side of objects.

Topographic Disorientation and Image Rotation

Patients can have topographic disorientation for several reasons, such as impaired spatial orientation, inability to recall the spatial relationships of landmarks, or failure to recognize landmarks. These disorders most often accompany bilateral hemispheric dysfunction, but right medial temporal lobe dysfunction may produce defects in the acquisition of topographic relationships (98).

Many defects of imagery exist (see Farah and Epstein (8) for a review) and can occur with lesions of the right parietal lobe (99).

Dressing Apraxia

Dressing apraxia most commonly occurs in the setting of degenerative diseases such as corticobasal degeneration, but focal right hemisphere lesions might also induce this deficit. Many patients with right hemisphere strokes have neglect and related disorders and might be inattentive to or unaware of the left side of space and/or the left side of their body. This inattention–unawareness can induce a failure to dress the left side of the body, but some patients without neglect also have trouble with dressing. Dressing apraxia can give rise to significant disability, so clinicians should keep this disorder in mind when evaluating patients with right hemisphere lesions. To test for dressing apraxia, the examiner can provide an inside-out jacket and ask the patient to put it on.

Treatment

Unfortunately, very few studies have systematically examined the treatment of the visuospatial disorders mentioned earlier. One randomized controlled trial found that, for patients with right hemisphere lesions, a detailed assessment of the cognitive contributors to dressing problems and a rehabilitation strategy tailored to those specific deficits resulted in improvement in dressing (100). Recently, some groups have explored virtual reality training as a means for improving topographic orientation deficits and other visuospatial problems, but work remains in the preliminary stage (101).

CONCLUSIONS

For many years, physicians and surgeons believed that except for the motor and sensory systems, the right hemisphere was "silent" and did not play a critical role in controlling higher-order neurobehavioral functions. Therefore, when surgeons had to take a brain biopsy or insert a tube through the cortex into the ventricles, they would operate on the right hemisphere. Over the past several decades, however, it has become apparent that the right hemisphere mediates many of human beings' most important cognitive functions, such as attending to relevant stimuli, as well as deciding when to initiate an action, when to persist at an action, when to complete an action, and even when not to act. Emotions play a critical role in our lives, and the right hemisphere appears to be dominant for verbal–prosodic and facial–emotional communications. In addition, the right hemisphere appears to mediate spatial operations such as drawing and dressing. Developing effective and readily accessible rehabilitation strategies for right hemisphere deficits remains an important yet unfulfilled goal.

Overall, the evidence indicates that right hemisphere damage induces severe disabilities that reduce independence more frequently than does left hemisphere damage. Thus, despite its traditional designation as the "nondominant" hemisphere, the right hemisphere in many respects is the "governing" hemisphere. Health providers who deal with patients having brain injuries or neurodegenerative conditions must understand the right hemisphere's functions—and we hope that this chapter will aid this understanding.

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16

Memory, Executive Function, and Dementia

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POSTSTROKE COGNITIVE DYSFUNCTION: THE SCOPE OF THE PROBLEM

Cognitive impairment following symptomatic stroke is one of the most important aspects of stroke recovery, and historically also has been one of the least appreciated. Despite the self-evident importance of cognitive function to quality of life, widely used scales of stroke-related disability, such as the Barthel index (1), have typically focused on motor-dependent skills, such as ambulation, transfers, bathing, toileting, and feeding, without reference to cognition. One contributor to this tendency to exclude cognition from the stroke recovery field may have been the belief that dementia is caused primarily by Alzheimer's disease (AD) and is largely unrelated to cerebrovascular disease. With increased understanding of the key role played by vascular injury in cognitive dysfunction (2) and of possible overlaps and synergies between vascular processes and AD (3), however, has come greater appreciation of the cognitive dysfunction that follows stroke.

Stroke is a potent risk factor for cognitive impairment and dementia. Studies of hospitalized stroke patients using prospective follow-up (4) or analysis of Medicare Part A inpatient claims (5) estimated an approximately 10-fold increased risk for dementia and a prevalence of 20% to 25% (6). Prospective population-based studies (7–11) have yielded smaller—but still quite substantial (approximately two-fold)—increases in risk for dementia following stroke. As not all cognitive impairment meets the criteria for "dementia" (12,13) and not all cerebrovascular disease is diagnosed as "stroke," these figures likely underestimate the full contribution of vascular disease to cognitive dysfunction.

Once present, poststroke cognitive impairment and dementia are major independent risks for death and disability (14,15), underlining the importance of this complication from the stroke rehabilitation perspective. Poststroke dementia also causes attrition from research follow-up (16), and is another factor likely to lead to underestimates of its true prevalence.

Poststroke cognitive dysfunction, like poststroke dysfunction of any type, occurs only in subjects who survive their strokes. The improvements in stroke survival achieved over the past few decades (17) might thereby have the unintended effect of increasing the prevalence of poststroke cognitive dysfunction. At least some data have suggested such a trend. In an analysis of Medicare Part A inpatient claims from approximately 42,000 subjects age 65 and older participating in the National Long-Term Care Survey (5), a comparison of the time periods 1984 to 1990 and 1991 to 2000 demonstrated a 53% increase in the age-adjusted rate of all dementia types, with the greatest increase (87%) occurring in those subjects with symptomatic stroke. These secular trends occurred in the setting of increased one-year stroke survival from 53% to 65% over the same time interval, suggesting that gains in stroke survival indeed may be contributing to the increasing burden posed by poststroke cognitive dysfunction. Further, both cerebrovascular and AD pathologies are markedly age dependent, suggesting that the prevalence of each will rise with the aging of the population. The net effect of improved stroke survival, an aging population, and steady age-specific stroke rates thus is predicted to be a major increase in the number of patients affected by poststroke cognitive dysfunction.

THE SPECTRUM OF POSTSTROKE COGNITIVE DYSFUNCTION

Two issues have stood as barriers to a full appreciation of the role of vascular factors in cognitive impairment. One is the heterogeneity of the vascular contribution to cognitive dysfunction. The vascular role can range from relatively pure instances of cognitive devastation, caused by clinically recognized strokes with no apparent contribution from other neurologic disorders, to the more common situation where small vascular injuries combine with neurodegenerative processes like AD to produce mixed impairments. The second complicating issue has been the types of cognitive impairments that result from vascular injury. These also span a spectrum from frank dementia (defined as deficits of multiple cognitive domains, including memory, that interfere with functional activities (18)) to cognitive impairments not meeting these criteria but nonetheless causing substantial functional limitation.

Since disseminating the term "multi-infarct dementia" (19), Vladimir Hachinski has argued eloquently that

the field essentially should bypass these questions by considering vascular cognitive impairment as a spectrum of disorders with varying types of vascular contributors and varying types of cognitive deficits (20). The following discussion of poststroke cognitive impairment emulates this approach by considering first the range of factors (related to both the stroke and the patient in whom it occurs) that determine the likelihood of subsequent cognitive impairment, and then the array of cognitive deficits that can occur following stroke.

Determinants of Impairment

Stroke Factors

The effect of stroke on cognition likely represents the cumulative effects of location, number, and volume. In a subset of syndromes defined as "strategic" infarctions (21,22), location is the overriding factor allowing single discrete infarctions to cause multidomain cognitive impairment. Among these strategic locations are

1. The paramedian thalamus, typically supplied by branches from the distal basilar or proximal posterior cerebral arteries. Infarctions in this territory can give rise to widespread disturbances in memory, spatial processing, and personality as well as language (if the dominant side is included) (23).
2. The inferomedial temporal cortex, fed by the posterior cerebral arteries. If the dominant side is affected, this leads to verbal memory and verbal–visual impairments such as alexia and color anomia (24).
3. The dominant angular gyrus, fed by branches of the middle cerebral artery. This leads to impairments of memory, language, and affect (25,26).
4. The parieto–temporal association cortex in the territory of the middle cerebral arteries, leading to inattention and behavioral abnormalities.
5. The frontal lobe, fed by the anterior cerebral artery. This produces deficits in memory and initiative.

Neuropathological studies have also pointed to lacunar infarctions in regions such as the basal ganglia, thalamus, and hippocampus or the medial temporal lobe as mimicking strategic stroke syndromes (27). In practice, the preponderance of single strategic infarcts causing vascular cognitive impairments appears to occur in the posterior circulation (28).

The remainder of the spectrum of strokes causing cognitive dysfunction is comprised of multiple infarctions, clinically symptomatic or asymptomatic, that collectively impair cognition. In multivariable analyses controlling for other potential contributors to dementia (see later in this section), studies have implicated the total volume of infarcts in left and right vascular territories (29–31)—or more specifically, the volume of infarction in limbic and multimodal association cortex (32)—as predictors of stroke-related dementia. Efforts to identify specific radiographic features distinguishing patients with and without poststroke dementia, however, have proven difficult. In a study of 125 subjects with stroke, none of the radiographic characteristics proposed as supporting a diagnosis of vascular dementia (21) (such as infarction of a strategic area or extensive white-matter lesions) were overrepresented among those with dementia (33). These data suggest that the risk of poststroke dementia may depend substantially on factors other than the stroke itself, in particular the pre-existing state of the brain in which it occurs.

Patient Factors

Among demographic factors, age, low education level, and nonwhite race have been demonstrated as risks for poststroke dementia (8,29,31,34–36). The extent of pre-existing cerebrovascular disease also appears to contribute to the likelihood that a subsequent stroke will impair cognition, as suggested by positive associations with history of prior stroke, the extent of white-matter lesions or microstructural changes on neuroimaging, and vascular risk factors such as diabetes mellitus, cigarette use, or elevated low-density lipoprotein (29,31,34,35,37–39). The latter findings are consistent with broader studies of the general population, linking vascular risk factors of all types (including midlife hypertension, midlife cholesterol, diabetes/hyperinsulinemia, plasma homocysteine, tobacco use, metabolic syndrome, and a composite score of atherosclerosis) with impairments of cognition (40–56).

Presence of pre-existing AD pathology may be another key determinant of the effects of stroke on cognition, in keeping with the increasingly accepted concept that cerebrovascular disease and AD act synergistically in generating cognitive impairment (57–59). Supporting an important role for underlying AD is the observation that atrophy of the medial temporal lobe is a strong predictor of poststroke dementia (31,33,36). Similarly, prestroke cognitive impairment has been identified as a predictor of poststroke impairment (39,60). Some studies (61,62) (though not all (63)) have also identified the AD-associated apolipoprotein E (APOE) 4 allele as a genetic risk for poststroke cognitive decline and dementia. Interpretation of this finding potentially is confounded by the fact that APOE 4 also has associations with ischemic stroke (64) and cerebral amyloid angiopathy (65). With the development of noninvasive markers for senile plaques (66), assessing the interaction of stroke with AD pathology in determining poststroke cognition will be increasingly feasible (67,68).

In summary, the situation where widespread cognitive impairment can be attributed to individual strategic strokes appears to be the exception rather than the rule. Instead, poststroke cognitive impairment generally represents the cumulative effects of location, number, and size of strokes (both incident and remote) and white-matter lesions—"a matter of strokes large and small" in Fisher's widely quoted formulation (69)—and pre-existing brain pathologies, in particular, AD.

Characteristics of Impairment

Although stroke-related cognitive impairment might be expected to manifest immediately following the triggering stroke, studies have emphasized the ongoing incidence of newly diagnosed dementia months or even years after stroke. This phenomenon might be related partly to difficulties in diagnosing dementia during the medically active early poststroke period, but very likely also reflects an increased vulnerability of stroke patients to ongoing vascular and neurodegenerative events. One study of 154 stroke survivors initially free of dementia demonstrated that the incidence of new dementia remained substantially greater than that in elderly controls, with cumulative incidence of approximately 10% at 1 year after stroke, 15% at 2 years, and 22% at 3 years (70). Approximately two-thirds of the incident dementias in this study could be attributed to recurrent stroke, intercurrent medical illnesses potentially causative of brain hypoxia (such as seizure, heart failure, or pneumonia), or borderline poststroke cognitive test scores that left the patient close to meeting dementia criteria during follow-up. The remaining one-third had no clinically evident cause or event. Similarly, high rates of incident cognitive impairment during the years following stroke have been identified in other prospective studies (39,71,72), with recurrent stroke or borderline poststroke cognitive status acting again as risk factors (8,36,71,73).

Studies comparing the cognitive profile of AD and vascular dementia have often emphasized the relatively greater impairments of episodic memory in AD and increased impairments on tasks requiring executive function, information processing speed, and working memory, such as picture arrangement or object assembly, in vascular disease (74–76). Deficits in *short-term episodic memory* nonetheless are a common feature of poststroke cognitive impairment, even in those not meeting criteria for dementia (76–79). Memory impairment following stroke can be a result of infarction of medial temporal lobe structures directly involved in memory storage (27). Another possible mechanism is damage to white-matter structures involved in memory encoding and retrieval through connections with the medial temporal lobe. In a functional MRI study of older, cognitively normal subjects, T2-hyperintensities in the dorsal prefrontal cortical white matter correlated with decreased activation of the medial temporal lobe and worse performance on an episodic memory task (80). Another study used diffusion-tensor imaging of diabetic subjects to demonstrate a correlation between verbal memory impairment and microstructural damage to the inferior longitudinal fasciculus (81). These findings raise the intriguing possibility that vascular lesions may contribute to memory impairment through a kind of disconnection mechanism even without direct damage to the medial temporal brain regions.

Executive function is another prominent cognitive domain commonly affected following stroke. Executive function is a somewhat ill-defined, but nonetheless central, component of the cognitive abilities required for day-to-day functioning. It represents a constellation of higher-order skills used to manipulate available information to plan and execute complex activities. Among the elemental skills felt to comprise executive function are allocation of attention, mental flexibility, processing speed, set maintenance, set shifting, working memory, and error correction. Its importance to real-life functioning is demonstrated by strikingly high correlations in the elderly with institutionalized versus noninstitutionalized level of care (82) and with formal scales of activities of daily living (ADLs) (83,84). In a study of 337 testable stroke survivors (mean age 70.2 ± 7.6), executive dysfunction (performance at least 1.5 standard deviations below the mean for elderly control subjects on 8 tests) was present in 40.6% of subjects and was associated with more than a doubling of deficits on measurements of basic ADLs (84).

Many stroke survivors with insufficient memory loss, functional impairment, or other multidomain deficits to meet criteria for dementia (18) nonetheless demonstrate substantial cognitive impairments. These patients (sometimes designated "vascular cognitive impairment, no dementia" or CIND (85)) exhibit particular impairments in executive functioning, sequencing, attention, working memory, and cognitive processing speed (86). Analysis of 92 hospital-based subjects diagnosed with CIND found less memory impairment but essentially the same extent of executive dysfunction as in 33 similarly aged subjects diagnosed with vascular dementia (78). Another notable finding from this study was that even those stroke survivors who were considered to have *no* significant cognitive impairment demonstrated worse executive function than stroke-free controls (with no difference in memory scores), indicating that executive function may indeed be the most sensitive cognitive domain to the effects of stroke.

Other cognitive domains have been studied less extensively following stroke. A population-based study found no stroke-associated decline in *visual–spatial* or *language* performance (77), whereas the previously noted study of hospitalized stroke patients without significant cognitive impairment demonstrated subtle deficits in these areas (78). Increasing attention has focused on poststroke *depression*, *apathy*, and *anxiety* as other possible manifestations of vascular dementia (87,88), with psychomotor retardation as perhaps the most prominent neuropsychiatric feature to be seen in specific association with cognitive impairment (89).

MANAGEMENT OF POSTSTROKE COGNITIVE DYSFUNCTION

The high prevalence of cognitive impairment following stroke (even in subjects felt clinically to have no significant cognitive impairment (78)) argues that cognitive screening and follow-up should be a fundamental component of the stroke rehabilitation process. No cognitive test battery has emerged as a standard protocol for this purpose, however. Widely used instruments, such as the Mini-Mental State Examination (MMSE) (90) and the full or abbreviated

TABLE 16.1 NINDS-CSN Cognitive Test Battery for Vascular Cognitive Impairment

60-MINUTE PROTOCOL	30-MINUTE PROTOCOL	5-MINUTE PROTOCOL
Animal Naming	Animal Naming	Five-Word Memory Task (registration, recall, recognition)
Controlled Oral Word Association Test	Controlled Oral Word Association Test	Six-Item Orientation
WAIS-III Digit Symbol—Coding	WAIS-III Digit Symbol-Coding	*Supplemental Tests*
Trailmaking Test	Hopkins Verbal Learning	Remainder of Montreal Cognitive Assessment (www.mocatest.org)
Boston Naming Test (2nd edition, Short Form)	Test—Revised	
Rey–Osterrieth Complex Figure Copy	Center for Epidemiologic Studies—Depression Scale	Animal Naming
Hopkins Verbal Learning Test—Revised (with List Learning Strategies)	NPI-Q	MMSE
NPI-Q	MMSE	
Center for Epidemiological Studies—Depression Scale Informant Questionnaire for Cognitive Decline in the Elderly (short form)	Trailmaking Test	
MMSE		
Supplemental/Alternate Tests Rey—Osterrieth Complex Figure Memory		
Boston Naming Recognition		
Digit Symbol-Coding Incidental Learning		
California Verbal Learning Test—2		

Source: Adapted from Hachinski V, Iadecola C, Petersen RC, et al. National Institute of Neurological Disorders and Stroke-Canadian Stroke Network vascular cognitive impairment harmonization standards. *Stroke*. 2006;37(9):2220–2241.

Cambridge Cognitive Examination (CAMCOG) (91,92), offer little testing of executive function and therefore are not ideal for the poststroke setting. The National Institute of Neurological Disorders and Stroke–Canadian Stroke Network's (NINDS-CSN) vascular cognitive impairment working group (93) addressed the issue of cognitive testing by proposing 3 protocols requiring approximately 60, 30, or 5 minutes for administration (Table 16.1). Tests in the full 60-minute protocol address 4 primary cognitive domains: executive/activation, language, visual–spatial, and memory, as well as items such as the Neuropsychiatric Inventory Questionnaire (NPI-Q) to capture neurobehavioral change and mood. Items addressing the executive/activation domain in the 60- and 30-minute protocols are tests of semantic and phonemic fluency, digit-symbol coding, and trailmaking (the latter being an optional supplemental task in the 30-minute battery). The five-minute protocol, based largely on the Montreal Cognitive Assessment (MoCA) and designed for ease of use, as well as potential administration by telephone, tests phonemic fluency, orientation, and immediate and delayed recall. The NINDS-CSN authors note that instructions and norms in a wide range of languages for this short battery are publicly available for noncommercial use (www.mocatest.org). Comparisons of MoCA and MMSE in stroke patients suggest that the MoCA may have greater sensitivity for detecting impairments while maintaining specificity (94,95), supporting its use in clinical practice and research.

Once the presence of cognitive impairment is established, the question turns to potential nonpharmacologic and pharmacologic approaches to treatment. Cognitive rehabilitation is a widely used nonpharmacologic treatment for poststroke impairment (96), but has had little experimental testing. A Cochrane Review, published in 2000, of cognitive therapy for poststroke memory impairment found only a single study of 12 subjects meeting criteria (97), underlining the importance of further work in this area.

Pharmacologic approaches to poststroke cognitive impairment can be divided into disease-modifying treatments to prevent future declines and symptomatic treatments aimed at improving the current level of functioning. Among disease-modifying treatments, secondary stroke prevention is of paramount importance, as longitudinal studies of patients with symptomatic (8,36,70,73) or clinically silent (9) stroke demonstrate recurrent stroke as a major contributor to subsequent cognitive decline. Current guidelines for secondary prevention of ischemic stroke (98,99) include (a) antihypertensive treatment, with specific data suggesting that diuretics alone or in combination with angiotensin-converting enzyme

inhibitors are useful; (b) glycemic control in patients with diabetes; (c) statin therapy for those with atherosclerosis and a low-density lipoprotein cholesterol (LDL-C) level greater than or equal to 100 mg/dL (aiming for reduction in LDL-C of at least 50% or to less than 70 mg/dL); (d) antiplatelet, anticoagulant, or vascular reperfusion therapy as dictated by stroke evaluation (99); and (e) lifestyle modifications, such as smoking cessation, reduction of heavy alcohol use, increased physical activity, and weight loss, particularly in the setting of metabolic syndrome. The most relevant data for prevention of poststroke cognitive decline came from the randomized controlled PROGRESS study, in which perindopril plus optional indapamide significantly reduced the risk of both cognitive decline (MMSE drop of ≥3 points in 9.1% of treated versus 11% of placebo, representing a 19% risk reduction) and progression of white-matter lesions (mean increase in white-matter hyperintensity volume of 0.4 mm^3 versus 2.0 mm^3) (100,101). These data suggest that this or similar drug combinations may be useful through a wide range of baseline blood pressures for prevention of poststroke cognitive decline.

The association between markers of AD, such as medial temporal atrophy and apolipoprotein E 4, and poststroke cognitive decline suggests that AD pathology also contributes to this process. Slowing of AD progression is therefore a rational approach for stroke patients with cognitive impairment, but has not yet been demonstrated for any available agent. Rapidly growing understanding of the pathogenesis of AD provides grounds for optimism that disease-modifying agents will ultimately emerge (102), however, and serve as promising candidates for prevention of cognitive decline following stroke.

Trials of symptomatic treatments for poststroke cognitive impairment have focused largely on medications already demonstrated to provide symptomatic benefit in AD (Table 16.2) (103). A pooled analysis (104) of two 24-week randomized, controlled trials (105,106) of the acetylcholinesterase inhibitor (AChEI) donepezil in patients diagnosed with vascular dementia found improvement of approximately two points on the Alzheimer's Disease Assessment Scale—cognitive subscale (ADAS-cog) and a significant increase in the proportion of subjects with global improvement (37% and 30% on 5 and 10 mg of donepezil versus 27% on placebo). These modest improvements, largely replicated in a more recent study (107), appear slightly smaller than those achieved using the same agent for AD (103), possibly reflecting the lesser tendency of vascular dementia subjects in the placebo arm to decline during the study period, compared to placebo-treated AD subjects. Slightly larger effects on cognitive testing and global functioning were noted in a six-month randomized controlled trial of the AChEI galantamine in subjects diagnosed with vascular dementia or AD plus cerebrovascular disease (108), while a study restricted to probable vascular dementia subjects demonstrated a small benefit on ADAS-cog testing and borderline benefit to global function (109). The one study of the AChEI rivastigmine in a sizable (n = 710) study sample found a small benefit to cognitive performance without global functioning improvement and with primarily gastrointestinal adverse effects leading to significantly more medication withdrawals (110). Finally, two 28-week randomized controlled trials of the uncompetitive NMDA antagonist memantine in subjects diagnosed with vascular dementia reported improvements relative to placebo of approximately two points on ADAS-cog, with statistically insignificant improvements in global functioning (111,112).

Practical steps that merit strong consideration in patients with cognitive impairment following stroke are screening for and treating poststroke depression (113) and reduction or withdrawal of medications contributing to cognitive slowing, such as psychotropic or anticholinergic agents. Studies in animal models of brain injury have highlighted the possibility that common classes of drugs may slow the poststroke recovery process (114), although the relevance of these data to human stroke recovery remains

TABLE 16.2 Medications With Reported Efficacy for Vascular Cognitive Impairment

AGENT (TRADE NAME)	INITIAL DOSE	TITRATION SCHEDULE/ EFFECTIVE DOSE	MOST COMMON ADVERSE EFFECTS
Donepezil (104–107) (Aricept)	5 mg/day, single dose	Increase 5 mg/day after 4 to 6 weeks 5 to 10 mg/day	Nausea, diarrhea, vomiting, sleep disturbances
Galantamine (108,109) (Razadyne or Razadyne ER)	8 mg/day, single dose (extended-release formulation) or two divided doses	Increase 8 mg/day every 4 to 6 weeks 16 to 24 mg/day	Nausea, diarrhea, vomiting, anorexia
Rivastigmine (110) (Exelon)	3 mg/day, two divided doses	Increase 3 mg/day every 4+ weeks 12 mg/day, 2 divided doses	Nausea, vomiting, diarrhea, dizziness
Memantine (111,112) (Namenda)	5 mg/day, single dose	Increase 5 mg/day every week 20 mg/day, 2 divided doses	Dizziness, confusion, fatigue

largely unknown. Other potential symptomatic approaches to poststroke cognitive impairment have not been tested by large, randomized trials and their effectiveness remains unclear. These include stimulants, such as methylphenidate or modafanil (115), and antidepressants (in the absence of diagnosed depression) (116).

In summary, the treatment approach to poststroke cognitive impairment is based on aggressive secondary stroke prevention and symptomatic treatment. Although the U.S. Food and Drug Administration has not approved agents for the specific indication of vascular dementia, the AChEIs donepezil, galantamine, and possibly rivastigmine appear to be rational choices, with the possibility of further efficacy from added memantine, as has been demonstrated in moderate to severe AD (117). Among the highest priorities for future studies will be to identify vasculoprotective or anti-AD agents with specific effects on preventing further cognitive decline in stroke patients.

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17

Central Poststroke Pain

Anthony J. Pellicane and Richard L. Harvey

Central pain occurs commonly in disorders of the central nervous system (CNS). Although central pain affects a higher percentage of people with certain other CNS diagnoses (such as spinal cord injury and multiple sclerosis) stroke is the most common cause of central pain due to the higher prevalence of stroke. The overall incidence of pain during the first year of stroke is 14% to 43%, and more than one pain generator can be present in a patient at the same time, making diagnosis difficult (1,2). Furthermore, the diagnosis of central poststroke pain (CPSP) can be quite difficult because there are no pathognomonic features, uniform signs, or diagnostic tests, and CPSP can mimic other pain syndromes.

The purpose of this chapter is to place CPSP in its historical context and provide a clear definition and diagnostic criteria for this complex condition. We present theories on the pathophysiology of this condition and provide guidance for CPSP treatment, including pharmacologic and nonpharmacologic approaches. Our goal is to provide a framework for diagnosis and management, with a menu of treatment options. By doing so, we hope to provide the clinician with greater confidence in the care of this most difficult problem.

HISTORICAL PERSPECTIVES

The first published record of a central pain phenomenon associated with stroke was when Adolf Wallenberg described his now famous case of the lateral medullary stroke syndrome in 1895 (3). His original paper was a case study of a patient who suffered "vertigo without loss of consciousness." This patient developed hyperesthesia and spontaneous pain on the left side of his face and body. He also had hyperesthesia of his right face and loss of pain and temperature sensation in his right limbs and torso. Though not a typical description of central pain following the Wallenberg stroke syndrome, this case report represents the first case of central pain after stroke in the literature.

The classic description of central pain after stroke was that of Dejerine and Roussy in 1906 in their report of the *thalamic pain syndrome* following a thalamic infarction (4). This patient presented with persistent hemianesthesia, mild hemiataxia, severe persistent intractable pain that was unresponsive to treatment, and choreoathetoid movements (all located contralesionally). In a 1911 analysis of this and other cases of pain after stroke, Head and Holmes (incorrectly) concluded that any stroke within the cerebral hemisphere that causes pain must involve thalamic injury (5).

In a contradictory article published in 1935, Davison and Schick presented a series of clinical–pathological cases of spontaneous pain following thalamic stroke, cortical stroke, spinal cord injury, and peripheral nerve injury (6). Thus, it became clear that pain syndromes can occur following nervous system lesions outside of the thalamus. Three years later, Riddoch published a summary of the literature on central pain, describing it as a spontaneous pain associated with an overreaction to stimulation resulting from a CNS lesion (7).

In their book entitled *Central Pain* (1969), Cassinari and Pagni clarified that CPSP can result from a lesion anywhere along the spinothalamic and thalamocortical tracts, and suggesed that pain results from an alteration in the central processing of pain and temperature transmission through the CNS (8). Following this landmark publication, much work has taken place clarifying the definition, clinical presentation, and characteristics of CPSP.

DEFINITION

CPSP can be defined as a central neuropathic pain syndrome occurring after stroke in the body part(s) corresponding to a cerebrovascular lesion of the somatosensory system, characterized by pain and sensory abnormalities where other causes of obvious nociceptive, psychogenic, or peripheral pain have been excluded (9,10). It should be noted, however, that no agreed-upon definition or diagnostic criteria for CPSP currently exist. Despite this, since Hong et al. used diffusion tensor tractography to conclude that injury to the spino-thalamo-cortical pathway seems to be a requirement for the development of CPSP (11), this suggests that the aforementioned definition for CPSP is not without pathophysiologic basis.

TABLE 17.1 Diagnostic Criteria for CPSP

Mandatory Criteria

- Pain within an area of the body corresponding to the lesion of the CNS
- History suggestive of a stroke and onset of pain at or after stroke onset
- Confirmation of a CNS lesion by imaging or negative or positive sensory signs confined to the area of the body corresponding to the lesion
- Other causes of pain, such as nociceptive or peripheral neuropathic pain, are excluded or considered highly unlikely

Supportive Criteria

- No primary relation to movement, inflammation, or other local tissue damage
- Descriptors such as burning, painful cold, electric shocks, aching, pressing, stinging, and pins and needles, although all pain descriptors can apply
- Allodynia or dysaesthesia to touch or cold

Source: Adapted from Ref. (9). Klit H, Finnerup NB, Jensen TS. Central post-stroke pain: clinical characteristics, pathophysiology, and management. *Lancet Neurol*. 2009;8(9):857–868.

Despite the lack of agreed-upon terminology for CPSP, Klit et al. proposed diagnostic criteria (Table 17.1) and a grading system (Table 17.2) for this disorder (9). Although the grading system has received some criticism with regard to its utility (specifically, its ability to differentiate patients with CPSP from those with a peripheral injury causing activation of central pain mechanisms) (12), Klit et al. have provided the clinical and research communities with important initial guidelines that provide direction to those attempting to diagnose and study CPSP.

TABLE 17.2 Grading System for CPSP

Possible CPSP: Criteria 1–3 all fulfilled
Probable CPSP: Criteria 1–3 all fulfilled **PLUS** 4 **OR** 5 fulfilled
Definite CPSP: Criteria 1–5 all fulfilled

1. Exclusion of other likely causes of pain. No other obvious cause of pain
2. Pain with a distinct neuroanatomically plausible distribution. Either pain localized unilaterally in the body and/or face or unilaterally on one side of the body with contralateral involvement of the face
3. A history suggestive of stroke. Sudden onset of neurological symptoms with onset of pain at or after stroke onset
4. Indication of the distinct neuroanatomically plausible distribution by clinical neurological examination. Findings of positive or negative sensory signs in the painful area on clinical examination, pain localized within a territory of sensory abnormality, and anatomically plausible distribution of sensory abnormalities
5. Indication of the relevant vascular lesion by imaging. Visualization of a lesion that can explain the distribution of sensory findings (either CT or MRI)

Source: Adapted from Ref. (9). Klit H, Finnerup NB, Jensen TS. Central post-stroke pain: clinical characteristics, pathophysiology, and management. *Lancet Neurol*. 2009;8(9):857–868.

CLINICAL CHARACTERISTICS

The prevalence and incidence of CPSP has been reported as 7.3% and 8%, respectively (10,13). The majority of patients with CPSP develop symptoms within 3 months of their stroke. Specifically, Klit et al. (10) reported 60% of patients with symptom onset within 3 months of stroke; Andersen et al. (13) reported 63% symptom onset within 1 month and 82% within 6 months; Leijon et al. (14) reported 78% within 3 months; and Nasreddine et al. (15) reported 71% symptom onset within 3 months, in their respective samples. Importantly, it should be noted that delayed onset (>1 year or more) of CPSP can also occur; however, this is atypical (14–16). CPSP is considered to be a long-lasting (even lifelong) diagnosis; however, no prospective studies have documented its natural history (9). One study did note that 34% of the CPSP patients studied reported an increase in pain intensity or distribution since onset, 23% reported a decrease since onset, and 14% reported resolution in pain or dysesthesia within 4 years of stroke (10).

It is generally accepted that patient demographics (age, gender) or lesion characteristics (size, side) are not reliably associated with the development of CPSP (9,13,16–18). There has been a report suggesting that the right hemisphere is more susceptible to becoming a central pain generator (15); however, this report was not without criticism (19). As discussed previously, damage to the spino-thalamo-cortical pathway seems to be a necessary (but not sufficient) condition for development of the syndrome (20). There are reports that damage to the lateral medulla (21–23) or posterolateral thalamus (24–26) (key structures within spino-thalamo-cortical pathway) leads to the development of CPSP with a higher frequency than does damage to other structures.

There are no pathognomonic features or uniform signs of CPSP, and the characteristics and descriptions of CPSP vary among patients (9,14,27). CPSP has been depicted as indescribable and incomprehensible in character with a nagging, constant nature rendering patients functionless by deteriorating motivation, altering mood and intellect, leading to neurotic tendencies and depression, and even conferring suicide risk (28). Some studies describe the pain associated with this syndrome as being high in intensity, and mostly severe and incapacitating, with patients considering the pain to be a great burden (14,27). Andersen et al., however, reported only 19% of patients with severe pain, while 44% had moderate and 37% mild pain (13); Klit et al. reported that their sample generally had moderate pain that interfered little with daily activities, mood, sleep, and enjoyment of life (10). These varied reports speak to the heterogeneity of the disorder.

CPSP most commonly affects large body areas in the distribution of the stroke (13,14,16,20,27). The pain associated with CPSP is typically described as burning, aching, pricking, lacerating, or burning cold (10,13,14,16,27); however, scalding, throbbing, freezing, shooting, squeezing, stabbing, and painful pins and needles (13,14,16) have also been reported, with most patients experiencing more than one kind of pain (Table 17.3) (13,14). More specifically, paradoxical burning (like the sensation induced by immersion of the hand in ice water) has been reported as the most common descriptor of CPSP, with descriptors such as "cold" and "freezing" perhaps being unique to patients suffering from CPSP compared to those with other types of neuropathic pain (16). The pain and dysesthesias of CPSP are most

TABLE 17.3 Clinical Characteristics of CPSP

	SUBJECTIVE PAIN QUALITY	SUBJECTIVE EXACERBATING FACTORS	OBJECTIVE EXACERBATING FACTORS
Bowsher (19)[a]	Burning or scalding (47.0%) Aching or throbbing (34.5%) Shooting or stabbing (7.4%) Painful pins and needles (5.6%)	Environmental cold (48%) Stress (46%) Environmental cold and stress (28%) Orgasm (10%) Environmental warm (9%) None (9%)	Tactile (allodynia) (52%) Movement (allodynia) (22%) Thermal (allodynia) (19.5%) Both tactile and movement (allodynia) (12%) Both tactile and thermal (allodynia) (9%)
Leijon et al. (14)[b] Boivie et al. (27)[c]	Burning (59%) Aching (30%) Pricking (30%) Lacerating (26%) Shooting (11%) Squeezing (11%) Throbbing (11%)	Joint movements (70%) Cold (48%) Light touch (44%) Warmth (22%) Emotion (19%)	Touch, cold, or pinprick (hypersensitivity) (92%)[b] Touch, cold, or pinprick (dysesthesia) (41%)[c] Cold (allodynia) (23%)[c] Touch (allodynia) (5%)[c]
Andersen et al. (13)[d]	Lacerating (50%) Aching (25%) Burning (19%) Freezing (19%) Squeezing (19%)		Cold (allodynia and/or dysesthesia) (88%) Cold (dysesthesia) (75%) Touch (allodynia and/or dysesthesia) (75%) Cold (allodynia) (56%) Touch (allodynia) (56%) Touch (dysesthesia) (50%) Pinprick (increased sensibility) (19%) Warm (allodynia and/or dysesthesia) (0%)
Klit et al. (10)[e]			Cold (dysesthesia) (66%) Pinprick (hyperalgesia) (57%) Brush (dysesthesia) (51%) Cold (allodynia) (40%) Touch (dysesthesia) (40%)
Vestergaard et al. (20)[f]			Touch (allodynia) (55%) Cold (allodynia) (55%) Both touch and cold (allodynia) (36%) Pinprick (hyperesthesia) (20%)

Note: The fact that one patient may possess more than one quality or exacerbating factor explains why percentages may not add to 100% in this table.

[a] Touch defined as a low-intensity stimulus moving across the skin described in some cases as rubbing. Movement defined as isometric or isotonic muscle contraction. Thermal defined as contact with a cold object or warm stimulus. Note, cold allodynia predominated (89%) in patients with thermal allodynia.

[b] Hypersensitivity to cold and pinprick reported as "more common" than to cotton wool (touch). "A thorough and general somatic and neurological examination" was applied without reference to particulars of the stimuli.

[c] Evoked dysesthesias reported with "about [equal frequency]" by light touch, cold, and pinprick cutaneous stimulation. Touch defined as strokes of cotton wool. Cold defined as applying a round surface of a tuning fork of room temperature (area 3.9 cm^2). Pinprick defined as light prick with a pin. Allodynic patients also described as "extremely hyperaesthetic."

[d] Touch defined as cotton wool. Cold/warm stimulus applied using metal roller with temperature of 20°C/40°C. Pinprick not defined.

[e] Touch defined as a cotton swab. Cold stimulus applied using metal roller with temperature of 20°C. Pinprick stimulus applied using a monofilament. Brush stimulus applied using a brush.

[f] Touch defined as cotton wool stroking. Cold stimulus applied using a thermoroller. Pinprick defined as a sharp needle.

commonly constant and/or spontaneous; however, they can also be evoked by cutaneous stimuli (10,13,14,27).

In addition to pain, sensory impairment is present in the affected area(s). Sensory impairment in at least one, but commonly more than one, sensory modality is typical in patients with CPSP (16), and though the painful area is usually smaller than the area of sensory impairment, the two areas may also be identical in size (16,20). In the affected extremity of patients with CPSP, somatosensory dysfunction (in the form of hyperesthesia and/or hypoesthesia to stimuli) is often identified clinically. For example, one study reported 97% of patients with a deficit of pinprick and/or thermal (warm or cold) sensation (16); another reported decreased touch, cold, warm, and pinprick in 75%, 50%, 81%, and 69%, respectively (13); another reported hyperesthesia and/or hypoesthesia with touch, cold, and pinprick sensation in 85%, 93%, and 96% of patients, respectively (27); and still another reported hyperesthesia and/or hypoesthesia with touch, warm, cold, and pinprick in 100% of patients studied (20). Quantitatively, thermal and pinprick sensory deficits have been reported as more severe compared to tactile sensory impairment in CPSP patients (16). Despite the ubiquitous somatosensory deficits, it should be noted that CPSP patients typically present with mild to moderate motor deficits (14,16).

Positive and negative sensory signs and symptoms exist in CPSP just as they do in other neuropathic pain syndromes (29). The high prevalence of hyperesthesia and/or hypoesthesia to sensory stimuli described previously confirm the presence of these positive and negative sensory signs in CPSP. Additionally, the positive phenomena of allodynia, radiation of perceived sensation, and prolonged aftersensation have been reported in CPSP (10,13,16,20,27). *Allodynia* is defined as pain in response to a nonnociceptive stimulus (30,31). It has been reported as high as 72% of patients with CPSP, with nearly one in four of those patients with allodynia possessing more than one type simultaneously (tactile, thermal, movement) (16). Allodynia to cutaneous stimuli has been reported to a lesser extent in other studies (Table 17.3) (10,13,20,27). It should be noted that, in CPSP, tactile and cold allodynia are reported most commonly (16,20). The other positive phenomena of radiation and aftersensation have been reported in 29% to 50% and 34% to 45%, respectively, of patients with CPSP (10,27).

Factors reported to subjectively exacerbate pain in CPSP are listed in Table 17.3. In addition to those listed, studies also describe a small number of patients whose pain is exacerbated by walking, postural changes, showering, being rained on, micturition, physical pressure, or being exposed to bright lights or loud noises (14,16). Though documentation of alleviating factors is not common in the literature, keeping still, rest, warmth, movement, and cold have all been reported (14,16). The fact that the same stimulus may cause allodynia in some patients while improving symptoms in other patients again speaks to the heterogeneity of this disorder.

In summary, CPSP is not an uncommon occurrence after a stroke resulting from damage to the spino-thalamo-cortical pathway. Its onset is typically within the first three months after stroke, and duration is thought to be long (potentially lifelong). The painful area is typically large, and pain intensity and quality may vary from patient to patient. Patients with CPSP most commonly describe the quality of their pain as burning or aching. Sensory impairment in one or more sensory modalities within the affected area(s) should be demonstrable in all patients with CPSP, whereas allodynia or dysesthesia to one or more sensory modalities should be found frequently in patients with CPSP.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis for CPSP includes, but is not limited to, **complex regional pain syndrome (CRPS), radiculopathy, plexopathy, peripheral mononeuropathy, hemiparetic shoulder pain (HSP), deep venous thrombosis (DVT), and conversion disorder**. As CPSP is considered a diagnosis of exclusion (9), understanding how to differentiate CPSP from these diagnoses is extremely important.

Poststroke **complex regional pain syndrome (CRPS)** may present similarly to CPSP with regard to subjective pain complaints and objective pain findings. For example, both poststroke CRPS and CPSP patients may experience allodynia with wearing clothes or showering; in the clinic, they may complain of pain to light touch applied by the physician. However, the patient with poststroke CRPS will also possess numerous other specific subjective complaints and physical examination findings that will allow the practitioner to differentiate between poststroke CRPS and CPSP. Known as the "Budapest Criteria," clear, validated diagnostic criteria for CRPS exist for use in both clinical and research settings (Table 17.4) (32,33). In brief, the Budapest Criteria require the presence of continuing pain in addition to a certain number of symptoms and signs from four distinct categories (sensory, vasomotor, sudomotor/edema, motor/trophic). Thus, if a patient fails to meet the Budapest Criteria, poststroke CRPS can be moved lower on the differential diagnosis list of possibilities. It should be noted that the Budapest Criteria were not developed specifically for the stroke population. Further, as sensorimotor dysfunction (including spasticity) and autonomic dysfunction (34) may exist after stroke, the Budapest Criteria should be applied cautiously in this population. Regardless, they do supply guidelines to help the practitioner differentiate between poststroke CRPS and CPSP, and it has been suggested that "utilization of [the Budapest Criteria] in the stroke literature will advance our understanding and treatment of post-stoke CRPS and is highly recommended" (35).

Because of their unilateral presentation and symptomatology, **cervical and lumbosacral radiculopathy, brachial and lumbosacral plexopathy, and upper and lower extremity peripheral mononeuropathy** all may present similarly to CPSP (36–41). Differentiation between these diagnoses and CPSP can be made with careful history and physical

TABLE 17.4 Proposed Clinical Diagnostic Criteria for CRPS

General definition of the syndrome: CRPS describes an array of painful conditions that are characterized by continuing (spontaneous and/or evoked) regional pain that is seemingly disproportionate in time or degree to the usual course of any known trauma or other lesion. The pain is regional (not in a specific nerve territory or dermatome) and usually has a distal predominance of abnormal sensory, motor, sudomotor, vasomotor, and/or trophic findings. The syndrome shows variable progression over time.

To make the clinical diagnosis, the following criteria must be met:

1. Continuing pain, which is disproportionate to any inciting event
2. Must report at least one symptom in *three of the four* following categories:
   - **Sensory:** Reports of hyperesthesia and/or allodynia
   - **Vasomotor:** Reports of temperature asymmetry and/or skin color changes and/or skin color asymmetry
   - **Sudomotor/Edema:** Reports of edema and/or sweating changes and/or sweating asymmetry
   - **Motor/Trophic:** Reports of decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair, nail, skin)
3. Must display at least one sign at time of evaluation in *two or more* of the following categories:
   - **Sensory:** Evidence of hyperalgesia (to pinprick) and/or allodynia (to light touch and/or temperature sensation and/or deep somatic pressure and/or joint movement)
   - **Vasomotor:** Evidence of temperature asymmetry (>1°C) and/or skin color changes and/or asymmetry
   - **Sudomotor/Edema:** Evidence of edema and/or sweating changes and/or sweating asymmetry
   - **Motor/Trophic:** Evidence of decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair, nail, skin)
4. There is no other diagnosis that better explains the signs and symptoms

For research purposes, diagnostic decision rule should be at least one symptom *in all four* symptom categories and at least one sign (observed at evaluation) in *two or more* sign categories.

Source: Adapted from Ref. (32). Harden RN, Bruehl S, Stanton-Hicks M, Wilson PR. Proposed new diagnostic criteria for complex regional pain syndrome. *Pain Med.* 2007;8(4):326–331.

examination. For example, reproduction of symptoms with femoral nerve stretch or straight leg raise test, in the presence of pain centralization with lumbar extension and in the absence of provoked allodynia and hyperalgesia, points toward the diagnosis of lumbosacral radiculopathy and away from CPSP in the stroke patient who presents with burning, unilateral leg pain (37,42). When necessary, electrodiagnosis can be utilized to confirm or refute the diagnosis of radiculopathy, plexopathy, and peripheral mononeuropathy in the stroke patient (43–46). Although there have been reports of successful identification of these diagnoses in the stroke patient (47–51), it should be noted that testing may be challenging due to the electrodiagnostic abnormalities typically found after stroke (52,53).

HSP may be caused by a number of diagnosable problems, including but not limited to rotator cuff tendonitis or injury, impingement syndrome, adhesive capsulitis, bursitis, shoulder (glenohumeral) subluxation, and spasticity (54,55). The determination of the specific cause for HSP in a particular patient can be quite challenging for a multitude of reasons. First, there is substantial plasticity of the neurologic and musculoskeletal systems after stroke. Second, more than one cause for HSP can exist simultaneously, and some causes of HSP may exist transiently and resolve spontaneously. Finally, some causes of HSP cause pain indirectly (54). With a detailed history and physical examination of the shoulder, the practitioner can narrow the differential diagnosis for HSP in the stroke patient. To complicate matters, it should be noted that, regardless of the cause of HSP, central sensitization may result from the chronically painful shoulder (55). *Central sensitization* can be defined as an amplification of neural signaling within nociceptive pathways in the CNS that elicits pain hypersensitivity (for example, dynamic tactile allodynia or pressure hyperalgesia), aftersensations, and enhanced temporal summation (56). Roosink et al. demonstrated sensitization to innocuous and noxious stimuli in the affected body side in patients with persistent poststroke shoulder pain (57,58); thus, it is clear that chronic HSP (regardless of etiology) that has resulted in central sensitization can mimic CPSP. Additionally, specific causes of HSP can also mimic CPSP. For example, shoulder subluxation has been postulated to cause traction injuries to the brachial plexus, and these injuries can present similar to CPSP, as discussed previously (50). Also, as spasticity can cause pain with range of motion, it may also mimic CPSP (59).

DVT in the upper or lower extremity most typically presents as edema, pain, and/or warmth and erythema in the affected limb (60–62). In the stroke patient, varying combinations of these presenting symptoms may mimic CPSP, poststroke CRPS, infection, lymphatic edema, musculoskeletal injury, or other pathologies. In the upper extremity, DVT can also present with headache, chest or jaw pain, cough, limb cyanosis, superficial limb vein distension, collateral shoulder girdle vein distension, jugular vein distension, neck swelling, or fever—all of which may be useful in differentiating an upper extremity DVT from CPSP (62,63). However, as an upper extremity DVT may cause arm paresthesias, this may inappropriately lead to a CPSP diagnosis (62). In the lower extremity, DVT can present with fever, which would

not be expected in CPSP (64,65). For completeness, it should be noted that in the clinical assessment of lower extremity DVT, Homan's sign (posterior calf tenderness with passive ankle dorsiflexion) is present in only 13% of cases and a palpable cord is detectable in only 6% of cases (66). As clinical diagnosis alone is inadequate, whenever upper or lower extremity DVT is suspected, the practitioner should not hesitate to utilize compression duplex ultrasound as the initial diagnostic test, given its noninvasiveness and high sensitivity and specificity (60–62).

Conversion disorder is broadly defined as the presence of neurologic symptoms in the absence of a neurologic diagnosis, and four types have been specified (motor symptoms or deficits, sensory symptoms or deficits, pseudoseizures, or a mixed presentation) (67). Symptoms are not deliberate or consciously produced and are believed to reflect the "conversion" of conflicts, stressors, or underlying emotional distress into physical (neurologic) symptoms (67). Whereas many case reports describe conversion disorder presenting like stroke with sensorimotor deficits in the absence of pain (68–70), there is one case report of conversion disorder specifically misdiagnosed as CPSP (71). Given that a survey of outpatient neurologists estimated that 30% of their new patients possessed psychological factors thought to be of etiological significance to their presenting complaint (72), recognizing nonorganic symptoms is important. After determining that no neurological disease explains the presenting symptoms and that the patient is not feigning, several factors may help the practitioner identify conversion disorder: atypical or inconsistent neurologic signs, "la belle indifference," histrionic or borderline personality disorder, a "model" for the symptoms (in the form of a relative or other), or an associated stressor (recent or historic) (67,73). It should be noted, however, that none of the aforementioned are supported with compelling or unchallenged evidence (73). For completeness, it warrants mention that the American Psychiatric Association has proposed renaming conversion disorder to "conversion disorder (functional neurological symptom disorder)" in the fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (*DSM-5*), citing that the additional parenthetical term aligns with terminology currently used by neurologists and also is more acceptable to patients (74).

ANATOMY AND PATHOPHYSIOLOGY

The neuroanatomical processing of pain and temperature involves both localizing and thermoregulatory processes. Thermoregulatory processes maintain core body temperature in the presence of changes in metabolic activity and external temperature. Temperature control is comprised of both autonomic modulation and behavioral responses (for example, putting on a sweater when one is cold). Both pain localization and thermoregulatory processes are influenced by the motivational and emotional nature of the stimulus (be it pleasant, unpleasant, or damaging to the body). In 1906, Sir Charles Sherrington divided sensory input into categories: vision and hearing (teloreception), smell and taste (chemoreception), limb position (proprioception), touch (exteroception), and visceral (interoception) (75,76). Although Sherrington considered pain and temperature sensation to be exteroceptive processes, the thermoregulatory aspect of sensation is clearly interoceptive. Regarding the neuroanatomical basis of central pain, both exteroceptive and interoceptive processes are likely involved at multiple levels in the CNS (77).

The *exteroceptive pathway* involves the spino-thalamocortical pathway. Small unmyelinated and lightly myelinated fibers enter the spinal cord via the dorsal root, ascend or descend several levels via Lissauer's tract, and synapse in the substantia gelatinosa. From there, afferent nuclei send fibers that decussate in the spinal cord to the contralateral side and ascend in the lateral spinothalamic tract to the ventroposterior lateral (VPL) nucleus of the thalamus. The thalamus sends fibers superiorly that terminate in both the primary (S1) and secondary (S2) sensory cortex in the anterior parietal lobe. Additional fibers ascend from VPL to the motor cortex (M1) in the precentral gyrus.

The *interoceptive pathway* involves the lamina 1 spinothalamic tracts, which transmit afferent information about the state of body tissues (see Figure 17.1). The lamina 1 system therefore participates in the modulation of homeostasis, including that of visceral pain and thermoregulation (77). These fibers also decussate in the spinal cord and ascend in the lateral spinothalamic tract to the posterior ventromedial (VPM) nucleus of the thalamus. The thalamus then provides a rich supply of afferents to the insular cortex. The lamina 1 system also has direct input to the ventrocaudal mediodorsal (VMD) nucleus of the thalamus, as well as indirect input via the periaqueductal grey and parabrachial nucleus of the midbrain. The VMD then sends afferent fibers to the cingulate cortex, which influences the emotional state of the individual in response to these internal stimuli. The insular cortex can downregulate this latter pathway by providing inhibitory feedback to the periaqueductal grey and parabrachial nucleus (see Figure 17.1). Thus, the level of distress within the individual is modulated within the CNS via this lamina 1 system. Damage along the spino-thalamocortical pathway or within the lamina 1 system would disrupt the normal pain and thermoregulatory processing that can result in central pain, causing an alteration of sensory, emotional, and behavioral responses to stimuli, which in the clinical setting are often maladaptive.

However, it has also been proposed that central pain might be caused by disruption of the lemniscal pathway via dorsal columns in the spinal cord and medial lemniscus of the brainstem. Loss of lemniscal tracts that carry nonpainful sensory information (e.g., proprioception) might result in a kind of "release phenomenon," where central sensory processing is unbalanced toward pain perception (78). However, cases of central pain frequently lack neuroanatomical evidence of lesions within the lemniscal system, so injury within these tracks is not necessary for central pain (79,80). A more plausible release phenomenon might occur with injury to the descending inhibitory fibers from insula to periaqueductal

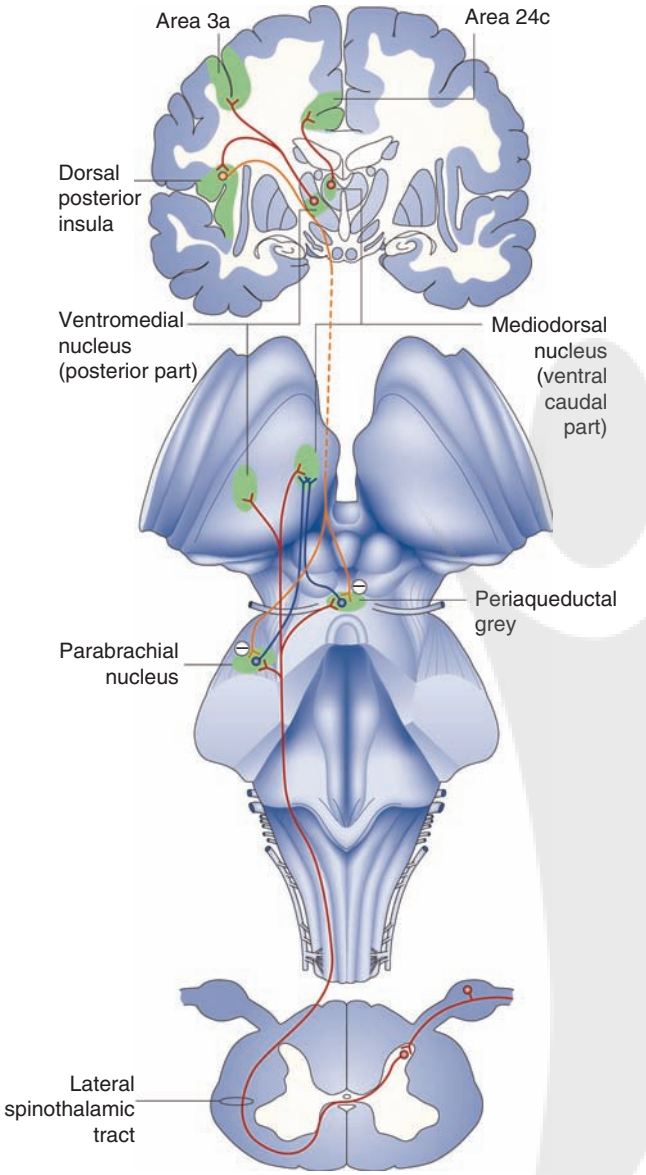

FIGURE 17.1 Central pain can result from damage to the lamina 1 spinothalamic anywhere along its ascending and descending tracts. Ascending tracts from the spinal cord (shown in red) have excitatory input to the periaqueductal grey and the parabrachial nucleus and within the thalamus to the ventromedial and mediodorsal nuclei. Periaqueductal grey and parabrachial nucleus also provide excitatory input to the ventromedial thalamus (shown in blue). The thalamic nuclei send fibers to area 3a of the primary sensory cortex as well as to the insula and cingulated gyrus (shown in red). The insula is capable of downregulating sensory input through descending inihibitory feedback to periaqueductal grey and parabrachial nucleus (shown in orange).

Source: Reprinted by permission from Ref. (77). Craig AD. How do you feel? Interoception: the sense of the physiological condition of the body. *Nat Rev Neurosci.* 2002;3:655–666. Macmillan Publishers Ltd.

grey and parabrachial nucleus (see Figure 17.1). This would reduce one's ability to downregulate interoceptive input, which could increase perceived pain and associated behavioral responses.

Based on current understanding regarding the anatomy and physiology of pain and thermoregulation and on our understanding of the pharmacology of central pain management, there are several theories on the cause of central pain after CNS damage.

Loss of Aminergic Modulation

Because medications that increase adrenergic and serotonergic stimulation have some effect on central pain, it is theorized that a reduction in adrenergic and serotonergic modulation within the CNS may alter the function of the afferent pathways and result in a greater perception of pain.

Alteration of the *N*-Methyl-d-Aspartate-Glutamate System

Inhibitors of *N*-methyl-d-aspartate (NMDA) activity also have been used therapeutically for central pain. This suggests that central pain may result from enhanced thalamocortical activity due to an increase in glutaminergic NMDA stimulation. In this theory, NMDA stimiulation leads to long-term potentiation and, subsequently, maladaptive neuroplastic changes that enhance pain perception.

Abnormal Central Modulation

CNS damage resulting in a loss of central nonnoxious temperature fibers along the lamina 1 spino-thalamo-cortical pathway above the motor decussation might cause central pain. This is proposed as affecting the capability of the CNS to modulate temperature perception, leading to symptoms of allodynia.

Thermosensory Inhibition

Loss of descending inhibitory control of the brainstem homeostatic structures, including the periaqueductal grey and peribrachial nucleus via cortical interoceptive regions such as the dorsal posterior insula, will result in unabated thermoregulatory drive to the medial thalamus and anterior cingulate cortex (see Figure 17.1). The excitatory drive to the cingulate cortex will cause emotional distress and, perhaps, associated pain perception.

Central Excitation

The central excitation theory proposes that pain is due to abnormal burst activity within the lateral and medial thalamic nuclei.

In any particular case of central pain following stroke, the pathophysiology involved could be one or more of the processes described in the preceding sections. Because different pathophysiological processes are involved in the generation of CPSP, it is no surprise that patients do not necessarily respond to a single medical treatment. Instead, the treatment of CPSP typically requires a combination of multiple pharmacologic and nonpharmacologic interventions that must be individualized to each patient.

TREATMENT

Introduction to Treatment

As pain relief in CPSP is often incomplete, patient expectations must be managed appropriately. After diagnosis and at the onset of treatment, it is vital to educate the patient that complete elimination of the pain is likely an unrealistic goal. Goals of treatment should focus on pain reduction and functional restoration. The diagnosis and treatment of any preexisting pain conditions or psychiatric disorders should occur simultaneously with the treatment of CPSP.

The management of chronic pain conditions like CPSP should follow an interdisciplinary model. Interdisciplinary pain rehabilitation programs with a greater appreciation for a biopsychosocial approach to pain management (as opposed to a biomedical approach) remain a growing area in the evolution of modern comprehensive pain management (81). These programs have shown that concomitant pharmacologic and nonpharmacologic pain management (including but not limited to physical therapy, occupational therapy, and pain psychology), in addition to adjunctive components like vocational rehabilitation, employed by a team familiar with the patient and each other represents the most likely paradigm for success in the treatment of chronic pain. For example, pain psychology can employ cognitive behavioral therapy, relaxation techniques (with or without biofeedback), autogenic training, meditation, and guided imagery, all in an attempt to help the patient self-manage pain and stress. In addition, pain psychologists help to educate patients with regard to the principles of goal setting and pacing. The involvement of a psychologist is also important to prepare the patient and family for the possibility of a life with pain (28). Further, the psychologist's ability to identify depression may also help with CPSP diagnosis, as one study demonstrated that patients with CPSP were significantly less likely to report depression compared to stroke patients with chronic pain not considered to be secondary to CPSP (10). Thus, the presence of depression may lower CPSP on the list of differential diagnoses in a patient with stroke. Clearly, many practitioners with varied backgrounds and expertise all must contribute to the care of the patient with CPSP to achieve a positive outcome. The following sections discuss pharmacologic and nonpharmacologic management of CPSP in greater detail.

Pharmacologic Management

Many review articles exist describing the pharmacologic management of CPSP (9,17,28,82–86). These reviews typically organize management options based on drug class or mechanism of action; however, some also attempt to organize based on efficacy (Table 17.5) (9,82–84). We have organized pharmacologic management of CPSP based on efficacy to generate a reasonable treatment algorithm for practitioners who encounter this diagnosis.

First-Line

There is consensus that **amitriptyline** (tricyclic antidepressant) is the most appropriate first choice in the treatment of CPSP (9,82–84). A randomized, blinded, crossover, placebo-controlled trial demonstrated that 75 mg daily of amitriptyline yielded significantly lower mean daily pain ratings on a 10-step verbal scale compared to placebo (4.2 ± 1.6 versus 5.3 ± 2.0 by week 4 of the treatment period). Perhaps more importantly, 67% of the amitriptyline patients reported improvement in pain on global assessment, compared to only 7% of the placebo group (87). It should be noted that there was a correlation between the pain-relieving effect and total plasma concentration of amitriptyline, with concentrations of more than 300 nmol/L being associated more consistently with positive outcomes. This may suggest that nonresponders to amitriptyline may benefit from a trial of dose escalation beyond 75 mg per day, barring untoward side effects (typically related to the anticholinergic side effects of this medication).

Most agree that **lamotrigine** (anticonvulsant) is also a first-line drug for the treatment of CPSP (9,82–84). A randomized, blinded, crossover, placebo-controlled trial demonstrated that a 200 mg daily dose of lamotrigine resulted in a significantly lower median daily pain ratings on an 11-point Likert scale compared to placebo (5 versus 7) after 8 weeks

TABLE 17.5 Hierarchy of the Pharmacologic Management of CPSP

DRUG	KLIT ET AL. (9)	KUMAR ET AL. (82)	FRESE ET AL. (83)	HARVEY (84)	RECOMMENDATION
Amitriptyline	1st line	1st line	1st line	1st line	1st line
Lamotrigine	2nd line	1st line	1st line	1st line	1st line
Pregabalin	1st line	Not ranked	Not ranked	1st line	2nd line
Gabapentin	1st line	2nd line	2nd line	1st line	2nd line
Fluvoxamine	Not ranked	2nd line	2nd line	2nd line	3nd line
Opioids	2nd line	Not ranked	Not ranked	Not ranked	3rd line
Mexiletine	Not ranked	2nd line	2nd line	Not ranked	3rd line

of medication titration (note that the lamotrigine dose was titrated up every two weeks per manufacturer recommendations to minimize risk of rash, and no effect was found at lower doses) (88). There was also significant improvement in evoked pain to cold stimulus in the lamotrigine group compared to placebo; however, there was no superiority with regard to improvement in tactile allodynia or change in size of painful body area, and only 44% were deemed clinical responders (defined by a lamotrigine pain score greater than or equal to 2 points lower than the corresponding placebo value). The authors suggested that higher doses of lamotrigine may improve efficacy in CPSP as required in other diagnoses.

Second-Line

Pregabalin (anticonvulsant) is considered by some to be a first-line agent in the treatment of CPSP (9,84); however, based on current data, use as a second-line agent seems more appropriate. A randomized, blinded, parallel group, placebo-controlled trial assessed the efficacy of 150 to 600 mg per day of pregabalin in 219 patients with CPSP (89). Mean pain score on the Daily Pain Rating Scale decreased in both groups, but there was no significant difference between the two groups at baseline or endpoint (6.5 to 4.9 in the pregabalin group; 6.3 to 5.0 in the placebo group). Additionally, the majority of patients treated with pregabalin did not achieve a 30% or 50% reduction in mean pain score compared with baseline. However, the pregabalin group did improve significantly over the placebo group in some of the secondary outcome measures, including those regarding sleep and anxiety, and on the Clinician Global Impression of Change rating scale. Also, it should be noted that a statistically significant difference in mean pain scores existed between the two groups at weeks 3, 5, 6, and 8 of the study. The authors attributed the disappearance of statistically different scores in weeks 9 through 12 to the continued improvement in pain scores in the placebo group, which has been described elsewhere as a problem inherent in neuropathic pain trials (90). As a result, the authors commented that the lack of statistical significance at the end of the study might represent a study limitation rather than drug failure. A randomized, blinded, placebo-controlled trial studied 40 patients with central neuropathic pain (48% of whom carried the diagnosis of stroke) and found that 150 to 600 mg per day of pregabalin led to significant differences in mean pain scores (7.6 ± 0.8 to 5.1 ± 2.9 in the pregabalin group; 7.4 ± 1.0 to 7.3 ± 2.0 in the placebo group), EQ-5D scores, and the pain domain of the Short Form-36 after 4 weeks of treatment (91). Notably, the authors reported no difference in pain relief following pregabalin treatment between the stroke patients and the remainder of the study participants; however, the data were not reported. Despite the improvement in secondary outcome measures in both trials, pregabalin was not superior to placebo with regard to decrease in pain in the trial that studied CPSP exclusively. For this reason, pregabalin should be considered second-line treatment for this diagnosis.

There is debate regarding the utility of **gabapentin** (anticonvulsant) in the management of CPSP (9,82–84). Whereas there are case reports of individual patients with CPSP who had failed with other pharmacologic interventions being treated successfully with gabapentin 300 mg three times daily (92,93), there are no controlled clinical trials testing gabapentin's efficacy specifically in CPSP. For example, one randomized, blinded, placebo-controlled trial demonstrated significant improvements in a group of 308 patients with neuropathic pain resulting from a variety of diagnoses who were given up to 2400 mg of gabapentin per day (94). However, because only 2.9% of the study population carried the diagnosis of CPSP, extrapolation to this population is difficult. The authors stated, however, that there were no differences in treatment effect among the various pain syndromes. Importantly, many of the clinical improvements demonstrated in this study were slight, even when statistically significant. Key findings include the small but significant decrease in mean pain diary score comparing the gabapentin group (1.5) to placebo (1.0), the lack of a significant difference in the percentage of responders between the groups (defined as a >50% pain reduction), and the fact that only two of the components of the short-form McGill Pain Questionnaire were significantly improved in the gabapentin group over placebo. That being said, the gabapentin group did perform significantly better on several of the components of the Short Form-36, and significantly higher percentages of "very much" or "much improved" responses were noted in the gabapentin group in the Patient and Clinician Global Impression of Change rating scales. Another study (open-label design) of 18 patients with neuropathic pain resulting from a variety of diagnoses who received up to 2400 mg of gabapentin per day demonstrated significant improvements in pain intensity on a visual analog scale (VAS) (74 ± 23 at baseline to 59 ± 25 at 6 weeks), number of daily pain attacks, and brush- and cold-induced allodynia (95). As in the prior study, only two of the patients studied here carried the diagnosis of CPSP, and the authors again reported no significant difference between patients with central and peripheral pain with regard to their findings. Given that no study dedicated specifically to patients with CPSP exists, we consider gabapentin a second-line treatment for this diagnosis.

Third-Line

Fluvoxamine (selective serotonin reuptake inhibitor) has been proposed as a second-line treatment for CPSP (82,83). In patients less than 1 year poststroke with CPSP, an open-label study demonstrated a significant decrease in VAS pain score (7.3 ± 2.2 to 4.7 ± 1.9) in patients given 25 to 125 mg daily of fluvoxamine (96). There was also a significant improvement in Zung's Self-rating Depression Scale (SDS) in this study; although the authors demonstrated no correlation between the changes in VAS and SDS, they state that the improvement in depression may have played a role in the relief of central pain. Given this, plus the lack of a placebo group in this study, fluvoxamine should be considered

a third-line treatment for CPSP. However, if a CPSP patient presents with concomitant signs and symptoms of depression, this medication should be considered earlier in the treatment algorithm. Note: Fluvoxamine should not be confused with fluoxetine.

In a small, randomized, blinded, crossover, placebo-controlled trial of 15 patients with central pain (5 with CPSP), intravenous **morphine** (opioid) was administered, and patients were monitored for 120 minutes after infusion (97). The mean dosage of intravenous morphine was 16 mg and intravenous saline was used for placebo. Additionally, after the infusion portion of the study, patients were trialed on various doses of oral morphine. There was no significant difference in VAS for ongoing pain intensity at any point after the two different infusions. However, it should be noted that 46% of patients receiving intravenous morphine gained more than 50% pain relief, compared to only 13% of patients receiving saline; also, 80% of the intravenous morphine patients compared to only 40% of the saline patients reported moderate or excellent pain relief after infusion. Additionally, although there was no significant effect on other types of evoked pain, intravenous morphine significantly reduced the intensity of brush-induced allodynia compared to placebo in this study population. In the oral morphine component of the study, the patients were titrated to 60 to 140 mg per day and the authors reported a significant decrease in VAS for ongoing pain intensity at 4 weeks compared to baseline (44 ± 20 versus 64 ± 13, respectively). A correlation between the analgesic effects of IV morphine and oral morphine was also noted. Limited efficacy, side effects, or both resulted in only 20% of patients continuing treatment with oral morphine at 1 year. The authors concluded that while opioids may represent a therapeutic alternative for central neuropathic pain, only a small group of patients seem to be able to continue long-term treatment because of an unfavorable balance between efficacy and side effects. Relatedly, in a randomized, blinded trial, 81 patients with central and peripheral pain were given high- or low-dose capsules of **levorphanol** (opioid) and were instructed to self-titrate their dose within predefined parameters (98). For the entire study population, the high-dose group demonstrated a significant decrease in pain intensity over the low-dose group (36% versus 21% reduction). However, only 3 of the 10 study patients with CPSP completed this study, and the small CPSP cohort did not demonstrate as robust pain reduction as the other diagnoses that made up the study population. Interestingly, a case report of a patient with chronic, treatment-resistant CPSP described complete resolution of symptoms after one intravenous infusion of 50 mg **tramadol** (opioid and serotonin/norepinephrine reuptake inhibitor) followed by 20 mg daily of oral **codeine phosphate** (opioid) combined with 25 g twice daily of **milnacipran** (serotonin/norepinephrine reuptake inhibitor) (99). The authors reported continued complete relief with the oral regimen for six days of treatment followed by symptom recurrence after cessation of the oral regimen. The authors selected the codeine phosphate and milnacipran combination to best replicate tramadol's mechanism of action. The effects of oral tramadol on CPSP have not been assessed. Given that **tapentadol** (opioid and norepinephrine reuptake inhibitor) has a similar mechanism of action to tramadol, perhaps these two medications warrant investigation as maintenance or abortive medications in the treatment of CPSP. The evidence described in this section, coupled with the fact that supraspinal central neuropathic pain (like CPSP) is considered the least responsive to opioids (100), indicates that this class of medications should be considered after other agents have been deemed ineffective. **Oxycodone** (opioid), **methadone** (opioid, NMDA antagonist, norepinephrine/5-hydroxytryptamine reuptake inhibitor), **buprenorphine** (opioid), tramadol, and tapentadol have been reported, conceivably, as effective agents in the treatment of neuropathic pain (100). As a result, if opioids are to be considered, these agents should be preferentially used when treating CPSP.

Three small studies with varying designs—two with a mixed population (101,102), one studying CPSP exclusively (103)—demonstrated some efficacy in the treatment of central neuropathic pain using intravenous **lidocaine** (antiarrhythmic, local anesthetic). More specifically, while improvements in spontaneous pain and some types of evoked pain were noted, these changes typically did not last much beyond cessation of the infusion (101,102). As a result of these studies, intravenous lidocaine has been reported as potentially having utility for short-term pain relief in patients with intractable CPSP (82,83). As a result of the positive effects of intravenous lidocaine, its oral analog **mexiletine** (antiarrhythmic) has also been studied. For example, in a small, open-label study, improvement in 7 of 8 patients with CPSP resistant to other treatments was noted using 10 mg/kg per day of mexiletine titrated over a 4-week period (104). Patients were titrated beginning with 150 mg daily and 300 mg daily for 3 days each prior to starting the 10 mg/kg per day dose. Additionally, two of the intravenous lidocaine studies described previously administered oral mexiletine after the intravenous portion of the treatment protocol. In one of these studies, 25% of the patients reported moderate pain relief (defined by a decrease in visual analog pain scale score of 30% to 50%); however, no patient was willing to be treated long term with mexiletine because of side effects (101). Similarly, in the other study, two of the four patients discontinued mexiletine due to side effects (103). Although mexiletine is often considered a second-line drug for CPSP (82,83), the lack of a placebo-controlled study coupled with patient intolerance and the need to monitor for QT interval prolongation suggests that mexiletine is more appropriate as a third-line agent.

Other Options

In the same study described earlier that demonstrated the efficacy of amitriptyline in the treatment of CPSP, there was some evidence that **carbamazepine** (anticonvulsant) might have some efficacy as well (87). Both amitriptyline and carbamazepine were compared to placebo in a blinded,

crossover trial and, by week 4 of treatment, the amitriptyline, carbamazepine, and placebo groups possessed daily mean pain ratings of 4.2 ± 1.6, 4.2 ± 1.7, and 5.3 ± 2.0. Despite having the same scores, the amitriptyline, but not the carbamazepine, group differed significantly from the placebo group; and only 36% of the carbamazepine group reported improvement in pain on global assessment. Despite this, the authors concluded that some CPSP patients may benefit from carbamazepine.

In a small, open-label trial, **phenytoin** (anticonvulsant) was given to eight patients with CPSP in escalating doses until either a clinical response or side effect was noted (105). Three of the eight patients reported a worthwhile reduction in pain (defined as a reduction of one to two levels of intensity on at least one pain scale) with concomitant family and clinician comments reporting decreased pain behaviors. Pain levels and behaviors returned in these three patients following withdrawal of phenytoin. The reported median phenytoin serum level for the population was 12.8 mcg/mL.

In two case reports, **zonisamide** (anticonvulsant) at 200 mg daily successfully treated CPSP refractory to other medications (106). Given that zonisamide has shown promise in the treatment of other neuropathic pain conditions, (107–110), it is not unreasonable to include this medication as a potential option for the treatment of CPSP, particularly if other medications have been tried unsuccessfully.

Ketamine (NMDA antagonist) has also been studied in the treatment of central pain. In a randomized, blinded, placebo-controlled trial of topical ketamine administered via iontophoresis to 33 patients (24% with CPSP), no difference was noted compared to placebo in the 50 mg daily dose; however, the 75 mg daily dose significantly improved components of the Pain Disability Index, EQ-5D, and Short Form-36 (111). There was no improvement in pain intensity visual analog scores with either dose compared to placebo, but because of the improvement in secondary outcomes with the 75 mg daily dose, the authors concluded that iontophoretic administration of ketamine can be therapeutic in central neuropathic pain refractory to typical interventions. In a single case report of a patient with CPSP, oral ketamine titrated to 50 mg three times daily (after an intravenous ketamine trial) was deemed beneficial in decreasing pain, allodynia, and hyperalgesia (112). Due to the patient's response to oral ketamine, gabapentin and opioids were discontinued. In this case, thrice daily diazepam was required to combat ketamine's side effects. Finally, in a study attempting to establish an intervention to predict successful motor cortex stimulation in patients with CPSP, 47.8% of patients demonstrated 40% or better pain reduction with 5 mg intravenous ketamine given every 5 minutes up to a total dose of 25 mg; however, these effects lasted less than 1 hour after completion of the infusion (113). With further investigation, ketamine may play a more significant role in the treatment of CPSP.

Several boluses of intrathecal **baclofen** (gamma-aminobutyric acid agonist) were given to five patients with CPSP over a week's time (doses ranged from 50 to 150 mcg) (114). Four of the five patients reported relief with these interventions that lasted for 12 to 24 hours after the procedure. In all patients, a bolus of intrathecal saline was administered at some point during the study period, with no patients reporting symptom relief with this intervention. All patients were given oral baclofen after the intrathecal portion of the case series, with no patients reporting relief with the oral formulation. In a study referenced previously that sought an intervention to predict successful motor cortex stimulation in patients with CPSP, 56.4% of patients demonstrated 40% or better pain reduction with a subanesthetic infusion of up to 250 mg of **thiamylal/thiopental** (gamma-aminobutyric acid agonists) (113). Effects, however, lasted less than one hour after discontinuation of the infusion. Another study showed that an intravenous bolus of subhypnotic **propofol** (gamma-aminobutyric acid agonist) at 0.2 mg/kg led to reductions in spontaneous ongoing pain and allodynia superior to placebo in a randomized, blinded, crossover trial of 44 patients with central pain (50% with CPSP) (115). Again, pain relief did not last beyond one hour in any of the patients studied. Given the findings in these three studies, gamma-aminobutyric acid agonists show some promise in the treatment of CPSP. Intravenous propofol, like intravenous lidocaine, has been suggested as a viable treatment option for short-term pain relief in patients with intractable CPSP (82,83).

A retrospective study of 12 patients with CPSP revealed significant differences in mean numerical rating scale for pain scores after treatment onset comparing seven patients treated with an oral **methylprednisolone** taper (1.7 ± 2.1) to five patients who had received varying combinations of typical medications used to treat CPSP (5.0 ± 1.9). This significant difference remained between the two groups at discharge from acute inpatient rehabilitation (0.3 ± 0.9 versus 4.1 ± 3.2) (116). Given the clinical and pathophysiological similarities between CPSP and post-stroke CRPS (9,35), coupled with the existence of studies demonstrating the successful treatment of poststroke CRPS with steroids (117,118), further study of the effect of steroids on CPSP is warranted.

Ineffective Treatments

In small studies, **reboxetine** (selective norepinephrine reuptake inhibitor) and **citalopram** (selective serotonin reuptake inhibitor) were deemed ineffective treatments of CPSP (119,120). In the reboxetine trial, the authors concluded that perhaps the combined action of serotonin and norepinephrine is needed to activate the endogenous brainstem pain-inhibiting system, thus explaining the selective norepinephrine reuptake inhibitor's lack of efficacy (119).

In a small study, seven patients with central pain (three due to stroke) received **topiramate** (anticonvulsant) without meaningful relief (121). The small size and mixed population of this study may result in an inability to completely exclude topiramate's utility in CPSP; however, the lack of value in the treatment of other neuropathic pain disorders (122) suggests a lack of efficacy in CPSP as well.

Levetiracetam (anticonvulsant) was studied in a randomized, blinded, placebo-controlled study consisting of 42 patients who received a maximum dose of 3000 mg per day (123). There were no improvement in primary or secondary outcome measures comparing drug to placebo, and the authors concluded that levetiracetam is not effective in the treatment of CPSP.

Dextromethorphan (NMDA antagonist) was given at 40.5 mg and 81.5 mg per day in a randomized, blinded, crossover, placebo-controlled trial of 21 patients (9 with CPSP) (124). No effect compared to placebo was noted for the entire population or the CPSP subgroup. Of note, this study used much lower doses of dextromethorphan compared to other studies, where efficacy was established in various types of neuropathic pain (125).

A blinded, crossover, placebo-controlled study of 20 patients with CPSP who received 8 mg intravenous **naloxone** (opioid antagonist) or saline reported equal numbers of patients reporting improvement in the treatment and placebo groups and four patients improving with both the naloxone and saline administrations (126). Additionally, no patients reporting improvement (irrespective of intervention) remained improved beyond the day of infusion. There was also no difference in percent change in visual analog pain scale score between the groups. The authors concluded that intravenous naloxone is of no value in alleviating the pain of CPSP.

The pharmacologic treatment of CPSP is often based on trial and error until pain relief is found, and the best results are usually achieved with a combination of several drugs (9). Furthermore, pharmacologic treatment typically results in only a subtle improvement in pain intensity. One review adds that enthusiasm for pharmacologic management in CPSP should be tempered, as only a fraction of patients benefit from drugs and those that do benefit will achieve only partial relief (84). Despite this, the utility of these agents should not be called into question as a clinically meaningful reduction in pain extends beyond numerical values to include the patient's subjective experience and the percent reduction in pain (which varies depending on the patient's baseline pain level) (127).

Nonpharmacologic Management

Historically, the use of simple desensitization techniques, such as rubbing painful areas or applying materials of different textures (cotton, wool, light sandpaper), has been recommended to treat neuropathic pain symptoms including CPSP. There are no clinical trials using these techniques. However, in complex regional pain syndrome, a diagnosis where maladaptive central processes are implicated, "pain exposure" physical therapy has been trialed sucessfully in a small number of patients (128). Application of this strategy to CPSP has not been attempted. In theory, exercise therapy might reduce pain-related symptoms by improving strength, flexibility, and functional use of the impaired body areas or limbs. Whether exercise therapy improves function and the emotional response to pain or directly reduces pain perception is not clear. Further, the overall efficacy of exercise therapy for the treatment of CPSP is unknown. Nevertheless, exercise therapy remains a key component of a comprehensive approach to the management of central pain.

Mirror therapy has been used to treat pain after stroke. In this therapy, the patient practices bilateral functional movements with the painful limb behind a mirror, so that only the reflected image of the unaffected limb is seen by the patient. This approach has shown efficacy in CRPS type 1 following stroke (129,130), but there are no trials assessing the efficacy of mirror therapy in CPSP (131).

Transcutaneous Electrical Nerve Stimulation (TENS)

In a single, unblinded cohort trial of patients with CPSP, application of either high-frequency (70 Hz) or low-frequency (2 Hz) TENS had positive clinical effect in only 4 of 15 patients (pain reduction 20% to 57%); only 3 of these patients reported long-term improvement. Other patients either did not respond or had a transient *increase* in pain of 20% or more.

Motor Cortex Stimulation

There has been a growing interest in the use of invasive and noninvasive methods of neuromodulation to treat chronic pain. Neuromodulation involves the therapeutic alteration of neurological activity either through stimulation or medication, both of which are introduced by implanted devices. The use of implanted cortical stimulators to treat CPSP has been explored for years. Tsubokawa and others have shown that pain relief can be achieved best when the stimulating epidural electrode is placed overlying the primary motor cortex (M1) rather than over the sensory cortex (132). Because of this finding, these researchers suggested that central pain is a result of aberrant plastic changes in the inhibitory receptive fields of the sensory cortex such that nonnoxious input can stimulate nociceptive neurons, centrally. It is theorized that motor cortex stimulation might block these aberrant connections through either orthodromic stimulation via motor neuron pathways to S1 cortex or through antidromic stimulation of sensory fibers that project transcortically from S1 cortex (133). However, positron emission tomography (PET) imaging during motor cortex stimulation does not demonstrate any increase in regional blood flow in either M1 or S1 cortex. Rather, there is an increase in blood flow within the ventrolateral thalamus, which has rich connections with both precentral and postcentral cortical regions (134). Goto and colleagues used diffusion tensor imaging to evaluate white-matter fiber tract integrity in patients with CPSP and noted that, when thalamocortical tracts were intact, pain reduction with motor cortex stimulation was more likely effective (135). PET imaging also demonstrates that during motor cortex stimulation, there is increased regional blood flow in the medial thalamus, anterior cingulate gyrus, upper brainstem, and contralateral insular cortex. These structures make up portions of the lamina 1 spino-thalamo-cortical (interoceptive) pathway and are critical in pain processing (see Figure 17.1). Thus, stimulation of the motor cortex might reduce CPSP-related pain through orthodromic or antidromic stimulation of the thalamus along thalamocortical pathways; this could

then modify pain processing activity within the anterior cingulate, brainstem structures, and insular cortex (135,136). Such cortical changes may be gamma-aminobutyric acid-mediated because patients who respond to an intravenous propofol infusion (gamma-aminobutyric acid A agonist) also respond well to motor cortex stimulation. It has also been proposed that motor cortex stimulation modulates pain through descending cortical spinal pathways that connect to dorsal horn structures (135).

Motor cortex stimulation is delivered by an electrode implanted on the dura overlying the precentral gyrus contralateral to the painful side of the body or directly on the M1 cortex (136,137). The electrode lead is tunneled subcutaneously to the chest region, where it is attached to a pacemaker-like pulse generator (137). Tsubokawa and associates achieved a 67% to 73% rate of clinically important reduction in CPSP symptoms with motor cortex stimulation, defined as at least a 50% reduction on the VAS (132,133). Most patients had effective pain relief for more than a year, though some had pain recurrence. In another study, motor cortex stimulation produced an average pain reduction of 83% in a small cohort of 32 central pain patients of which 11 had CPSP (138). Katayama and colleagues achieved a 60% reduction in pain for more than 2 years in nearly half the patients they implanted with a motor cortex stimulator (139). In a review of the existing literature, Fontaine and others noted several complications with cortical stimulator implantion, including infection (5.7%), hardware failure (5.1%), and postoperative seizures without long-term epilepsy (12%) (140). They concluded that, although motor cortex stimulation is not without risk, 54% of patients implanted will report a positive response to therapy, with the best responders being patients carrying the diagnoses of CPSP and trigeminal neuralgia (140).

The decision to implant a cortical stimulator should be reserved for patients whose clinical presentation suggests that they will respond positively to this treatment. For example, CPSP patients with little or no motor impairment respond best to motor cortex stimulation (139). Additionally, CPSP patients with a normal temperature sensory threshold within the affected cutaneous regions also respond better to motor cortex stimulation (141). Finally, as mentioned previously, pain relief with intravenous infusion of propofol, a gabaergic medication, is predictive of a positive response to motor cortex stimulation (137,142,143). Pain relief with intravenous ketamine has a similar predictive value to propofol; however, those who have favorable pain relief from intravenous morphine do not respond well to motor cortex stimulation (144).

Deep Brain Stimulation

Deep brain stimulation for CPSP has also been explored, but there is conflicting evidence with regard to efficacy. Owen and associates implanted 15 patients with CPSP that resulted from either cortical or subcortial stroke. They targeted both the periventricular grey (PVG) and the VPL thalamus and initially tested efficacy postoperatively with an external pulse generator. If pain relief was achieved, the pulse generator was internalized and either PVG or VPL was stimulated, depending on clinical response. In this study, 70% of implanted patients responded with a 43% to 54% reduction in visual analog score (145). Conversely, Rasche and colleagues found only an 18% response rate to deep brain stimulation of the PVG or VPL (2 patients out of 11 with CPSP); some nonresponders reported an increase in pain with the intervention (146). PVG, rather than VPL, may be the preferred implantation site for deep brain stimulation. This has been suggested because stimulation in the PVG reduces low-frequency field potentials in the thalamus to a higher degree than stimulation in the VPL, which corresponded to more robust pain relief (147). In a single case study of PVG deep brain stimulation for CPSP, the patient reported significant pain reduction along with improved sensory function, including resolution of allodynia and better sensory discrimination (148). It has also been suggested that the centromedian thalamus may be an appropriate site for deep brain stimulation, as it is involved with the motivational aspects of pain, but this has yet to be tested clinically (149).

Noninvasive Neuromodulation

The invasive nature of motor cortex stimulation and deep brain stimulation limits their clinical application due to the risks associated with surgical implantation. An alternative is to use noninvasive techniques to stimulate the motor cortex for CPSP management. Repetitive transcranial magnetic stimulation (rTMS) uses a magnetic coil to deliver electromagnetic pulses over the cranial surface that induce local currents in the underlying cortex and can induce a peripheral motor evoked response. In patients with CPSP, rTMS can provide transient pain relief when delivered over the motor cortex contralateral to the painful region. rTMS over the motor cortex is superior to stimulation over the sensory cortex, premotor cortex, or supplementary motor cortex in patients with CPSP (141). Both high-frequency and low-frequency rTMS have shown efficacy, and provision of several daily sessions of rTMS can result in a longer duration of pain relief (142,150–153). Given that pain relief in CPSP after rTMS typically only lasts a few hours, its utility is limited. Further research is needed to explore the best stimulation frequency, intensity, and location to improve duration of pain relief. Additionally, the investigation of pharmacologic agents to be used in conjunction with rTMS to enhance efficacy is warranted (154).

Transcranial direct current stimulation (tDCS) is another method that can be used to provide noninvasive motor cortex stimulation. This simple method involves the delivery of 1 to 2 mA of direct electrical current, with one electrode over the motor cortex and the other typically placed on the forehead just above the opposite orbit. Using this device, Fregni and colleagues have effectively reduced pain in patients with fibromyalgia and with central pain after spinal cord injury (155,156). tDCS has not been studied for the treatment of CPSP, but it would be appropriate to trial the application of anodal stimulation over the motor cortex contralateral to

CPSP symptoms. If effective, tDCS might have more utility than rTMS, because tDCS is relatively safe and easy to use. With proper education, patients could use tDCS at home.

Clinical Correlation in Treatment

A careful history and physical examination are extremely important in monitoring response to treatment in patients with CPSP. The documentation of specific subjective and objective exacerbating and alleviating phenomena is vital from encounter to encounter. For example, detailed documentation of a patient's subjective complaints of an inability to wear a bra and shower due to allodynia, coupled with objective demonstration of light touch and cold allodynia in the affected upper and lower extremities, serves as an excellent clinical baseline. After treatment initiation, this patient returns and reports no subjective improvement in symptomatology, and the practitioner sees no improvement in visual analog pain scale score. During this return visit, however, the practitioner recognizes that the patient now presents to the clinic tolerating a bra, inquires and learns about her newfound ability to tolerate showering, and demonstrates the alleviation of light-touch allodynia in the arm and leg while noting persistence of only the cold allodynia in the upper extremity alone. Referring back to prior documentation, the practitioner realizes the significant improvements achieved based on these new clinical findings despite the patient's poor insight into these improvements and the lack of change on conventional pain measures. Without the specific baseline clinical documentation, the efficacy of the treatment may have been missed and led to an alteration in management. Instead, in this clinical scenario, the practitioner would obviously continue treatment, consider dose escalation, and/or add adjunctive therapies. In addition to a detailed history and physical specific to each patient, the use of detailed pain measures like the short-form McGill Pain Questionnaire (157) to monitor change relative to treatment has utility in the clinical as well as the research settings.

CONCLUSION

CPSP continues to be a poorly understood potential consequence of stroke. To improve our understanding of this diagnosis, reliable, valid, user-friendly diagnostic criteria that can be applied in clinical and research settings must be developed. Here, we propose new diagnostic criteria for CPSP (Table 17.6). These new criteria seamlessly meld the existing diagnostic criteria and grading system proposed by Klit et al., as displayed in Tables 17.1 and 17.2 (9), while also altering and adding some important components. The melding of the scheme proposed by Klit et al. leads to easier diagnosis of CPSP, as it creates a more straightforward set of diagnostic criteria. The proposed criteria alter the existing criteria in that they separate the **objective negative** and **objective positive sensory signs** into *different* components. The rationale for this is based on the information discussed in the "Clinical Characteristics" section of this chapter. According to the studies described earlier, some form of sensory deficit (**objective negative sign**) can be demonstrated in all patients with CPSP, whereas allodynia or hyperalgesia (**objective positive signs**) are not necessarily demonstrated in all patients with CPSP. Hence, the criteria were altered accordingly, making the demonstration of somatosensory deficits fundamental to the diagnosis of CPSP while making the demonstration of allodynia or hyperalgesia on physical examination more confirmatory. Finally, existing criteria do not include **subjective** reports of allodynia; thus, this component was added to the proposed criteria. As discussed in the "Clinical Characteristics" section, a patient with CPSP will complain of pain, but might not report allodynia (**subjective positive symptom**). Again, the subjective report of allodynia was added as a confirmatory component of the proposed diagnostic criteria. Of course, this new set of criteria must be validated before being utilized in clinical or research settings.

The establishment of universally agreed-upon, validated diagnostic criteria will add much-needed reliability to the study of CPSP. This will ultimately help with the determination of pathophysiologic mechanisms and, subsequently, the development of pharmacologic and nonpharmacologic treatments. For example, there are reports that lesion location actually affects pain quality in patients with CPSP (158–160). Exploring such a concept may lead to further elucidation of the pathophysiology that underlies CPSP and, potentially, other central pain processes. Additionally, the exploration of such a concept may lead to changes in treatment planning, as lesion location might guide a clinician to trial one

TABLE 17.6 New Proposed Diagnostic Criteria for Central Poststroke Pain

Probable CPSP: Criteria 1–3 all fulfilled

Definite CPSP: Criteria 1–3 all fulfilled **PLUS** 4 **OR** 5 fulfilled

1. Pain in a body area(s) corresponding to and beginning after a radiographically confirmed stroke damaging the spino-thalamo-cortical pathway
2. Objective demonstration of somatosensory deficits (touch, cold, warm, and/or pinprick) surrounding or within the painful body area(s)
3. Elimination of other diagnoses that may better explain symptoms (nociceptive, peripheral neuropathic, psychogenic)
4. Subjective report of allodynia to touch and/or thermal (cold or warm)
5. Objective demonstration of allodynia to touch and/or thermal (cold or warm) **OR** hyperalgesia to pinprick

therapeutic option over another. This level of exploration, however, requires consistency among trials in the form of patient identification and accurate diagnosis in the form of clear, universal diagnostic criteria. Regarding treatment, much remains to be discovered in CPSP. The study of promising pharmacologic and nonpharmacologic treatments is warranted. These include, but are not limited to, serotonin/norepinephrine reuptake inhibitors, zonisamide, tramadol, tapentadol, methylprednisolone, intrathecal baclofen, "pain exposure" physical therapy, rTMS, and tDCS.

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18

Visual, Ocular Motor, and Vestibular Deficits

Judith E. Goldstein, Nicole C. Ross, Daniel R. Gold, and Amir Kheradmand

Stroke commonly impacts the visual and vestibular systems. These sensory systems play critical roles in mobility, communication, and daily activities, and deficits in either (or both) systems can be quite disabling. Rehabilitation of these impairments can substantially improve quality of life, yet these areas are often less emphasized in stroke rehabilitation than other sequelae of stroke. In this chapter, we review the anatomic and physiological basis of these systems, the impact of stroke on vestibular and visual function, and rehabilitation approaches.

VISUAL SYSTEM

Estimates of the proportion of stroke survivors with visual manifestations range from 30% to 50% (1,2). The variability of effects on the visual system alone is remarkable, including, visual field loss, oculomotor deficits, visual perceptual problems, and reduction in visual acuity (VA). In isolation or together, these deficits can cause problems with mobility, reading, driving, socialization, and depression. It is the impact on the visual processing system that causes loss of *visual ability*—the ability to perform vision-mediated tasks, comfortably and independently. In the absence of spontaneous resolution of deficits, a carefully tailored rehabilitative plan of low vision therapy can be instrumental in regaining visual ability, and a safe, more independent life state (3,4). Despite the potential devastating impact on visual ability function, there is often a delay in identification of visual deficits and referral for low vision rehabilitation (LVR). This is in part because of a lack of awareness of LVR services and systematized treatment approaches as are present in language, speech, and motor rehabilitation (5).

In reviewing visual and oculomotor deficits, we will describe the epidemiology, natural history, impairments, and the impact on visual ability, and rehabilitative and/or restorative therapies in stroke-related vision loss. Like most other aspects of the neurologic system, the location and etiology of the lesion generally assists in identifying the type and magnitude of the deficit. For the purposes of this chapter, we will restrict the discussion to postchiasmal loss, which typically involves interruption to the middle or posterior cerebral arteries or vertebral basilar circulation. Most notable, and familiar to readers, is infarct or hemorrhage affecting the posterior cerebral artery that nourishes the occipital lobe, also known as the visual cortex. Stroke causing damage to the occipital lobe is the most common cause of homonymous hemianopia-visual field loss in both eyes to the same side. Approximately 30% of stroke admissions are found to have homonymous hemianopia, hemi-inattention, or visual neglect (6–8), and 70% of all hemianopias result from stroke. Hemianopia is likely the most debilitating and common visual complication of stroke that must be addressed during rehabilitation.

Although therapies for speech, language, motor disorders, and cognitive dysfunction are universally accepted and implemented as part of stroke rehabilitation, vision–sensory and oculomotor disorders are still widely neglected. The most likely reason is that rehabilitation strategies in vision have shown limited success (5). They require lengthy therapy of a typically unmotivated cohort and, when successful, often entail a specialized clinical skill set and rehabilitation team that is readily accessible in only a handful of hospitals and facilities.

KEY AREAS OF VISUAL IMPACT

Homonymous Visual Field Disorder (HVFD)

HVFDs represent a loss of vision in both eyes on the same side; because of the decussation of fibers occurring at the chiasm, the effective visual field loss is contralateral to the side of the lesion (Figure 18.1). The term "hemianopia" is typically included in the description of visual field loss secondary to cortical stroke and implies loss to one-half of the vision; however, loss may not necessarily be complete, but rather quadranopic, partial, or even relative (see Figure 18.2) (9). Depending on the location of the stroke, the symmetry of the loss between the eyes will vary. Typically, more anterior lesions result in incongruity, whereas posterior damage to the radiations result in more congruous loss. Although HVFDs are not solely vascular in origin, 70% of all occurrences are a result of arterial infarctions (10). The remaining nonstroke causes include head trauma, brain tumor, neurosurgical procedures, and multiple sclerosis (11).

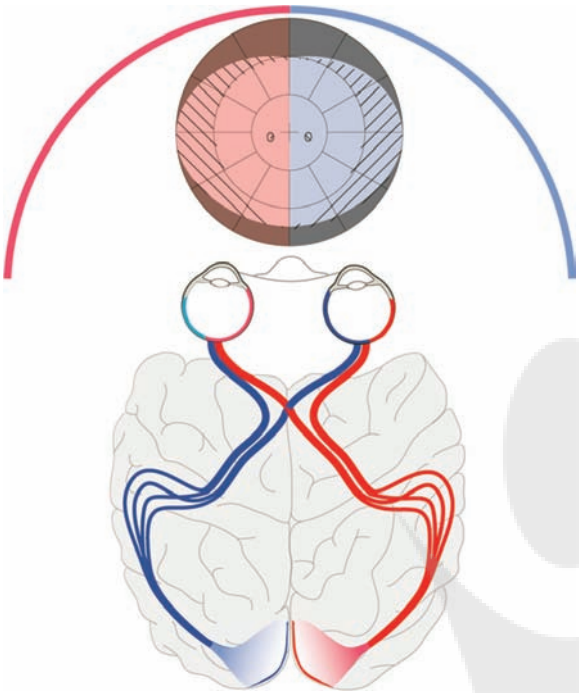

FIGURE 18.1 The visual pathway and corresponding visual fields. The red color highlights the left visual field, which is projecting on the temporal retina of the right eye and the nasal retina of the left eye. Those areas highlighted in blue represent information from the right visual field. Hatched areas represent the portions of the visual field, which are only viewed by the nasal retina of one eye, known as the temporal crescents. At the optic chiasm, right and left visual space is segregated with fibers from each nasal hemiretina passing into a single corresponding optic tract (left and right, respectively). Fibers in each tract connect through the lateral geniculate nucleus and continue through the optic radiations to terminate at the striate cortex in the occipital lobe. Any lesion to the right post chiasmic optic tract, or any of its terminal projections, will result in an homonymous left visual field defect.

Source: Reprinted with permission from Dr. Eli Peli, Schepens Eye Research Institute.

HVFD typically manifests itself as a lack of response to visual stimuli presented on the affected side. It is essential for patients, families, and caregivers to understand that in HVFD, the vision loss is in both eyes on the same side as opposed to loss in one eye. Approximately 70% of all HVFD cases are thought to have central visual field sparing of five degrees or less (see Figure 18.3) (5). This is commonly referred to as macular or foveal sparing and provides for what is typically considered normal VA or 20/20. Some controversy exists as to whether macular sparing is real, the relevance of it, and whether it represents scanning during VF testing (i.e., perimetry) and rather is an artifact of testing (12,13). Macular sparing does not help predict the location of the lesion within the retrochiasmal visual pathway; however, it does provide significant benefit in tasks where VA is a strong predictor of visual ability such as reading (12–15).

When a stroke impacts both the parietal and occipital lobe (especially on the right side), an important distinction must be made in the continuum between HVFD with and without unilateral spatial inattention (USI) (see Visuospatial Perception Deficits below). The complicating factor of inattention may change the prognosis and rehabilitation training in such activities as reading, mobility, safety, and driving.

Reading

Reading is the most common complaint in patients seeking LVR services (16) and is a common concern among patients with HVFD. Paracentral visual field or, more appropriately, preview area, along with VA has been correlated with impaired reading (17). For efficient reading, it is necessary to scan ahead using the preview area to assist with planning for rightward reading saccades (18,19). During reading from left to right, the necessary window for fluent reading extends three to four characters to the left of fixation and seven to eleven letter spaces to the right of it (this can also be translated to 5 degrees to the right of fixation) (20). Right-sided loss will typically cause greater reading impairment than left-sided loss in the absence of inattention or neglect, as the former forces reading into the scotoma or blind area and eliminates the possibility of anticipatory scanning. This may result in reading errors and reduced reading speed (5). Right-sided loss and problems in reading are also known as hemianopic alexia (21). This disorder is evident through disrupted eye movement scanpaths, prolonged fixations, inappropriate small amplitude saccades to the right, and saccadic regressions (19). Left-sided loss primarily accounts for deficits in omissions in the first letter or word on a line and is often responsible for difficulty with return eye movements to the beginning of a new line of text.

Other Functional Domains

Effects on mobility and navigation are evident early after stroke when HVFD is present. Several recent studies evaluating detection during mobility and visual–motor-related tasks in real and virtual environments have demonstrated significant impairments in object detection on the side of the field loss (22–25) such that individuals frequently bump into people, trip over unseen obstacles, spill when pouring liquids, and experience reading difficulty (26). Visual–motor skills (such as reaching and grabbing) are often impaired because of visual exploratory deficits in the blind and intact hemifield caused by inaccurate saccades and disorganized visual search patterns (27–29). In addition, impaired walking (bumping into obstacles) and impaired detection of potential hazards when driving may occur depending on the extent of the visual field deficit, presence of inattention, or other comorbidities. In the majority of U.S. states, motor vehicle laws prohibit individuals with HVFD from driving; however, there are states without visual field requirements and states with special programs that enable patients to drive with HVFD (30,31). Vision-related quality-of-life studies indicate that patients with HVFD have a significantly

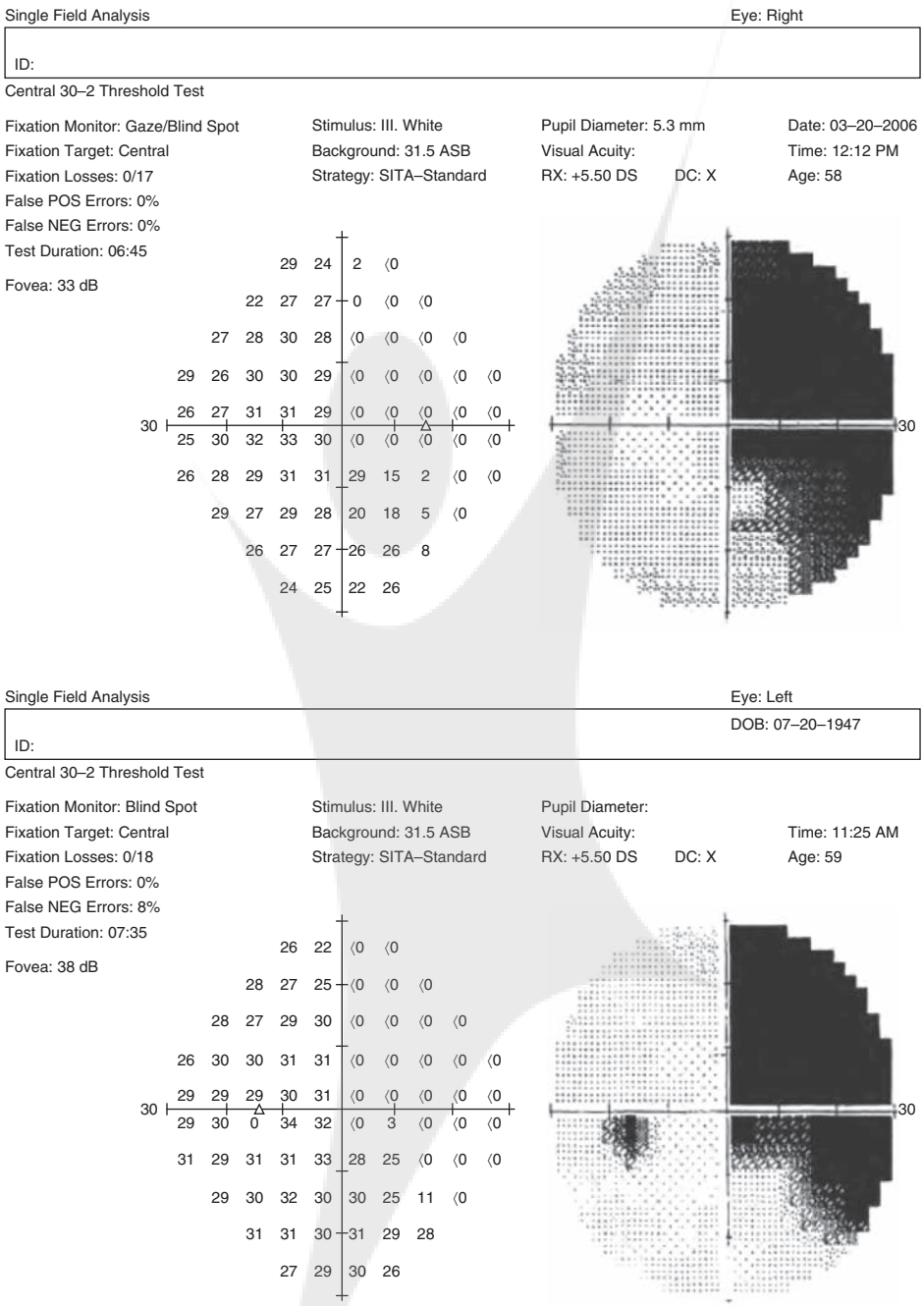

FIGURE 18.2 Incomplete right homonymous hemianopia with sparing inferiorly on the right side evaluated by Humphrey visual field.

reduced quality of life specifically with respect to social functioning, role difficulties, mental health, driving, and increased dependency on others (32,33). The consequence of driving cessation alone has significant impacts on the ability to work and maintain social networks (34). In addition, up to 48% of patients report significantly increased stress and anxiety levels when moving in crowded community environments (35). Overall, the presence of HVFD has been associated with significantly lower likelihood and increased time in achieving independence with walking and with instrumental activities of daily living (6).

VISUOSPATIAL PERCEPTION DEFICITS

In the case of stroke involving the occipital and parietal lobes, visual function may be compromised by the loss of visual field and/or the loss of visual attention because the parietal lobe is responsible for the brain's representation of personal space, or body image, and external space (36). When the secondary pathway fibers from the occipital lobe to the parietal lobe (known as "dorsal stream") are disrupted, disorders of perception, spanning the continuum from USI to visuospatial neglect may occur (37–39). This occurs most frequently

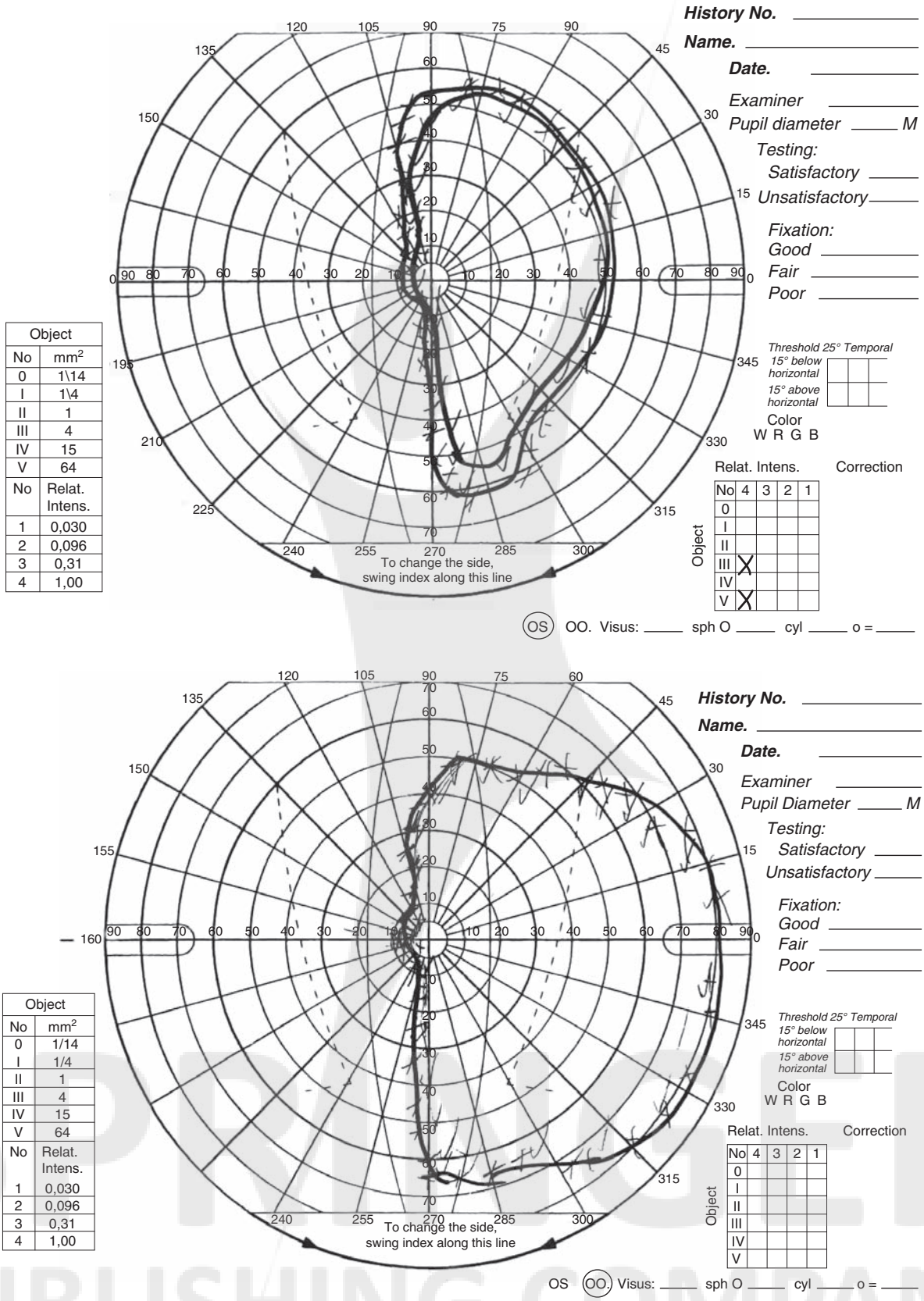

FIGURE 18.3 Left homonymous hemianopia with macular sparing evaluated on Goldman visual field for the right and left eyes respectively, to the size V4e and III4e isopters.

when there are right hemispheric lesions involving the right inferior parietal lobe. The result is reduced awareness or inattention on one's left side of the body, extending out into left visual space (40,41). A practical distinction to assist in the management of visual ability loss in these patients is to detect whether the inattention occurs in peripersonal space, which primarily tends to affect near-oriented activities (e.g., missing food on plate or failure to perform personal care on the affected side), and/or extra-personal space that causes more orientation and mobility problems (e.g., bumping into objects on the affected side when walking).

The visual evaluation after stroke requires differentially diagnosing HVFD from inattention or in some cases, the presence or absence of both. Typically, when solely postchiasmal nerve fibers extending from the retina to the lateral geniculate to the occipital lobe are compromised, the result is an HVFD that can be diagnosed by perimetry. In everyday function, these patients often retain good awareness and a self-intentioned effort at compensating for the loss (e.g., head turning or scanning to the affected side). In contrast, if the lesion occurs when fibers are traveling along the secondary pathway, occipital to parietal cortex, the result is more likely USI without evidence of HVFD on perimetry. When both pathways are involved, HVFD and spatial inattention can coexist, resulting in a bleak outlook, as disorders of perception are a poor prognostic factor for rehabilitation of stroke outcomes (41,42). The presence of inattention creates barriers in reading and mobility rehabilitation as the loss of awareness reduces responsiveness to new learning.

Diagnosing the continuum of USI to visual neglect as part of the LVR evaluation involves patient observation, testing of VA, visual fields with assessment of visual extinction, ocular pursuits, saccadic testing, and standardized paper and pencil tasks. The extinction phenomenon occurs when a patient shows awareness to a singular stimulus in the affected visual field; however, when two of the same stimuli are presented simultaneously (one in the affected and one in the intact visual field), the patient becomes unaware of the contralesional stimulus. Extinction exemplifies the variable presentation in performance shown by patients with mild inattention deficits, such that these individuals may show functional deficits when over-stimulated such as navigating in crowded unfamiliar environments but appear completely intact when walking in very familiar environments. Paper and pencil tests incorporated in the LVR assessment are consistent with the standardized battery including the line bisect test (43), Bell's test (44), and other cancellation tests. In prior reviews, the most sensitive clinical measure of neglect was a rightward orientation bias, whereas others have shown the best sensitivity from an assessment involving observation of behavior in ten everyday life situations (45).

VISUAL ACUITY

After stroke, the ultimate, best-corrected acuity, or clarity, will impact an individual's reading and mobility ability, including risk for falls (46). The level of VA loss is an important consideration in the rehabilitation plan and prognosis for improved visual function. After bilateral postchiasmatic lesions, VA declines with great variability (47). Generally, the more posterior the lesion, the more symmetrical the acuity and visual field loss. With that said, many patients retain good VA after stroke. One cross-sectional study indicated that only 13% of patients following stroke exhibit reduced VA at distance and near, and in one third of these cases, the low vision was attributable to prior ocular pathology not as a result of the stroke (48).

Measuring VA in a stroke patient can be challenging, especially in the presence of aphasia and cognitive impairment, and at times it is necessary to deviate from standard Snellen acuity testing. Portable charts with numbers can work well, as there are fewer optotypes, and verbalization of numbers in aphasic patients often provides better success than letters. Matching characters and tracing can be an effective testing method when detailed explanation can be repeated and reinforced. With severe aphasia, alternatives such as tumbling E, Landolt C, Cardiff, or even Teller VA cards (preferential looking test that takes advantage of one's natural preference to look at a bold pattern as opposed to a blank homogeneous area) can be helpful in obtaining measurable responses, although correlation to Snellen visual acuities can be poor (49). Line and letter isolation during VA measurement can also help to enhance attention during testing and limit confusion.

VA testing can be useful in distinguishing hemianopia from USI. In absolute terms, patients with hemianopia without USI may miss letters on the side of the eye chart contralateral to the lesion (e.g., letters on the left with a right-sided occipital stroke); however, when made aware that they are doing so, the HFVD patient will typically initiate looking to the left and pick up letters on the left, a behavior often applied during therapeutic activities. When assessing VA in patients with USI, reminders regarding omissions rarely result in a consistent performance in scanning into the affected area. VA measurement can also be of diagnostic assistance in spatially locating inattention effects (e.g., peri-personal vs. extra-personal space). Patients with extra-personal involvement may miss letters more so on the distance VA chart whereas personal and peri-personal impact may show greater loss when testing VA at near. Carefully evaluating patients VA at distance and near becomes that much more important for patients with USI and their caregivers, as they will often deny or be unaware of the differential effects of loss at different locations and when different level of stimuli are present.

When there is VA loss, it is helpful to understand whether VA and visual ability were intact prior to stroke, both for the purposes of understanding the presence of ocular comorbidities and expectations of refraction testing to determine the appropriate spectacle correction. In one series, 14% of patients had visual impairment that benefited from refractive correction alone (50). Improved spectacle correction, whenever possible, can assist with training of

visual processing skills, speech and language therapy, and improved safety in activities of daily living. In cases where visual field cuts are also present, it is necessary to educate the patient and family members that spectacles do not eliminate field loss; therefore, many of the problems with mobility and reading will persist even with new glasses.

EYE MOVEMENT DISORDERS

The rate of ocular misalignment and symptoms of double vision (diplopia) vary between 28% (51) and 54% (52), with higher incidence occurring with brainstem involvement. In both the studies, the majority of the cases were diagnosed with cranial nerve III palsy. In these cases, many patients experience diplopia (i.e., double vision) as the eyes maybe pointed in differing directions in primary or alternate gaze. Diplopia was reported in 38% of consecutive patients with posterior circulation stroke admitted to a rehabilitation service (53). Although up to 15% of stroke rehabilitation patients have had brain stem involvement, there is a relative lack of research in rehabilitating these cases (54). More detailed descriptions of posterior circulation oculomotor deficits are provided in Chapter 6 (Infratentorial Stroke Syndromes). When internuclear ophthalmoplegia is the predominant or only manifestation of a dorsal brainstem stroke, the prognosis is very good (55).

Reading

Double vision, that is, diplopia, secondary to ocular motor paresis causes significant reading impairments secondary to the inability to following a line of text as a consequence of disrupted eye movements. Examples of disrupted eye movements include: prolonged fixations and inability to make appropriate saccades to the next word (or next line). As a result, many diplopic patients clinically report they have discontinued or are completely unable to read without either complete or partial occlusion of the paretic eye.

Mobility and Safety

Symptomatic and constant diplopia can be disruptive to mobility safety and distressing during everyday viewing. A patient may not be able to discern the real location of the object from the two images he or she is seeing. Falls and misjudgments in reach and grasp tasks are obvious consequences of this problem. Therefore solutions to ameliorate diplopia should be a significant priority in a patient's stroke rehabilitation plan.

RECOVERY FROM VISUAL SEQUELAE

Even prior to rehabilitation, however, some individuals experience spontaneous visual recovery depending on the underlying pathology (11). In less than 10% of cases, individuals with HVFD caused by ischemia fully recover their visual field (56–58). This recovery is largely complete within the first 10 days from the time of stoke. Recovery of a partial defect occurs within the first 48 hours and is typically complete within 10 to 12 weeks (56–58). The extent of visual recovery negatively correlates with age and other comorbidities. The documented course of recovery shows that vision returns to the affected field in definite stages, starting with perception of light, motion, form, color, and lastly, stereognosis (59,60). In addition to spontaneous visual improvement, we see improvement from natural compensatory strategies that occur within the visual system; these are likely associated with some degree of cortical reorganization and individual adaptation. Possible evidence for this is in HVFD patients where fixation is directed into the blind hemifield perhaps to increase the effective size of the "seeing visual field" or scanning that occurs to minimize bumping into objects.

There is evidence that loss within damaged cortical areas is not absolute and areas that appear to be nonfunctional do in fact retain certain visual function through subcortical mechanisms (61). Given this, much effort has been placed in exploring methods to enhance adult neurogenesis and neuroplasticity (4) by stimulating and/or regenerating areas that appear deficient to enhance current rehabilitation strategies. Potential therapies, such as stem cell therapy, hyperbaric oxygen treatment, exogenous tissue engineering and brain–computer interface technologies, could hold promise and are currently being explored with respect to enhancing motor control in postischemic stroke (62,63). Additional investigations exploring potential to restore the penumbra—tissue that has been damaged by the stroke event but has not yet undergone apotoptosis—offers some promise for recovery (64). As efforts at restorative therapies continue to develop, the lack of an effective treatment has emphasized the role of rehabilitation strategies to maximize visual ability function.

REHABILITATION STRATEGIES

Visual rehabilitative strategies can be divided into compensatory optical and training approaches. As each case is unique, it is necessary to tailor therapy for the individual because of the complexity and variety of effects from stroke. To be maximally successful, these therapies should be implemented in a task-oriented approach—for example, reading, writing, navigation, etc. In coordination with other therapies, the ultimate objective of vision rehabilitation is to improve visual ability at the goal level (e.g., managing finances, shopping, personal care, etc.). Once the visual effects of stroke are diagnosed, vision rehabilitation services should be initiated. Of utmost importance is education of the patient, family, caregivers, etc. on the visual deficit, how that impairment affects function, and the type and extent of support needed at discharge. Education on driving resumption is critical for stroke patients with vision impairment, assuming that they were driving prior to admission. Regardless of state law, patients with new onset visual field loss, spatial inattention or diplopia should defer any driving until they have been further evaluated and cleared. Vision rehabilitation can be provided in a continuum starting with inpatient moving to outpatient, with success often dependent on the degree of

nonocular comorbidities. Early intervention can be considered for enhancing safety (e.g., walking with compensatory strategies) and visual comfort (e.g., prism or occlusion for double vision).

Optical Approaches for Acuity Loss and Diplopia

The Role of Maximal Spectacle Correction

Decreased VA may exacerbate the impact of other impairments on overall disability (65). Although VA often remains intact after stroke, every effort should be made by the inpatient team to ensure that stroke patients have and wear their glasses as they would have habitually prior to the stroke (e.g., most patients over the age of 40 require reading correction and thus would need to use their reading spectacles for all near tasks during their therapies). Careful refraction with a trial frame should be performed to ensure that best-lens correction is obtained for both distance and near. Although refraction will not address postchiasmal HVFD loss, it is possible that patients were not maximally optically refracted in their distance or near correction prior to the stroke. To assist with clarity and comfort and enhance function at near, a stronger or weaker power in the bifocal along with a directed, well-placed light source and appropriate material positioning will be beneficial. Prescribing distance only glasses should be considered when navigation is impaired from visual field and gait effects. When walking down steps or off curbs, a bifocal can have the effect of altering perception of depth, which may further impair safe mobility. Separate spectacles for mobility and reading may be the most advantageous solution with regard to safety, although patient cognition, memory and tolerance may dictate the most effective strategies.

Optical-Based Solutions for Diplopia Resolution

The presence of diplopia, or double vision, because of ocular misalignment can be visually disturbing to the patient and can interfere with their progress in other aspects of their safety and care during their inpatient and outpatient clinical care. Partial or complete occlusion of the paretic eye may improve reading ability and/or comfort. Alternating patching is a quick, simple solution that can minimize visual discomfort without risk of sensory deprivation in an adult patient. This approach may also be appropriate for mobility tasks; however, this is often a less than acceptable solution, as patients lose stereoscopic/depth cues when functioning with one eye only.

Alternatively, in some cases, the diplopia can be resolved in primary gaze with the use of a prism. In this manner, a prism is used to shift the location of the image to account for any deviation in the position of the eyes. In this case, careful measures of ocular deviation, prism type, and prism placement must be carefully considered. Depending on the nature of the oculomotor impairment, the ocular deviation may improve either partially or completely. Given that the ocular deviation may change over time, Fresnel press-on temporary prisms are often prescribed, such that the prism amount can be changed throughout the course of recovery and limit the added expense of frequent spectacle changing. Use of Fresnels creates optical aberrations, which unfortunately do degrade VA and contrast sensitivity through the prism, which is proportional to the amount of prism power prescribed (66,67). In lieu of patching, limited use of prisms can be prescribed early on after stroke depending on the individual patient needs.

Optical and Rehabilitation Aids for Those With Reduced Visual Acuity

The use of low vision aids incorporating magnification can be of some assistance when VA is not spared or if VA loss was present prior to stroke. Moderate-powered reading lenses and magnifiers may be of use for spot-reading purposes (e.g., mail, bills, and medicine bottles), understanding that, if an HVFD is present, tracking and fixation may complicate continuous reading. Video magnifiers, or closed-circuit television (CCTV) provides magnification, enhanced contrast, and scrolling of the printed material to improve visibility and, in the case of eye movement disorders, improve one's ability to accurately follow a line of text (68). Video magnification is also now manufactured in a portable fashion, providing greater flexibility for affected individuals, especially those returning to work.

Technology has advanced to the degree that visual and auditory support through screen reading can further enhance a person's overall function. Several e-book readers offer text-to-speech conversion. Specialized software applications, such as Zoom Text Kurzweil 1000, now provide magnification of computer screen information, including both icons and text. The speech output component can read documents at varying speeds, like e-mail and Web pages. These approaches can be most effective in cases where the visual ability function benefits from augmentation with auditory processing. In a vocational environment, this can reduce fatigue and increase work efficiency in a visually impaired individual.

Focused lighting and proper illumination is another treatment strategy that is often overlooked in the performance of activities of daily living, especially reading. Several types of lighting are now available, including full-spectrum, high-intensity, and halogen. Careful selection and positioning of appropriate lighting can be useful in the overall improvement of daily functioning, including reading in patients with reduced vision secondary to ocular pathology.

Optical Treatments in HVFD and USI

Optical approaches aim to improve mobility function in patients with HFVD by improving detection performance of potential obstacles located on the blind side. As of now, few optical approaches have been developed to improve reading function in these patients. These differing spectacle designs attempt to either relocate the field of view of the visual image or to expand field of view (69). Prismatic glasses have most commonly been employed as a rehabilitative device for HVFD. Prisms, in this approach, are used to

shift the image of objects located within the blind hemifield to the seeing field. This differs from the approach of using prisms to ameliorate diplopia. Different configurations of prismatic glasses can provide either visual field relocation or visual field expansion. Visual field relocation results in exchanging visibility of parts of the blind field for parts of the seeing field whereas visual field expansion is a perimetrically measurable widening of the visual field (70). Both approaches are aimed at improving mobility, navigation, and awareness rather than reading. Visual field relocation is typically achieved with bilateral sector prisms (discussed further below) and reflecting mirrors. If the prisms cover the entire field of view (as in full-field bilateral yoked prisms) neither expansion nor relocation occurs.

Visual field expansion can be created by inducing binocular visual confusion—the placement of different images in the same position in visual space. Confusion is achieved by taking an image from the blind hemifield in one eye and superimposing it onto the seeing hemifield in the other, this is typically created with many unilateral prism designs, or partially reflecting or dichroic mirrors. As the use of mirrors is relatively uncommon in clinical practice, we will limit our discussion to prismatic spectacle designs.

Yoked Prism Spectacles

Full-diameter binocular prisms, or yoked prisms, were among the first prismatic spectacle designs to be developed (71,72). Typically, a prism of approximately 10 to 20 diopters with the base toward the defect can be placed in training goggles or ground into spectacles, causing shifting of the image by 5 to 10 degrees respectively into the seeing field (Figure 18.4). This technique assumes that patients do not neutralize the effect by making compensatory eye movements of 5 to 10 degrees. The effect of yoked prisms on normal individuals is a displacement of an image or space toward the apex of the prism causing an initial disagreement between the visual and motor systems, which, for example, causes errors when trying to reach for an object. Within just a few attempts of making errors, conscious correction occurs and the accuracy of motor judgment is restored, this is often termed prism adaptation. When prisms are removed from normal subjects, reaching inaccuracies of the same magnitude that occurred initially results, however, to the opposite side. Again, after a few attempts, spatial realignment occurs. Much work has been done with yoked prism placement in patients with USI with the underlying theory that these patients' perception of "straight ahead" has been shifted to the right (73). Using base-left yoked prism spectacles shifts the image to the right, thus potentially alleviating the disconnect between the objective and perceived "straight ahead" in the patient with visual spatial inattention or neglect. In some cases, the perceptual effects of yoked prism placement persisted up to 2 hours after removal of prism goggles, though the results are quite variable (74). Although several reports emphasize the usefulness of this technique as part of rehabilitation training in practice, the beneficial effect on activities of daily living from yoked prisms is individual, uncertain, and unsustainable in many.

FIGURE 18.4 Yoked prism spectacles of 18 prism diopters, bases are directed to the left for left homonymous hemianopia and/or left inattention.

Source: Reprinted with permission from Joe Nelson, Xtreme Optics Inc.

Optical Visual Field Relocation Strategies

Yoked bilateral prisms have also been fitted for patients with HVFD in the form of sector prism segments (covering only part of the spectacle lens) (Figure 18.5). Prismatic powers of up to 30Δ (75–77), but usually under 20Δ (6), have been prescribed. In this design, each prism segment covers nearly one half of the spectacle lens and is offset by 1 to 6 mm from pupil center into the blind hemifield (75–79). For a patient with left HVFD, one prism segment is placed base-left (base out) into the temporal half of the left lens, and the other prism segment is placed base-left (base in) on the nasal half of the right lens.

The patient is instructed to look into the prism segments to detect obstacles on the blind side. It has been suggested that the primary intent of the bilateral segment prism spectacle is to reduce the amplitude of scanning movements

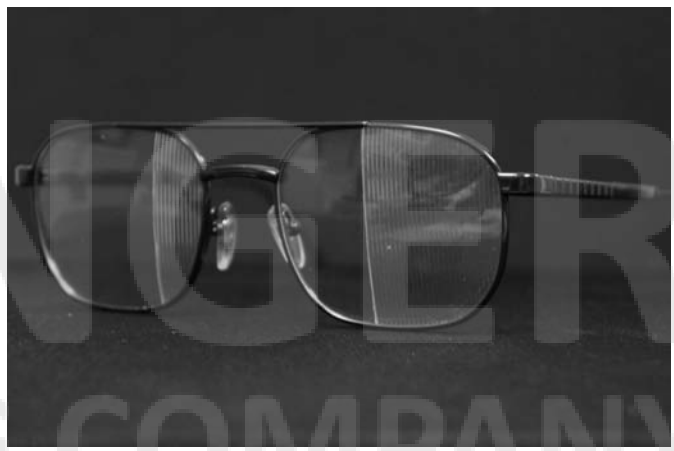

FIGURE 18.5 Bilateral sector prism spectacles utilizing a 20-prism diopter Fresnel prism, placed on the left portion of each spectacle lens. Bases are also oriented to the left for a patient with left homonymous hemianopia.

necessary to detect objects in the blind field (79). This design is only helpful if the patient actively looks into the prism (as the prisms are mounted on the side of the blind hemifield). There is no effect in primary gaze or when a gaze is shifted to the seeing side. The other shortcoming to the use of bilateral segment prism designs is the optical scotoma induced (in the binocular visual field) when looking into the prism. Images from the prism obscure those within the central area of the seeing hemifield creating a scotoma in the physical space. This optical scotoma is referred to as a prism apical scotoma (70) or "Jack-in-the-Box" scotoma and occurs at the apex of any prism (80).

It is important to emphasize that one of the limitations in this treatment strategy is that it requires intentional, self-directed scanning into the affected field/prism, which can be difficult in patients with inattention and cognitive impairment. In addition, the scotoma induced by the prism jump at the transition of lens into prism, causing the jack-in-the-box phenomenon, can be disconcerting to the patient (70). In one clinical trial using Fresnel prisms binocularly in stroke patients with HVFD or unilateral visual neglect, improvement of visual perceptual test scores were evident; however, they did not generalize to improvement in activities of daily living (6).

Optical Visual Field Expansion Strategies

Monocular sector prisms expand the field of view as scanning occurs into the blind field. The Fresnel prisms are placed in a very similar fashion to the binocular prisms, except that only one lens is fitted (76,81). Unlike bilateral sector prisms that only provide visual field relocation, unilateral sector prisms may provide visual field expansion through binocular visual confusion when looking into the prism. However, the patient will also likely experience central diplopia (82), which may deter the patient from looking into the prism. It is both the confusion and diplopia that make this treatment strategy less than desirable and should be avoided in cognitively impaired individuals. However, Gottlieb et al. (83) suggest that implementing the prism in this way can train and encourage a patient to scan toward the blind hemifield, although no formal study or evidence has been published in this regard.

A more promising approach to field expansion is through the use of monocular peripheral prism segments (see Figure 18.6) that are restricted to the peripheral field (superior, inferior, or both) of the lens (69). Therefore, obstacles within the blind hemifield can be detected using the patient's peripheral vision without the bothersome central diplopia present in other unilateral designs. However, although the peripheral prisms expand the accessible visual field immediately on first application, the perceived direction of objects detected through the prism is incorrect, as in all prism designs. When a patient detects an obstacle through the prism, he or she is instructed to turn his or her head and look at the object directly using the clear interprism area of the spectacle lens. The peripheral prism of 40 or 57 prism diopters is placed monocularly with base in the direction of the HVFD across the vertical midline of the spectacle lens, above and below the visual axis. The prism expands the field 22 to 30 degrees, depending upon the power utilized.

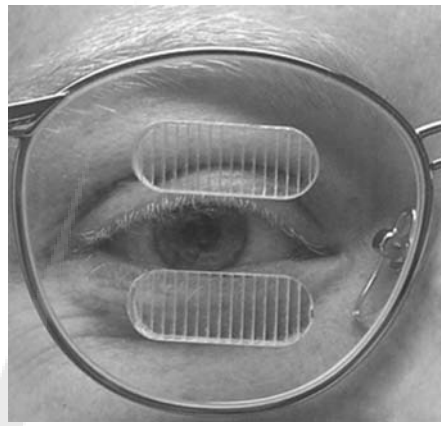

FIGURE 18.6 Monocular peripheral prism correction for visual field expansion, placed on the right spectacle lens for a patient with a right homonymous hemianopia.

Practically, the prisms enable individuals increased detection of obstacles above and below the line of sight, such as open cabinets or a trash can on the floor. The ability to detect objects in areas of visual field expansion provided by peripheral prisms has been assessed using conventional kinetic perimetric techniques (69,84–86), and in more complex viewing environments (87). In addition, improvements in mobility, especially in unfamiliar situations (88) and improvements in activities of daily living (86) have been reported. Like all optical relocation and expansion strategies, this approach requires good cognition as well as patient motivation and training.

Saccadic Training for Homonymous Hemianopia

Saccadic Training Treatment for Visual Exploration

Eye movement and scanning training strategies arose from exploratory work analyzing the eye fixations of patients, using computer-based apparatus, looking at simple patterns (89) and natural images (90). Patients concentrated gaze toward their blind side in both cases. This behavior potentially represents a compensatory strategy in HVFD; by deviating fixation into the blind field, more of the visual scene is brought into the seeing hemifield. In addition, the saccadic eye movements and visual search techniques were found to be slow, less regular, and inaccurate in patients with HVFD when asked to find a target within their blind field (27). Various fixation and saccade parameters seem to correlate with increasing lesion age but not its location or size. This may reflect the evolution of a compensatory eye movement strategy (90,91). Forty percent of hemianopic patients show dysfunction in saccadic activity, number of fixations, and, ultimately, scanpaths found in both the blind field and unaffected field, leading to longer search times (92). Scanpaths are

series of saccades and fixations undertaken when viewing a structured scene. Functionally, this translates to reduced efficiency with navigation and visual exploration tasks, such as driving, crossing the street, bumping into objects, and finding objects on a table. This suggests that patients with HVFD do not naturally or adequately compensate for their visual field loss with eye movements or eye scanning behaviors. These investigations inspired efforts and attempts to "train" patients to adopt different oculomotor strategies that may improve performance of visual search tasks and visual search area (i.e. visual search field size) to ultimately improve visual function.

Systematic training of saccadic eye movement strategies does seem to provide valuable compensatory techniques, which transfers to improvement in ADLs (28). Treatment often includes a series of steps to improve the oculomotor function:

1. Training first with quick, large amplitude (30–40 degree) saccades into the scotoma
2. Systematic training on visual search tasks (i.e., row by row or column by column)
3. Transfer of strategies into natural situations

The magnitude of improvement in visual search gain is measured by decreases in search time, number of fixations, and lengths of scanpaths in both the intact and blind fields. These eye-scanning training strategies have shown training task-specific improvements in efficiency of scan paths and a shortened response time after training (18), significant expansion of visual search field and increased effectiveness in searching for specific objects on a table (28). Many studies have also utilized patient-reported outcome measures, through use of questionnaires, and report modest improvements in activities of daily living after rehabilitation (3,28,93). Of interest, head movements during eye movement training do not appear to be of any benefit and perhaps delay rehabilitative progress (94). No differences in visual search effects have been found between the deliveries of early or late visual training, as has been shown for aphasia rehabilitation (28). Saccadic training was found to be a more effective training strategy in a recent comparative study of saccadic and flicker training therapy (95).

Saccadic Training Treatment for Reading

Reading difficulty in patients with HVFD is proportional to the extent of visual field loss and seems to correlate with the side of loss. In left-to-right reading, right homonymous hemianopes typically have more difficulty reading than individuals with left-sided loss, presuming there is no spatial inattention. Individuals with right-sided loss are reading into their scotoma or blind area and do not have the anticipatory preview area necessary for efficient reading. This preview ability of seeing the shape and location of ensuing words allows for planning of reading saccades. Whereas reading accuracy in a number of patients with HVFD may remain excellent, reading endurance is often compromised with complaints of frustration caused by frequent loss of place during reading, or potentially because of other stroke-related comorbidities (e.g., inattention, loss of comprehension, upper body weakness). Once maximal spectacle correction, low-vision aids, and lighting have been addressed, treatment involves compensatory training of eye movements with the objective of improving saccadic accuracy and decreasing reading errors:

- Reading of short, high-frequency words requiring few fixations
- Reading of increased word length and complexity
- Reading of numbers
- Reading material of importance to individual (books, magazines, computer, and so forth)

Approaches to incorporating optokinetic therapy, which offers the use of scrolling or moving text (right to left) in patients with hemianopic alexia, are another training strategy to improve saccadic activity and reading speed (96). Theoretically, the scrolling text encourages small-field involuntary eye movements (optokinetic nystagmus reflex), inducing the patient to saccade into the blind field. Sufficient practice with this technique is thought to improve patient's rightward eye movements and overall reading speed when they return to reading standard static (nonscrolling) text (96,97). This approach has been incorporated into an at-home computerized training suite, "read-right" (98). Though the software does not adequately screen for the various configurations of visual field loss (presenting targets only at the horizontal midline in a short screening test), it can be a helpful prescribed adjunct therapy. Early trials with this program have recorded improvements in reading rate with continued training, up to 20 hours at which point a plateau is observed (98). Though considerable individual variability was noted, greater improvement was noted for patients with right-sided visual field loss.

Other strategies to improve reading endurance include using an L-shaped ruler in left-sided hemianopes to maintain place during reading and assist with appropriately returning eye movements to the next line of text. This can be also be accomplished by using finger placement on the left and right side of a column to limit omissions and loss of place. Typoscopes (a black card with a cutout for a line of text) can also facilitate tracking when glare or contrast is a complicating factor. Turning a book or document 45 to 90 degrees can be effective in moving the print into the unaffected field. In these cases, patients may read up or down, avoiding the scotoma. It is important to note that in most cases, patients with HFVD frequently do not return to their prehemianopic reading ability.

Computerized Flicker Therapy

Flicker therapy involves repeatedly presenting light stimuli at the visual field border between the seeing and nonseeing

zones. It is hypothesized that training reactivates surviving neurons of the partially damaged brain structure, particularly within the "border zone" (99). It has been suggested that a minimum number of surviving neurons, of the order of 10%, may provide a sufficient substrate for visual recovery (99). A number of studies have claimed "*restored vision*" or "a modest improvement in visual fields following 3 months of visual restoration therapy," one type of flicker therapy (100–103). Intense controversy, however exists regarding the proposed benefit of flicker therapy and whether any training can be effective in creating clinically meaningful visual field expansion.

A computerized software company, Nova Vision, offers VRT for treatment of visual field defects caused by optic nerve diseases and postchiasmal brain lesions (99). Once patients are determined appropriate for therapy through diagnostic testing, revealing HVFDs, in-home computer therapy can be initiated. According to Nova-Vision, in postchiasmal disorders, VRT improved perimetric performance in 30% of patients and scotoma border shift of 4.9 degrees. VRT has significant limitations in its reliability data of fixation controls, false positives, and false negatives. During an independent study using scanning laser ophthalmoscopy combined with microperimetry, no improvement in the absolute visual field border could be detected after VRT (104). It is still unclear whether it is the frequent saccades toward the blind field or a raised level of attention that may account for the reported expansion in visual field by Nova Vision studies (104). Cross-over trial studies have indicated no significant differences in visual field diameter between flicker therapies and saccadic/exploratory eye movement training (95,105). Importantly, the minimal five degrees of "restored" visual field found in these studies represents a very small improvement of questionable value for functional performance in activities of daily living.

Sensory Substitution Strategies in Patient's With Stroke-Related Vision Loss

In cases where resolution of visual deficits does not occur, and visual ability function remains impaired despite optical approaches and saccadic training, the use of sensory substitution techniques remains an essential component of the rehabilitation plan. Sensory substitution includes environmental modifications incorporating tactile support, auditory approaches (e.g., tactile markings, braille, conversion of text to speech and talking devices), and orientation and mobility instruction. In many cases of HVFD, mobility function appears to improve over time, although it remains unclear how much of this is natural adaptation, a result of therapy or simply a reduction in life space minimizing independent activity in unfamiliar areas. When there are intractable mobility problems as a result of visual field loss or inattention, and saccadic and scanning strategies are ineffective, support cane, long white cane, and sighted guide techniques should be considered. In addition, wall-trailing techniques, holding a partner's elbow or hand, cane tapping, and receiving verbal cues can be effective in reducing the incidence of mishaps and falls caused by the visual impairment. Equally important to consider is that many patients who are impacted by stroke are older and already have the physical impairments that put them at risk for falls, irrespective of vision loss, and therefore, the use of a cane or other ambulatory aid may be the safest strategy.

VESTIBULAR REHABILITATION AFTER STROKE

In this section, we will highlight the principles underlying recovery from vestibular injury and the impact that changes in vestibular function have on patients. First, we describe the types of symptoms and deficits that occur with lesions of the vestibular apparatus and their central connections. We will then discuss mechanisms of central compensation, including changes in neuronal firing that rebalances static activity in the vestibular nuclei and mechanisms that restore dynamic vestibular function. We will also provide an outline of rehabilitation techniques for central vestibular deficits. Finally, discussion of diagnosis and treatment of benign paroxysmal positional vertigo (BPPV) is included because of the prevalence of this condition in the stroke population. It should be noted that the general principles of vestibular rehabilitation also apply to strokes involving the vestibular system, with the caveat that central vestibular lesions are more difficult to rehabilitate given the complexity of the underlying dysfunction and recovery mechanisms.

The vestibular system is a multimodal sensory network with pathways extending from the labyrinths to the cerebral cortex. Aside from maintaining images stable on the fovea via the vestibulo–ocular reflex (VOR), sensory information from the vestibular system allows us to orient to our position in space relative to the environment and gravity. Vestibular inputs to the cerebral cortex, unlike those from other sensory systems, do not cause an isolated conscious sensation. They are incorporated to self and spatial perception via multimodal sensory integration with visual and proprioceptive systems. This multimodal sensory integration is vital to generate an accurate percept of one's relationship to the environment, and subsequently, make accurate movements or maintain balance while standing, walking, or running. It is therefore important to emphasize that (a) vestibular function is not synonymous with activity in the labyrinth of the inner ear and (b) the perception of motion is unique for being multimodal as visual stimuli can cause feelings of motion indistinguishable from actual head acceleration. A common example is the feeling of one's automobile moving in reverse when a nearby vehicle begins moving forward. The auditory and somatosensory signals can similarly induce a sense of motion, which is known as vection. This multimodal property of the vestibular system has been used to alleviate symptoms in patients with syndromes of hemineglect. In these patients, vestibular stimulation (e.g., caloric irrigation) can transiently improve hemineglect as well as associated somatosensory and motor deficits (106,107).

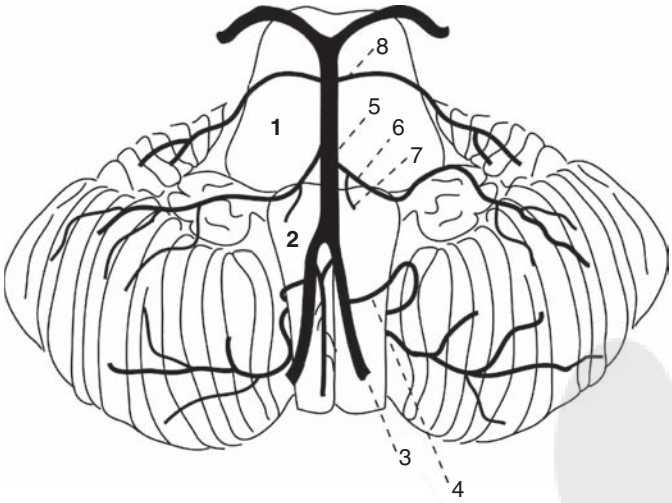

FIGURE 18.7 Schematic view showing major arteries that supply the brainstem and cerebellum. The posterior inferior cerebellar artery (PICA) is the largest branch of vertebral artery that also supplies the lateral medulla. The anterior inferior cerebellar artery (AICA) arises from the basilar artery. It supplies lateral pons and also gives off the labyrinthine artery. 1: pons, 2: medulla, 3: vertebral artery, 4: PICA, 5: basilar artery, 6: AICA, 7: labyrenthine artery, 8: superior cerebellar artery.

Although the term *stroke* is generally reserved for infarction of central nervous system structures, similar mechanisms and blood vessels are involved when ischemia occurs in the vestibular labyrinth (108). The entire blood supply to the inner ear comes from the internal auditory artery, a branch of the anterior inferior cerebellar artery (AICA) (Figure 18.7). The syndrome of AICA stroke (also known as pseudo-labyrinthitis) often includes ipsilateral loss of hearing and vestibular function, facial numbness or weakness, or cerebellar ataxia owing to ischemia of lateral pontine and midcerebellar structures (109). Vertigo and hearing loss can be the sole manifestation of AICA stroke, and ischemic lesions of the labyrinth or lateral pons at the root entry zone can mimic peripheral vestibular or auditory lesions (110). Thus, it's important to recognize that audiovestibular deficits in the AICA syndrome may result from ischemia of peripheral or central (or both) vestibular structures. Lateral medullary syndrome (also called Wallenberg syndrome) is another brainstem ischemic syndrome that commonly causes vertigo because of involvement of the vestibular nucleus in the posterolateral medulla. Other associated signs and symptoms may include ipsilateral perception of visual tilt relative to earth (true) vertical or diplopia or skew deviation (both owing to involvement of graviceptive pathways, which are connections between the utricles and those ocular motor nuclei responsible for vertical eye movements), ipsilateral ataxia, dysphagia, dysarthria, dysphonia (hoarseness, hiccups), and ipsilateral facial or contralateral body paresthesias. This syndrome is generally caused by vertebral artery or posterior inferior cerebellar artery (PICA) ischemia (Figure 18.7). A PICA stroke affecting the caudal cerebellum can likewise cause isolated vertigo that may closely resemble vestibular neuritis (also known as pseudovestibular neuritis). The absence of a positive head impulse test (HIT) (which is generally a sign of peripheral vestibular dysfunction—discussed later) may be the only sign to differentiate the two. The perception of visual tilt, or less commonly vertigo, can also arise from stroke in the anterior circulation, for instance, in the dorsal insula (111–113). Hemispheric stroke may affect the VOR and the degree of involvement correlates with disequilibrium (114,115).

BASIC PATHOPHYSIOLOGIC MECHANISMS

Vertigo is best understood as arising from an asymmetry in vestibular function. Unilateral vestibular loss, caused by the VIIIth nerve or labyrinthine lesion, can account for a range of acute signs and symptoms, including nystagmus, vertigo, and imbalance. Central nervous system compensatory mechanisms must operate to balance and recalibrate the system after unilateral injury. A lesion that results in an imbalance between vestibular information from each side presents unique challenges to the central nervous system. In some ways, this may be analogous to the idea that hemineglect syndromes may arise because of a competition in directing attention to one or the other side. When the head of a healthy individual is still, both vestibular nerves and the vestibular nuclei have equal resting discharge rates (vestibular tone), so there is no perception of linear or translational motion. Movement of the head toward one side excites that labyrinth and inhibits the other—for example, rightward head turning stimulates the right horizontal canal and simultaneously inhibits the left horizontal canal. This initiates the VOR, causing equal and conjugate eye movements opposite to the head movement. If there is a loss of tone on the left side, the brain perceives a rightward head rotation because of the relative hyperactivity of the right (opposite) side, and the eyes would drift slowly to the left because of the VOR (slow phase of nystagmus toward the pathologic side). A position reset mechanism brings the eyes back to midline (fast phase for which nystagmus is named after), and therefore spontaneous nystagmus ensues. With peripheral vestibular lesions, the nystagmus is unidirectional in that it beats in the same direction on lateral gaze to either side. It is usually more intense when the gaze is pointed in the direction of the quick phase (Alexander's law). With central lesions in the cerebellum or brainstem, however, the nystagmus can be bidirectional or direction-changing and may not follow Alexander's law.

An injury can also lead to a dynamic vestibular imbalance based on Ewald's second law: excitatory stimuli produce a relatively greater vestibular response than inhibitory stimuli. Thus, in the case of a unilateral loss of vestibular function, a greater response is elicited with rotation toward the intact side than toward the lesioned side. This is best appreciated with high-acceleration, high-velocity, and high-frequency stimuli through the "head impulse" maneuver, which is used to examine the VOR or track recovery after vestibular deficits (discussed later in this chapter). With complete bilateral vestibular loss, tasks such as reading street signs

or labels in the grocery store while walking become nearly impossible—where the VOR constantly adjusts eye position to compensate for head movements induced by each step.

Following a vestibular injury, for postural and oculomotor balance to be restored, a neuronal balance must be achieved within the vestibular nuclei. The repair mechanisms may occur within hours of the lesion without requiring any external inputs or stimuli, whereas recovery of paretic limb motor function involves recruitment of alternative pathways (115). This spontaneous recovery may be inhibited to some degree if vestibular suppressants are used for too long to treat symptoms. Such medications artificially lead to more symmetric vestibular inputs by dampening the relatively hyperactive side, thus alleviating symptoms, but normal compensatory processes may be forestalled and recovery delayed. The ultimate recovery from acute vestibular lesions is driven by interactions between the adaptive and repair mechanisms to restore function. In this process, if the tone from the paretic side is suddenly restored because of the partial repair of function, a new level of excessive spontaneous activity may arise on the paretic side relative to the central state of compensation. This mechanism may lead to ''recovery'' nystagmus, in which, owing to the new imbalance, slow phases are directed toward the intact ear (i.e., opposite to the paretic nystagmus with slow phases toward the lesioned side). Very early after a unilateral lesion, transcription events occur, leading to a restoration of spontaneous firing on the damaged side. In rodent models, evidence of immediate early gene expression (Fos-like immunoreactivity) peaks as early as 2 hours after a lesion and is differentially expressed predominantly in the ipsilateral vestibular nuclei and contralateral inferior olive (116,117). Symmetric activity is increased in locus coeruleus, autonomic nuclei, and other reticular-related nuclei (118). Some pontine and medullary nuclei also show a second peak in Fos expression between 1 and 7 days after-lesion. These two phases of transcription in animal models correspond temporally with the early restoration of static balance and later adaptive mechanisms underlying dynamic recovery. Central compensation is more efficient in unilateral loss of vestibular function and most patients recover from the initial deficits. Patients with bilateral vestibular loss also undergo central compensation, but they are usually left with residual deficits.

The cerebellum is also very important in modulation of vestibular function, and when the cerebellum is affected by a stroke, vestibular rehabilitation is less effective (119). For example, an important property of the vestibular nuclei, which are modulated by the vestibulocerebellum, mainly nodulus and uvula, is to improve the ability of the brain to sense head movement when it is prolonged at a relatively unchanging speed (i.e., low-frequency motion which is not an ideal condition for normal VOR responses). This central amplification phenomenon, called "velocity storage," extends the range of patterns of head motion that are accurately sensed by the brain beyond the mechanical properties of the cupula and endolymph, thereby supplementing the normal VOR. Lesions of the cerebellum can alter or disinhibit this normal velocity storage mechanism and lead to an increase in the duration of vestibular responses to head movements (i.e., cause uncalibrated responses or an excess of velocity storage). The vestibulo–ocular response to rapid head rotations can also be hyperactive in cerebellar lesions—for example, head impulse to the right would result in an overshoot of the examiner's nose (point of fixation) to the left (120). Moreover, "cross-coupling" of the VOR may occur with cerebellar lesions causing inappropriately directed vestibulo–ocular responses—for example, horizontal head shaking may result in vertical nystagmus (121).

Graviceptive Pathways

The otolith organs in the vestibular labyrinth detect linear head acceleration: utricle for horizontal translation or head tilt, and saccule for vertical translation. If the head is not moving, these inner ear structures are stimulated only by gravity and therefore provide information about how the head is oriented relative to the earth vertical (tilt position) (122). When the head is tilted toward one side, the ipsilateral vestibular labyrinth is excited. The calcium carbonate crystals embedded in the otoconial membrane serve as the mass upon which gravity acts, resulting in deflection of hair cells and change in firing of primary afferents in the VIIIth nerve (These crystals are the culprits in BPPV, described later). Damage to the otoliths (mainly utricle) or their central projections results in the ocular tilt reaction (OTR) that constitutes of skew deviation (vertical misalignment of the eyes not caused by muscle palsy), head tilt, and ocular torsion or counterroll (conjugate rotation of the eyes about the line of sight) (123,124). Vestibulospinal pathways originating in the lateral vestibular nucleus facilitate ipsilateral extensor motor neurons, constituting the righting reflex. Following a unilateral loss, asymmetry in spinal reflexes results in decreased ipsilesional recruitment and relatively increased extensor activity on the opposite side (125). This contributes to patients' tendency to fall or lean toward the damaged side.

Brainstem strokes can cause a sensation of being pulled toward the side of a lateral medullary stroke or away from the side of a paramedian pontine infarction (i.e., lateropulsion) (126–128). Similarly, there is often deviation of the eyes under closed lids toward the side of the lesion in lateral medullary stroke (ocular lateropulsion). In hemispheric stroke involving the posterolateral thalamus, a different phenomenon termed contraversive pushing may occur (129). This is the tendency for patients to use their nonparetic limbs to force their body away from the side of the stroke toward the paretic side. This has been found acutely in up to 10% of strokes, without a predilection for right- or left-sided lesions, and its presence is associated with a longer period of time required for functional recovery (130). Patients with acute unilateral peripheral vestibular lesions misperceive the true (earth) vertical as being tilted toward the side of the labyrinthine loss. When asked to align their bodies with the true upright, however, they perform as well as control subjects (131). By contrast, patients with contraversive pushing consider themselves

upright when they are actually tilted 18 degrees toward their unaffected side, while their perception of true vertical and head orientation are normal (132,133). The altered perception of upright can be accompanied by the OTR, which constitutes head tilt, skew deviation, and ocular counterroll toward the lesioned side. The emergence of OTR is analogous to spontaneous nystagmus that occurs because of tone imbalance with the loss of semicircular canal function. If, for instance, the right vestibular nerve or vestibular nucleus (as in a Wallenberg) is damaged, this results in relative hypofunction of the right utricle-ocular pathway, and relative hyperfunction of the left side. The brain perceives the asymmetry as a leftward head tilt (though none is actually occurring) and attempts to compensate with a rightward head tilt, ocular counterroll, and adjustment of the vertical eye position so that the right (lower eye) is on the side of the lesion (124). In the brainstem, the direction of OTR and tilt of upright perception can be toward or away from the side of the lesions, determined by where along the vestibular pathway a lesion occurs (134). In addition, perception of upright may be altered following hemispheric stroke, suggesting that its presence may influence balance recovery after stroke (135,136).

Vestibular Effects on Cortical Processes

The vestibular system is important in navigation and spatial memory, domains that also have been localized to the hippocampus. Distinct areas of the cerebral cortex mostly within the temporoparietal region (also known as the vestibular cortex) receive and integrate information from vestibular, visual, and somatosensory systems to generate a unified spatial orientation (137). Lesions involving these cortical regions can also produce pathological tilt of upright perception (112,136,138). The link between vestibular information and cognitive mechanisms underlying spatial memory and processing has been demonstrated using quantitative volumetric MRI imaging (139,140). The vestibular-related activity is stronger in the nondominant hemisphere (i.e., right hemisphere in right-handers and left hemisphere in left-handers) (141). The results from functional imaging studies also show a reciprocal inhibitory interaction between the visual and vestibular cortical regions (142,143). The cortical activity pattern is modified in patients with unilateral peripheral vestibular lesions, reflecting compensation within the central vestibular system of the unaffected side (144). Patients who have chronic bilateral peripheral vestibular loss were found to have a significant 16.9% decrease in hippocampal volume compared to controls. In addition to this selective atrophy of the hippocampus, these individuals also showed a deficit in performing a virtual navigation and spatial memory task, though general memory function was unaffected. A remarkable aspect of this study was that an intact vestibular system was required for performing a virtual task that did not involve any actual head or body motion (145). Moreover, caloric stimulation of the labyrinth has been demonstrated to transiently ameliorate left-sided visual neglect after right hemispheric stroke (108,146). A patient with left brain damage also showed a transient remission in right-sided hemianesthesia after caloric stimulation (147).

In recent decades, new technologies have emerged to promote neuromodulation through their effect on various neuronal networks. These techniques such as transcranial magnetic stimulation (TMS) or transcranial direct current stimulation (tDCS), although still in their early stage for clinical use, may open new doors in rehabilitation of patients with stroke. TMS is a noninvasive method based on the principle of electromagnetic induction of an electric field in the brain. As a brief pulse of electric current passes through a coil held over the scalp, a magnetic field is generated that can penetrate through the skull and depolarize neurons and axons. The effect of TMS has behavioral consequences and therapeutic potential. For example, a two-week course of TMS stimulation over the left parietal cortex can accelerate recovery from visuospatial neglect in patients with subacute stroke in the right hemisphere (148). tDCS modifies ongoing neuronal activities through weak direct currents up to 2 milliamperes. It can promote tonic depolarization of the resting membrane potentials in the underlying cortical brain regions by inducing excitatory effects (anodal tDCS) or lead into inhibitory effects by increasing the hyperpolarization (cathodal tDCS) (149).

ASSESSMENT OF VESTIBULAR FUNCTION

Damage to peripheral and central vestibular structures can result in vertigo, postural imbalance, oscillopsia (perceived movement of the stationary visual scene), tilt of the visual scene, or spatial disorientation. Oscillopsia or visual blur that only occurs with head movement is usually caused by bilateral vestibular loss as the underactive VOR is unable to maintain fixation during activities such as walking. When oscillopsia is present without head movement, it is generally caused by spontaneous nystagmus or other types of ocular oscillations. With lesions of the central vestibular pathways, several factors can impact the extent of recovery and central compensation such as location of the lesion, scale of the neural injury, or involvement of other sensory or motor pathways. For example, a perceptual tilt of the visual upright can occur with injuries to the pathways carrying graviceptive information at the level of brainstem or higher up within the temporoparietal cortex. The central compensations following these lesions are not similar, as brainstem injuries are generally associated with oculomotor sequelae such as skew deviation or torsional misalignment of the eyes (owing to disruption of graviceptive pathways), whereas lesions of the cerebral cortex would mainly affect integration of vestibular information into a coherent spatial perception. It is therefore important to consider pathophysiology of the underlying injury and related central compensation to individualize rehabilitation strategies in patients with vestibular deficits. The key initial step in this process is a comprehensive vestibular examination, which helps to assess the current level of physiologic and functional compensation and determine appropriate candidates for vestibular rehabilitation.

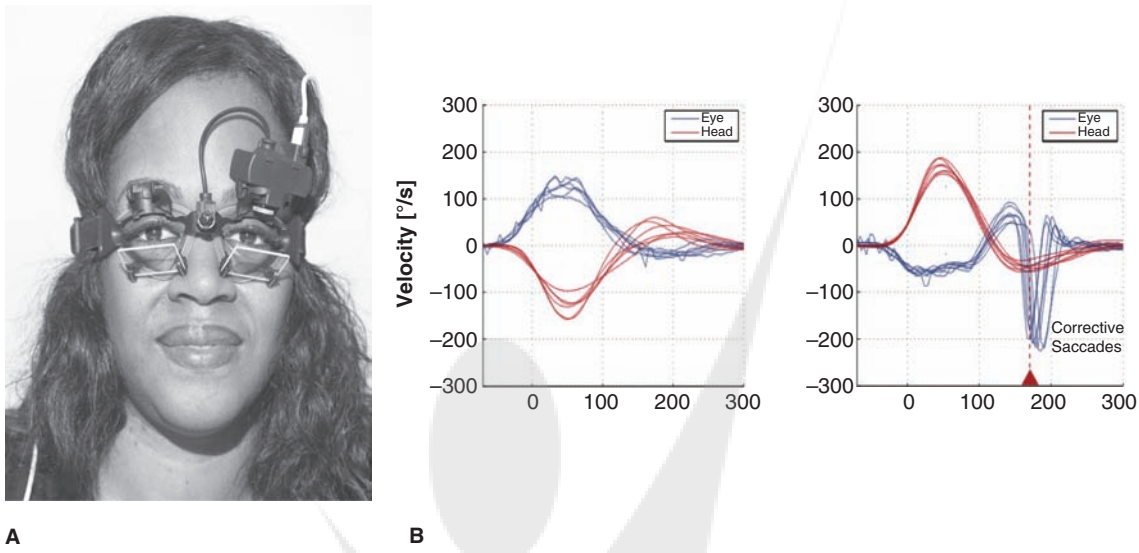

FIGURE 18.8 A video-oculography goggle (VOG) system with lightweight glasses frame, mounted high-speed digital cameras that track the pupils and sensors that quantify head movements (A). Head and eye velocity samples recorded by the VOG system showing normal (left) and abnormal (right) VOR response during head impulse test (B).

Usually, clinical findings such as spontaneous nystagmus provide evidence for failure of physiologic compensation after a vestibular injury. As discussed earlier, spontaneous jerk nystagmus is the characteristic sign of a static tone imbalance between the inputs from both labyrinths to the vestibular nuclei. The nystagmus of peripheral origin typically increases or only becomes apparent when visual fixation is eliminated. This can be appreciated by observing nystagmus under the Frenzel goggles, which, besides eliminating fixation, allow the examiner to get an illuminated, magnified view of the eyes. In patients with unilateral loss of vestibular function, the asymmetry of peripheral inputs during high-velocity head rotations leads to an unequal accumulation of activity in the central "velocity storage" mechanism within the vestibular nuclei. This can be detected by looking for head-shaking induced nystagmus (HSN) under the Frenzel goggles (150–152). For example, a patient with a chronic right peripheral vestibulopathy may no longer have spontaneous nystagmus. However, with horizontal head shaking, asymmetry is induced by the mechanisms above, and the slow (pathologic) phase of nystagmus drifts toward the weak side. The presence of HSN in such cases is associated with a greater level of disability. A reversal phase of HSN may also develop during recovery from vestibular injuries with the slow phases directed toward the intact ear (i.e., a biphasic nystagmus). This reversal phase reflects the presence of an adaptive mechanism that balances out the initial phase of HSN. The vestibular tone imbalance can be also detected by a significant directional preponderance in the caloric test (greater than 30%). The directional preponderance is a numerical expression of the overall amount of nystagmus in the right or left direction after bithermic caloric stimulations. With rotational chair testing, a persistent asymmetry in the eye velocity responses (slow phase of the nystagmus) between the rightward and leftward rotations suggests uncompensated, asymmetric loss of vestibular function.

A brief, high-acceleration head rotation or head "impulse" test is a key bedside evaluation for dynamic vestibular imbalance (153). The head impulse maneuver is performed while the patient is fixating on a target, usually the nose of the examiner. The head is quickly rotated by the examiner in a short excursion from one position to another (e.g., horizontal in the plane of the horizontal semicircular canal). With a "negative" (normal) HIT, the eyes stay perfectly on the fixation point (usually the examiner's nose). With a "positive" HIT, the eyes and head initially move together, and then there is a corrective or "catch-up" saccade opposite to the rotation of the head, which is the signature of an underactive VOR response toward the direction of the head rotation (Figure 18.8B) (154). Following the recovery, the head impulses in well-adapted patients may trigger preprogrammed "covert" saccades, which are generated so early that they become embedded in the response during the head rotation. These covert saccades are hard to discern, as opposed to the "overt" catch up saccades during the early phase of the vestibular injury, which can be easily detected by the naked eye. In recent years, the advent of 2D video-oculography (VOG) systems has provided quantitative testing of the VOR at the bedside, which helps to track recovery in patients with loss of vestibular function and assess the efficacy of rehabilitation techniques (155–157). These portable VOG goggle systems consist of a lightweight frame with mounted high-speed digital cameras that track the pupils and sensors that quantify head movements (Figure 18.8A).

In patients with acute vestibular symptoms, a normal (negative) head impulse response strongly suggests a central etiology, whereas an abnormal (positive) head impulse most

TABLE 18.1 Differentiation Between Central and Peripheral Vestibular Disorders

SIGN	PERIPHERAL	CENTRAL
HIT	Positive	Usually negative Positive HIT may be seen with lesions of vestibular nucleus, root entry zone of CN VIII, caudal cerebellum
Skew	Absent Can see a small skew and OTR with peripheral lesion if utricle is involved, but rarely causes diplopia	May be present
SVV tilt (OTR)	Ipsilesional	Ipsilesional or contralesional
Nystagmus	Unidirectional, increases in direction of fast phase (Alexander's law)	Unidirectional or bidirectional (direction-changing/gaze-evoked)

Abbreviations: HIT, head impulse test; OTR, ocular tilt reaction; SVV, subjective visual vertical.

often occurs with peripheral lesions and occasionally with a stroke (central lesion) (e.g., labyrinthine ischemia in an AICA stroke, vestibular nucleus ischemia in a Wallenberg stroke, or lesions of the caudal cerebellum) (158–160). In such cases, besides neurologic symptoms or signs of the brainstem or cerebellar involvement, a three-step ocular motor examination can specifically help to tease out a central or peripheral etiology (where up to 20% of presentations are likely caused by a stroke) (Table 18.1): A stroke should be strongly suspected when (a) head impulse testing is negative, (b) there is bidirectional nystagmus (i.e., direction changing with gaze), and (c) skew deviation is present (161). As mentioned previously, skew deviation is a vertical misalignment of the eyes because of imbalance in the graviceptive pathways, which is often seen with other features of the OTR (head tilt and ocular counterroll) (124). The disturbance in the utricle-ocular pathway can also lead to perceptual tilt of true (earth) vertical or upright (162,163). This can be assessed by a simple test of subjective visual vertical (SVV), during which a visual line is adjusted to a perceived upright orientation while the environmental visual vertical cues are eliminated (e.g., by conducting the test in darkness). The tilt of SVV is a sensitive sign that can be used to track recovery from central vestibular lesions that usually produce larger and more enduring tilts of the SVV.

The balance examination is also essential to track recovery in patients with vestibular deficits and assess the risk of falls. Patients with vestibular loss frequently restrict their head movements to avoid conflicting sensory information (i.e., vestibular and visual or vestibular and proprioceptive mismatch). They also have difficulty maintaining posture in case of sensory conflict because of the inability to suppress inaccurate inputs (164). The balance evaluation is done under static or dynamic conditions. Some of the static tests include the Romberg (standing with heels together), tandem Romberg (standing heel to toe), and single-leg stance tests. The best static measures of imbalance are those that isolate the contribution of different sensory modalities. For example, a quick and efficient way to measure static balance is the modified clinical test for the sensory integration and balance (CTSIB-M). This test is a battery of four separate, progressively difficult tasks in which the patient stands on a firm and then a foam surface (i.e., proprioceptive challenge), both with eyes open and closed: (a) eyes open standing on the firm surface (normal vision/normal proprioception), (b) eyes closed standing on a firm surface (absent vision/normal proprioception), (c) eyes open standing on a foam surface (normal vision/altered proprioception), and (d) eyes closed standing on a foam surface (absent vision/altered proprioception). For all these tasks, each attempt is considered normal when balance is maintained for 30 seconds. The dynamic balance evaluation can be done by simply observing the gait or while the patient is repeatedly moving the head in the horizontal or vertical planes while walking at normal speed. Postural sway under dynamic or static conditions can be measured by posturography in which displacement of the center of foot pressure is recorded on a force platform. This method is particularly helpful when comparing effects of treatment in different subject groups or following recovery in individual patients.

Recovery Symptoms

The vestibular system operates by comparing information from both sides to make a determination of how the head is oriented or moving through space. This push–pull arrangement has certain advantages. If labyrinthine function is completely lost on one side, the intact ear is still able to signal rotation in both directions because each side is capable of both inhibition and excitation (e.g., with a right head turn, the right horizontal canal is stimulated as endolymph flows in an excitatory direction, whereas the left horizontal canal is simultaneously inhibited as the endolymph flows in the opposite direction). An acute loss of function on one side is interpreted by the brain as rotation toward the intact side, accounting for the symptoms of vertigo and vestibulospinal manifestations of falling and veering toward the lesioned side. Early on, compensatory mechanisms alter firing in the brainstem vestibular nuclei so that neuronal activity is more symmetric and the nystagmus and vertigo are decreased. Inhibition of the normal firing rates on the intact side occurs first, which is also

the effect of various medications used appropriately during the acute phase of the illness (165). As mentioned previously, the use of vestibular suppressant should be limited to a few days because, ultimately, the goal would be to maximize utilization of the remaining function rather than inhibiting it.

Once the nervous system has responded to the initial loss of vestibular function, a second phase of compensation requires an error signal to recalibrate the system under the new postinjury conditions. Two aspects of this compensation process are worth discussing. The first is adaptation, in which an overall decreased sensory signal can be used to drive a normal motor response. A common example of this process occurs when one is prescribed a new spectacle correction; there is a brief period of disorientation before the VOR can be appropriately recalibrated for the new degree of lens-induced magnification or reduction of the size of visual field. The second aspect of compensation is habituation. By this, we mean the reduction of symptoms resulting from a mismatch between the expected sensory input from a given movement and the deficient postinjury response.

Why Some Patients Do Not Improve Following Vestibular Damage

Several factors that may delay or prevent recovery after vestibular loss include age, activity, medications, mood, fluctuating symptoms, or maladaptive strategies. Patients with vestibular deficits do not like to move their heads. In the case of dynamic symptoms, however, the brain only solves problems with which it is confronted. Several studies point to the importance of early intervention in treating a unilateral vestibular loss. Primates given a peripheral vestibular lesion regained postural and locomotor control much sooner if they were allowed to perform early active motor exploration (166). Cats subjected to motor restriction had a delayed recovery. If a 7-day interval of sensorimotor restriction was applied within the first 3 weeks of a unilateral vestibular loss, there was a delayed and limited recovery with incomplete restoration of postural abilities (167).

A unique aspect of vestibular injury is that symptoms occur even during the recovery of function. In other words, the central vestibular compensation although reliable can be somewhat fragile. This means there may be occasional periods of symptomatic relapse because of decomposition after an apparent full recovery. The common triggers are periods of inactivity, extreme fatigue, or change in medications. A relapse of vestibular symptoms in this setting should not be confused with ongoing or progressive dysfunction.

VESTIBULAR REHABILITATION THERAPY

The use of vestibular exercises dates back to the 1940s when first used by Cawthorne and Cooksey to rehabilitate patients with vestibular symptoms (168). Improvement after vestibular rehabilitation has been shown regardless of the patient's age and gender or even etiology of the vestibular dysfunction, as patients with deficits caused by stroke may show improvement without the need to increase the number of vestibular therapy sessions (169–173). Patients with cerebellar lesions, however, improve the least (119). Even one course of physical therapy has shown to reduce the risk of falling in vestibular patients from 98% to 67% (174). In most cases, there is no one-size-fits-all approach and individualized therapy has been found to be the most effective rehabilitation method (175–178). During the recovery period, each patient may have a predisposition toward relying upon one or another sensory modality (vision or somatosensation), or may adapt a different motor strategy (walking slower, widening the base of support, etc.). These early strategies used to cope with aberrant vestibular information may result in sensorimotor reorganization that is maladaptive in the chronic phase. For example, even though individuals with asymmetric vestibular inputs deviate from their intended path more when walking slowly, fear of instability (i.e., poor falls efficacy) can lead to a slowing of gait and an overreliance on visual and somatosensory cues, which can amplify symptoms and discourage participation in rehabilitation (179). Hence, attention to vestibular symptoms and awareness of their impact on basic mobility function are critical for rehabilitation planning.

The aim of vestibular rehabilitation is to promote neural plasticity and accelerate central compensatory mechanisms to recover from vestibular lesions. The initial central compensation following a vestibular injury is enhanced by head movement and delayed by physical inactivity (180,181). Again, during the rehabilitation period it is essential to avoid traditionally used vestibular suppressants such as meclizine, as these medications can impede central compensation (182). The standard vestibular therapy consists of exercises based on a set of principles focused on postural stability, gait, and gaze stabilization (183–185). These principles include (Table 18.2): (a) adaptation exercises that assist the brain to compensate for a loss of function, (b) habituation exercises that involve repeated exposure to a provoking stimuli to reduce the pathologic response, and (c) substitution exercises that promote the use of other intact sensory modalities to compensate for a deficit (e.g., use of vision or proprioception to compensate for a vestibular deficit). With all these mechanisms, the adaptation is the most effective principle in vestibular rehabilitation (185). Adaptation exercises are aimed at recalibrating the relationship between labyrinthine signals as well as vestibulo–ocular and vestibulo–spinal motor commands. It should be noted that vestibular adaptation is context-dependent, meaning that the greatest change will occur at the adapting frequencies and less significantly at other frequencies (186). In addition, there are multiple time scales of learning during the adaptation period (seconds to days), during which different rates of learning, forgetting, and relearning (i.e., recall) may occur. The pattern of training can influence these time scales, and also the retention of learning (consolidation). These complexities are important to consider when designing vestibular exercises, especially to determine whether the effect of a rehabilitation paradigm can be transferred to other daily activities (187).

TABLE 18.2 Key Rehabilitative Principles for Disorders of the Vestibular System

REHABILITATIVE STRATEGIES	DEFINITION AND EXAMPLE
Adaptation	Assist the brain in adapting to or compensating for a loss of function; e.g., unilateral loss of vestibular function on the right, and through therapy, optimizing the response of the left side to excitatory and inhibitory vestibular stimuli
Habituation	Repeated exposure to a provoked stimuli to reduce a pathologic response; e.g., repeated head movements to desensitize a patient with head motion intolerance
Substitution	Using intact sensory modalities to compensate for a deficit; e.g., promoting use of vision and/or proprioception in a patient with bilateral vestibular loss

The adaptation exercises with eye and head movements specifically improve the VOR function and enhance stabilization of the image on the retina during head movements. The improvement in gaze stability is more apparent with active than passive head movements (188,189). The VOR exercises are all variations of one principle: the patient is required to focus on a target while repeatedly moving the head in the horizontal or vertical planes (Figure 18.9). The duration recommended for each exercise is based on the difficulty level of the task and the required exposure time to error signals to see recovery. The mechanism of adaptation with VOR exercises is similar to adaptive changes with spectacle magnifiers (190). When magnifying or minifying lenses are placed in front of the eyes, because of the rotational magnification induced by spectacles, visual images will no longer be stable on the retina during head movements. The positive diopter lenses cause images to move faster than normal on the retina during head movements, whereas negative lenses cause an opposite effect. After wearing spectacles, the VOR response can adaptively change within a few hours to stabilize the visual images on the retina during head movements (191). The cervico–ocular reflex (COR) can also be adapted in some patients by using exercises that move the body under the stationary head (192,193). The COR interacts with the VOR and drives eye movements based on the cervical proprioceptive inputs. The balance training and gait exercises mainly target vestibular adaptation through postural vestibulo–colic reflex (VCR) and vestibulo–spinal reflex (VSR). These are the key reflexes that stabilize position of the neck and body according to the head movements. In patients with vestibular deficits, the postural control exercises can specifically correct asymmetries in weight bearing, improve mobility about the center of gravity, or help with sensory input selection (178).

The habituation exercises consist of provocative visual and vestibular stimuli or balance tasks with a gradual increase in difficulty. These exercises can facilitate tolerance of conflicting or novel sensory stimuli associated with head motion (194). The vestibular system may not fully recover after injuries, especially when there is severe loss of function with central lesions. The recovery is usually limited to low frequencies of head movements and a marked and permanent vestibular deficit can be demonstrated with rapid, unpredictable head movements. Under these circumstances, the brain can substitute other mechanisms to stabilize gaze or improve postural control. On this basis, substitution exercises are focused on sensory reweighting between three major sensory modalities: vision, vestibular, and somatosensory inputs. For example, if the patient is dependent on somatosensory input despite the availability of accurate visual cues, the rehabilitation program may involve exercises that require balancing on thick foam with eyes open to reduce reliance on proprioception cues. Substitution exercises are especially indicated in patients with bilateral loss of vestibular function to promote the use of

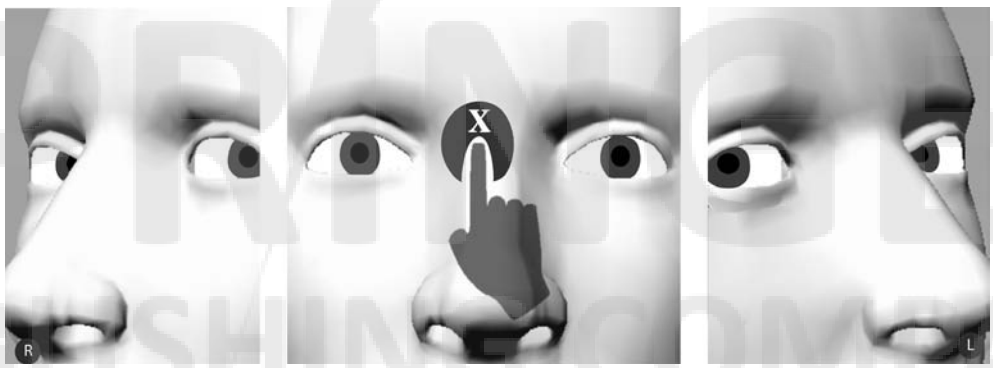

FIGURE 18.9 VOR adaptation exercises in the yaw plane. The patient moves the head to the right and left while fixating the eyes on the target.

Source: Adapted from aVOR, a free vestibular education app.

alternative strategies for gaze and posture control. Similar to adaptation exercises, substitution exercises can be modified as the patient improves. Many patients with central deficits will show impaired timing and uncoordinated strategies for postural control. In general, three main postural strategies are used to improve balance while standing: ankle, hip, and step strategies. The ankle strategy involves standing with a wide stance and performing sway maneuvers using ankle torques. This strategy is more dependent on somatosensory function. The hip strategy is more dependent on vestibular function and involves standing in a narrow stance, performing torques around the trunk. Patients with vestibular loss tend to use the ankle strategy for postural stability even when the hips strategy is required—for example while standing in tandem (195). The step strategy involves stepping movements under an altered center of body mass and is usually used after improvement in balance with other postural strategies.

Patients with vestibular dysfunction caused by stroke benefit significantly from a customized treatment program including balance and gait training, general strengthening and flexibility exercises, as well as adaptation and substitution exercises (119,195,196). Although the signs and symptoms of static vestibular imbalance (e.g., spontaneous nystagmus) resolve independently without intervention, the dynamic instability and head movement-provoked symptoms often require specific treatment (166). The objective measures of static and dynamic postural stability or gait pattern can be used to track improvement in these patients (175,195,197). In particular, it is shown that scores on the dynamic gait index may improve by an average of 4.7 points, with a 4.0 point or more change considered clinically significant. Patients with hemispheric stroke and chronic hemiparesis exhibit excessive sway when visual and somatosensory information are unavailable (i.e., when tested with eyes closed on a support surface that swayed with the subject) or inaccurate (i.e., when tested both visual surrounding and support surface swayed with the subject) (198). Overreliance on visual input in hemiplegic patients has been demonstrated in a task that involved aligning a rod to the vertical when a frame is tilted to the right or left. These patients were twice as likely to be biased by the orientation of the frame when compared to controls (199). There was a significant improvement in postural control after these patients underwent a rehabilitation program, regardless of whether they performed their exercises with or without visual input. The vision-deprived group, however, achieved greater improvement, suggesting the possibility that traditional treatment may have reinforced visual overreliance and limited potential benefit from treatment (200). As to the effect of visual correction, there are many anecdotal reports that bifocal glasses or progressive lenses increase the risk of falls in conditions that affect gait and balance (201).

In general, once the patient has enrolled in the rehabilitation program, progress should be assessed periodically to make appropriate adjustments. In this process, exercises that no longer produce symptoms are eliminated and replaced by those that trigger symptoms. The procedure continues until the improvements begin to plateau. At this point, maintenance exercises are important to ensure stability of the initial improvements. The efficacy of vestibular rehabilitation in patients with abnormal sensory organization was demonstrated in a prospective study in which over half of the patients showed objective improvement in balance function (202). Significant improvements are also reported in daily functions, emotional aspects of the symptoms, and overall quality of life (175,194,203,204). In a single-blind, randomized, controlled trial of primary care-delivered treatment, 170 patients with chronic dizziness were randomized to vestibular rehabilitation; the other received usual medical care. The treatment group received just one 30- to 40-minute appointment with a nurse, who instructed the patient in a home exercise program that was reinforced with a treatment booklet and log (available online as an appendix to the article). At 3 months, there were significantly fewer spontaneous and provoked symptoms of dizziness as well as improved dizziness-related quality of life. Postural stability with eyes open and eyes closed was objectively improved as well. Clinically significant improvement occurred in 67% of treated patients and benefits were maintained at 6 months, whereas only 38% of the control patients improved (205). For such a program to succeed, patients need to be motivated to carry out the exercises despite the fact that they may exacerbate the very symptoms targeted by the treatment. Patients must be reassured that they are not causing additional damage. Too often, patients abandon their exercises because, after several weeks of performing them, they still have the same symptoms of dizziness. What they often fail to realize is that they are doing much more activity before experiencing these same symptoms and are thus actually progressing in the therapy.

Safety is an important consideration with respect to the risk of falling during the rehabilitation period. Patients should be educated about common fall hazards in the indoor and outdoor environments and strategies that can be used for falls prevention (e.g., proper shoes/socks, assistive devices, etc.). Patients with vestibular loss often have falls because of larger than normal postural responses to perturbations, rather than failing to trigger a larger enough postural response. Light touch that provides somatosensory cues but not mechanical support can especially help these patients by providing a contact reference to earth vertical (206).

Patients with vestibular deficits also benefit from natural exercises or activities that involve coordinated eye, head, and body movements such as Tai chi, table tennis, and Tango dancing (207,208). In recent years, new technologies have also emerged for vestibular rehabilitation. One of these promising interventions is virtual reality, which can create the illusion of immersion in a real environment using computer-generated graphics. This technology specifically allows better control of the rehabilitation environment. For example, the patients who rely on vision to maintain balance can be immersed in a virtual environment enriched with challenging proprioceptive stimuli to train the use of proprioception for postural control (209–211).

The Nintendo Wii Balance Board is an alternative, user-friendly technology to rehabilitate patients with vestibular symptoms (212). Vibrotactile feedback devices, which fit around the waist and provide augmented feedback on body tilt position, can also reduce postural imbalance and trunk sway (213,214). Another useful intervention is based on the stimulation of mechanoreceptors in the sole of the foot with a balance-enhancing insole (215). The footwear insoles have a built-in wedge under the lateral aspect of the foot and can improve the ability to walk in a straight path (216).

BENIGN PAROXYSMAL POSITIONAL VERTIGO

Although cerebral ischemia can predispose patients to the development of BPPV, the occurrence of this common condition in the subacute or chronic stroke patient is probably more likely caused by the age of the population and their prolonged immobility. Acute management of stroke often includes maintenance of the head-down position, which could also promote the development of BPPV. It is important to recognize this condition so it is not confused with a recurrence of the patient's cerebrovascular disease. Often, BPPV symptoms are initially attributed to vertebral basilar insufficiency, although a careful history and brief examination is sufficient to distinguish these conditions, sparing the patient further evaluation or transfer from a rehabilitation facility back to an acute care setting. Imbalance and vertigo from BPPV may also interfere with the progress of rehabilitation in the poststroke population.

Symptoms of BPPV are always brought about by changes in head position with respect to gravity (217). Rotation of the head, as if the patient is saying "no," when upright is generally the only head movement that does not provoke symptoms. Rolling over, getting in or out of bed, and reaching to a high shelf when standing are other provocative maneuvers. The diagnosis and localization can readily be made using the Dix–Hallpike maneuver, particularly for the most common posterior canal variant (Figure 18.10). This begins with the patient seated in the bed with the legs extended. The head is turned 45 degrees to one side and then the patient is brought into the supine position. The examiner should observe the eye movements and query the patient about their typical symptoms of vertigo. Maintaining the head turn, the patient is then brought back into the sitting position. The head is turned 45 degrees to the other side, and the procedure is repeated. Generally, symptoms will only develop in the right- or left ear-down position, although bilateral cases do occur. Nystagmus that accompanies the symptoms of vertigo is mixed upbeating and torsional (beating toward the lower eye). The direction of nystagmus is determined by stimulation of the posterior canal. For instance, right posterior canal BPPV is diagnosed in right Dix–Hallpike when upbeat-torsional (toward the right ear) nystagmus is seen. Stimulation of the right posterior canal during this maneuver causes both eyes to conjugately move down and rotate toward the left ear (pathologic slow phase). Then, there is a position reset mechanism (fast, or named phase of nystagmus) to get the eyes back to midline, which is upbeat-torsional (toward right ear). This can be best observed if the effect of visual fixation on nystagmus is eliminated by using Frenzel goggles during the exam (Figure 18.10). The nystagmus develops seconds after the head is moved (latency) and usually lasts less than 30 seconds (duration). Although the vertical component may be suppressed by visual fixation, the torsional nystagmus can be visualized without the use of any specialized equipment because of a poor torsional fixation mechanism.

FIGURE 18.10 Dix–Hallpike maneuver for diagnosis of right posterior semicircular canal BPPV by using Frenzel goggles. The test is performed with the patient sitting upright with legs extended (A). The head is then rotated by approximately 45 degrees to the right (B). The examiner helps the patient to lie down backwards quickly, maintaining the head turn in approximately 30 degrees of extension (right ear is below the right shoulder) (C). The examiner would then observe for the typical BPPV nystagmus (torsional upbeating toward the ground).

The diagnosis of BPPV is certain if four criteria are met:

- There is a latency before the onset of the nystagmus.
- The duration of the nystagmus is less than one minute.
- The nystagmus is elicited only in the appropriate head orientation.
- The direction of nystagmus matches the head position (218).

If these four criteria are not met, alternative diagnoses should be considered, mainly including horizontal canal BPPV (pure horizontal nystagmus that changes direction when the supine head is turned from one side to the other) or central positional nystagmus. Treatment is extremely effective and can be performed readily at the bedside using the canalith repositioning procedure (CRP, or Epley maneuver) (219,220). Unlike Dix–Hallpike testing, during which the patient would be brought back into a seated position, the CRP proceeds with the patient supine: (a) Keeping the neck extended, rotate the head 90 degrees so that the unaffected (e.g., left) ear is now pointed 45 degrees downward, (b) Rotate the patient's head another 90 degree so the nose is now pointed 45 degrees toward the ground. The patient rolls themself into the left lateral decubitus position. Again observe for nystagmus, which should still be upbeat, with the torsional component (upper poles of the eyes) beating toward the affected (left) ear. The presence of nystagmus with a downbeat component indicates an ineffective procedure, (c) Instruct the patient to bring the knees up toward the chest and drop the legs over the edge of the table while the head is kept in the nose-down position, (d) Bring the patient up into the sitting position, keeping the head rotated 45 degrees on the body to the right with the chin down. In the upright position, keeping the chin tucked down, the head is rotated straight ahead, and then the patient may assume a normal head position. Hold on to the patient when he or she is brought upright, as vertigo and imbalance may occur. The entire procedure may be repeated as often as necessary until no further nystagmus or symptoms are present. Instruct the patient to keep the head upright (no more than 45 degrees from the vertical) for the remainder of the day to inadvertently avoid reintroducing the debris into the semicircular canal. It is not necessary to have the patient sleep sitting up after the procedure.

CONCLUSION

Because of the limited objective evidence of strategic and effective approaches, the decision to treat and type of treatment for patients with visual, ocular motor, and vestibular impairments secondary to stroke needs to be individualized. The associated deficits, level of functional impairment, as well as desired tasks and goals identified by the patient and family must enter into the tailored rehabilitative plan. Recovery of dynamic control of balance and gait after vestibular damage requires exercises that often provoke symptoms of dizziness and should be performed as soon as possible after the stroke. Encouraging normal head movement (like the forced use of the paretic limb) decreases symptoms (habituation) and improves function (adaptation). Visual, vestibular, and somatosensory information can substitute for one another in a variety of tasks, but overreliance on one modality can be maladaptive and should be addressed explicitly in a customized rehabilitation program.

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IV

SENSORIMOTOR IMPAIRMENTS AND THEIR TREATMENT

19

Patterns of Locomotor Recovery After Stroke

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The main objective of this chapter is to describe patterns of locomotor recovery in persons who have sustained a cerebral stroke. A second objective is to examine the effects of stroke severity on locomotor recovery. This chapter:

1. Reviews recovery trajectories after stroke obtained from longitudinal studies using clinical measures and underlying mechanisms associated with the recovery of strokes of different severities.
2. Argues for the use of walking speed as a marker of recovery.
3. Presents data describing the recovery, from stroke onset to two years after stroke, of walking speed and its relation to movements and muscle activations of the lower extremity in a cohort of subjects with a middle cerebral artery ischemic stroke who participated in a clinical trial (1).
4. Uses data from a second clinical trial (2) to examine the magnitude of change in gait speed after two months of task-oriented physical therapy and the relationship between selected clinical measures and gait speed; also briefly reviews the kinetic patterns related to propulsion and generation of walking speed in healthy subjects.
5. Describes compensatory kinetic strategies during gait of persons with different stroke severities.
6. Summarizes the concepts introduced and their clinical implications.

RECOVERY AFTER STROKE AS MEASURED BY LONGITUDINAL STUDIES USING CLINICAL MEASURES

Traditionally, studies have described patterns of recovery on the basis of repeated assessments of recovery by means of clinical measures that rate change with recovery on the basis of observations made by trained evaluators or clinical benchmarks. Thus, it is generally accepted that the recovery curve after stroke rises rapidly in the first six weeks after stroke, when rehabilitation interventions supplement natural recovery, and that it reaches a plateau at about three months after stroke, with little further recovery after six months (3,4) although there are reports of recovery much later (5). Duncan et al. (4), on the basis of serial Fugl-Meyer (6) assessments over time in 95 patients with anterior circulation ischemic stroke, reported that, although in some patients the pattern of recovery (degree and time course) differed in the upper and lower extremities, for most the recovery patterns were similar and the most rapid recovery occurred within 30 days after stroke. Patients with initially severe motor deficits, however, had heterogeneous outcomes, with some recovering dramatically and others showing little change in the Fugl-Meyer motor score 180 days after stroke.

These results were confirmed and extended by the results of the Copenhagen Stroke Study (7–9), conducted in a cohort of 1,197 persons treated in the stroke unit of a hospital in Denmark. The capacity to return home after rehabilitation is often taken as a measure of recovery: 64% were discharged to their own homes, whereas 15% were discharged to a nursing home, and 21% died during the hospital stay (8). Stroke severity, as determined by the Scandinavian Stroke Scale, was initially very severe in 19%, severe in 14%, moderate in 26%, and mild in 41% of the patients. After rehabilitation, 11% of survivors still had severe or very severe neurologic deficits, 11% had moderate deficits, and 78% had no or only mild deficits.

One might ask how stroke severity relates to return of function. In the Copenhagen Stroke Study, the timecourse of functional recovery (8) was described by weekly assessments with the Barthel index (BI) (10). As expected, the timecourse of recovery was strongly related to stroke severity. Nevertheless, functional recovery was completed within 12.5 weeks from stroke onset in 95% of the patients, with best recovery attained by 8.5 weeks in those with initially mild stroke and within 20 weeks in those with very severe stroke. Furthermore, best functional recovery was reached by 80% of the patients with initial mild strokes within 3 weeks and by those with initial moderate strokes within 7 weeks.

In a more recent study, Verheyden et al (11) confirmed in 32 patients with ischemic stroke that the most striking improvement, as measured by a series of clinical measures (Trunk Impairment Scale [TIS], Fugl-Meyer arm [FMA] and leg [FML] subscores and the BI), occurred between 1 week and 1 month after stroke onset. Further significant improvements, though much smaller, occurred between one month and three months but not between three and six months after stroke. Like Duncan et al. (4), they described similar patterns

of recovery for the FMA and FML. They also found the TIS and BI to have a recovery pattern similar to the FMA and FML. Between 1 week and 1 month after stroke, the median improvement was 16% for the FMA and FML, 22% for the TIS, and 30% for the BI (a measure of functional independence); between 1 month and 3 months the median improvement in the TIS score was 2%, whereas all other measures had a median change of 0%, thus indicating that 50% of the patients showed no further improvement or deterioration.

The specific timecourse of recovery of walking function and lower extremity paresis was also assessed by the BI and the Scandinavian Stroke Scale at weekly intervals in a subgroup of 804 patients in the Copenhagen Stroke Study (9). Initially, 51% had no walking function, 12% could walk with assistance, and 37% could walk independently. At the end of rehabilitation, 21% had died, 18% had no walking function, 11% could walk with assistance, and 50% were independent walkers. A plateau in the BI score was attained in 95% of the patients within the first 11 weeks after stroke and, as expected, the rate and magnitude of recovery were related to both the level of initial impairment of walking function and severity of lower extremity paresis. Thus, when using the BI as a measure of walking function, Jorgensen et al. (9) state that a valid prognosis of walking function in patients with mild or moderate leg paresis can be made in three weeks and that further recovery should not be expected after nine weeks.

The longitudinal studies mentioned earlier indicate that after stroke, patients can be expected to have at least some predictable degree of functional recovery in the first three months and that the largest gains occur in the first month after stroke, with little change thereafter, as measured with clinical outcome measures that have a ceiling effect and are less sensitive to change in the later stages of recovery (7–9,11). This nonlinear pattern of recovery as a function of time is, however, not well understood. Several mechanisms have been invoked in an attempt to explain the "natural" recovery that occurs in the first weeks, including the restitution of penumbral tissue surrounding the lesion, resolution of the diaschisis, and recovery of neurotransmission in spared tissue near and remote from the infarct (12). This recovery process, which is presumed to underlie the recovery pattern early after stroke, has been referred to as "spontaneous neurologic recovery," and its contribution to the patterns of stroke recovery has been largely overlooked (13,14). Kwakkel et al. (14) have proposed the use of progress of time as a surrogate, independent covariate to reflect spontaneous recovery and have shown by means of a regression model that it explains 16% to 42% of the observed improvements in body functions and activities in the first 6 to 10 weeks after stroke onset.

In addition to so-called natural recovery, one must consider the effects of rehabilitation interventions that were not considered in the earlier studies. We do not know the exact parameters of the rehabilitation interventions (precocity after stroke, intensity, duration, and content). Also, after their poststroke rehabilitation phase, many patients may require further therapy in the three- to six-months poststroke phase to maintain their gains (11). It is not possible to tease out the effects of rehabilitation as opposed to spontaneous recovery in the first three months after stroke without a control group that does not receive rehabilitation. For obvious ethical reasons, rehabilitation cannot be withheld.

Another question that begs to be addressed after reviewing the studies on poststroke recovery profiles is whether there is a "window of opportunity" for optimal gains with rehabilitation. Studies in rats (15) have shown that the upregulation of growth-promoting factors that mediate recovery predominates over the upregulation of inhibitory factors in what is known as a critical period for rehabilitation in the first 15 days after stroke. We do not know specifically how this early "window of opportunity" relates to human recovery, but early intervention in the first days after stroke is recommended best practice (16). But how early is early? Recent work (17) shows that mobilizing medically stable persons in the first 24 hours after stroke is both safe and beneficial.

The main question appears to relate to intensity rather than to precocity. The current best practices recommendation is that intensity should be provided according to the patient's tolerance. For the upper extremity, the lesser gains obtained by high-intensity constraint-induced movement therapy (CIMT), in comparison to CIMT at an intensity similar to usual practice, provided to patients in the first month after stroke (18) have been interpreted to suggest that such a high-intensity approach should be avoided in the first month after stroke. For the lower extremity and mobility training, we know, from RCTs carried out in patients after stroke caused by a middle cerebral artery infarct, that patients tolerate very well the initiation of task-oriented therapy (including treadmill training) 1 week (1,19) or within 14 days (20) after stroke.

Unfortunately, studies have not compared the effects of initiating locomotor therapy early, defined as in the two weeks after stroke, to that of later initiation after the "window of opportunity." If we accept the existence of a "window of opportunity" for optimal results early after stroke, then it is important to understand the impact of recovery in this time period on long-term recovery potential as well as on how stroke severity affects its duration. The LEAPS study (21), which showed no difference in locomotor outcome at 12 months when the intervention was initiated 2 or 6 months after stroke, provides a partial answer to this question.

NEURAL PLASTICITY AND BEHAVIORAL COMPENSATIONS

Rehabilitation is believed to modulate recovery by interacting in some way with natural recovery processes. But, as mentioned, it is very difficult to tease out therapy effects when a control group receiving no therapy and relegated to recovering only by natural recovery is not possible. Prediction models that are adjusted for the effects of time after stroke suggest that outcome is largely defined within the first weeks after stroke, although functional improvement has been found to extend beyond six months after stroke (14,22,23).

The ground-breaking work of Nudo and colleagues (24,25), who examined neural plasticity in an animal model of stroke using cortical lesions in primates, demonstrated the potential of task-specific training to modulate brain plasticity and heralded a new era in the field of poststroke neurorehabilitation that is still evolving. In the past 15 years, there has been a dramatic change in the type and intensity of therapy provided to persons recovering from a stroke, as new information has emerged from animal and human studies of brain plasticity. Various types of noninvasive brain stimulation as an adjunct to task-specific training have generated much interest for the optimization of upper-extremity recovery (26,27), and promising studies point to its potential to promote the recovery of locomotion (28,29). These advances, spawned by the interest generated by brain plasticity mechanisms and technological advances in brain imaging that are able to document changes in the brain related to recovery over time or induced by specific therapies, give promise for further therapeutic developments and bode well for the field of neurorehabilitation. It is likely that these new, more effective approaches to enhancing motor recovery will lead to improved patterns of locomotor recovery after stroke.

Neuroplasticity mechanisms of recovery of the upper extremity after stroke can be divided into (a) those associated with spontaneous recovery and (b) treatment-induced recovery (30). Several patterns of change arise spontaneously during the weeks after stroke onset. A reduction in hemispheric laterality occurs. Instead of activity mainly in the contralateral hemisphere associated with normal unilateral arm movement, after a stroke, activity is often seen in both hemispheres. Activity also increases in multiple brain areas throughout the motor network. Moreover, these patterns occur along a gradient, such that in general, the poorer the behavioral outcome, the more these two mechanisms are invoked (31–33). Another pattern of spontaneous poststroke plasticity is a shift in the location of primary sensorimotor cortex (SMC) activity to a more posterior or ventral representation (34).

Behavioral gains in the affected arm following specific therapies in patients with chronic, plateau-phase stroke have been associated with an increase in the extent of activity, increased excitability of the motor cortex (35), and an increase in laterality back toward normal (36), such that there is a greater predominance of activity in the stroke-affected motor cortex rather than bilateral activation. Little is known, however, about the combined effects of spontaneous recovery and therapy-induced recovery in the acute poststroke phase.

Recovery mechanisms underlying unilateral upper-extremity function cannot be assumed to be the same as those for bipedal gait, a complex sensorimotor function controlled by integrated cortical, subcortical, and spinal networks. Given the technical difficulties associated with recording from the brain while walking, few studies have described patterns of brain activation during gait, even in healthy persons, and the neural substrates associated with gait recovery are only beginning to be understood.

Using motor imagery as a surrogate for actual walking in healthy elderly adults, Malouin et al. (37) studied the involvement of supraspinal structures in locomotion. They compared patterns of brain activation when imagining standing, initiating gait, walking, and walking while avoiding obstacles by means of positron emission tomography (PET). Their study revealed that higher brain centers become progressively engaged when demands of locomotor tasks require increasing cognitive and sensory information processing.

Imaging studies have started to elucidate the contributions of cortical activations to recovery associated with rehabilitation interventions such as treadmill gait training. Miyai et al. (38), using a near-infrared spectroscopic (NIRS) topography technique, found that body weight-supported treadmill training (BWSTT) led to a lower activation in the SMC as assessed by task-related changes of oxygenated hemoglobin levels. Importantly, changes in the SMC activation correlated with changes in the cadence, and improvement in the asymmetry of SMC activation also correlated with improvement in gait asymmetry. In a second NIRS study, Miyai et al. (39) measured cortical activity in persons with subacute stroke before and after two months of inpatient rehabilitation. They concluded that locomotor recovery after stroke may be associated with improvement of asymmetry in SMC activation and enhanced premotor cortex activation in the affected hemisphere (39,40).

Yen et al. (41), using focal transcranial magnetic stimulation, documented the relationship between motor improvement and corticomotor excitability change after gait training in persons with chronic stroke. They compared the effects of 4 weeks of general physical therapy in a control group (n = 7) to general physical therapy with the addition of BWSTT in an experimental group (n = 7). They found that, after general therapy, the patients improved their walking speed and cadence but had no significant changes in corticomotor excitability. The addition of BWSTT, however, led to changes in corticomotor excitability. The motor threshold for tibialis anterior muscles (TA) in the unaffected hemisphere, map size for TA in both hemispheres, and map size for the abductor hallucis muscle in the affected hemisphere were significantly improved. These changes in corticomotor excitability with BWSTT were correlated with improvements in balance and gait performance.

To date, functional magnetic resonance imaging (fMRI) studies attempting to document the neural correlates of recovery in locomotor function after stroke have used ankle dorsiflexion (42–44), knee extension movements (45), or activation of the tibialis anterior muscle as a surrogate to assay locomotor control. Sullivan et al. (46) documented activity-dependent cortical reorganization using fMRI mapping of the brains of persons with stroke who practiced walking on a treadmill. The fMRI changes were correlated with faster overground walking speeds and more precise voluntary control of the TA. Luft et al. (45) compared brain activations by fMRI during knee extensions in persons with chronic stroke due to cortical, subcortical, and brainstem lesions.

They found differences in brain activations between healthy controls and subjects with brainstem and cortical strokes and between subcortical and cortical strokes. Importantly, better walking ability was associated with reduced contralateral SMC activation in the brainstem but greater recruitment of ipsilateral sensorimotor and bilateral somatosensory cortices in subjects with subcortical and cortical strokes. These data thus reveal adaptations in networks controlling unilateral paretic knee movements in persons with chronic stroke that are related to walking ability and that are dependent on lesion location.

Enzinger et al. (43), using an ankle dorsiflexion paradigm and fMRI imaging, also demonstrated in persons with a single subcortical ischemic stroke that the degree of impairment of the paretic lower limb affected cortical activation. They observed that the extent of cortical activation, particularly in the primary SMC and supplementary motor area of the unlesioned hemisphere, increased with disability as measured with the Motricity Index. They interpreted this finding as potentially adaptive recruitment of undamaged ipsilateral motor control pathways from the supplementary motor area and possibly maladaptive disinhibition of the ipsilateral SMC (43).

In a second study (44), they used the same ankle dorsiflexion paradigm to demonstrate training-induced recovery of the lower limb associated with 4 weeks of BWSTT in a group of 18 persons with mild to moderate chronic stroke. Improved walking endurance after training (distance walked in 2 minutes [103.6 ± 38.1 vs. 119.7 ± 39.0]) was correlated with increased brain activity in the bilateral primary sensorimotor cortices, the cingulate motor areas, and the caudate nuclei bilaterally, and in the thalamus of the affected hemisphere during active ankle dorsiflexions of the paretic foot. They concluded that rehabilitation-associated walking improvements were associated with cortical activation changes despite the strong subcortical contributions to gait control. As in upper-limb studies of the effects of rehabilitation, they found bihemispheric activation to increase with greater recovery both in cortical and subcortical regions with movements of the paretic foot. They did not, however, find evidence of the involvement of the dorsal premotor cortex, important in upper-limb recovery.

Using a knee movement paradigm and fMRI, Luft et al. (47) studied the changes in brain activation related to 6 months of treadmill exercise (T-EX) in persons with chronic stroke in a large randomized controlled trial (RCT) that compared the effects of T-EX (n = 37) with stretching exercises (control group, n = 34). As expected, T-EX led to a significant improvement of 51% in walking speed and 18% in cardiovascular fitness in comparison to 11% and 3%, respectively, in the control group. Only the T-EX group, however, had changes during paretic but not nonparetic knee movements, with an increase of 72% activation in the posterior cerebellar lobe and 18% in the midbrain as well as in frontal, temporal, and parietal cortical areas. Moreover, subcortical recruitment in the cerebellum and midbrain was associated with exercise-mediated improvements in walking speed. The authors conclude that the observed changes in regional brain activation suggest that they are putative neuroplastic mechanisms by which T-EX restores functional walking capacity after stroke.

Contrary to reports of fMRI correlates of upper-extremity recovery of function (30), they (47) did not observe reductions in cortical activation after six months of T-EX, potentially reflecting the fact that subcortical, instead of cortical, networks are involved in mediating T-EX effects. They suggest that the increased activation in subcortical regions with T-EX may point to enhanced signaling in two candidate neural circuits: one consisting of the red nucleus (RN), the cerebellum, and inferior olive. Via projections to the RN, this circuit receives input from the cortex. It may provide timing cues and corrective signals necessary for coordinated phasic movements and movement learning (48). The second candidate circuit involves the cerebellum and the midbrain locomotor region that is part of the reticular formation in the immediate vicinity of the RN. The midbrain region receives neural signals from basal ganglia and cortex.

Together with the cerebellum, the midbrain locomotor region activates spinal locomotor pattern generators via the pontomedullary reticular formation (49). The findings of Luft et al. (47) could thus be interpreted as an activation of this pathway by T-EX to promote locomotor relearning.

The earlier mentioned studies suggest that therapy-induced changes in cortical plasticity may be related to the stimulation provided by treadmill walking with its entrained repetitive stepping and speed control, and also that these changes were associated with weeks or months of training. You et al. (50), however, showed that four weeks of exercising to target mobility, balance, and locomotor skills in a virtual environment that did not use a treadmill induced cortical plasticity. More specifically, using a knee flexion–extension paradigm, they showed fMRI changes in the laterality index in the primary SMC, which suggested that virtual reality (VR) training could induce cortical reorganization from aberrant ipsilateral to contralateral SMC activation. Other studies, using transcranial magnetic stimulation (TMS) have shown that 30 minutes of walking with functional electrical stimulation (FES), but not when walking alone, increases the corticospinal excitability of the tibialis anterior muscle and that this effect is related mainly to increased excitability of the cortex or its connections to the spinal cord more than that of spinal pathways (51). Liepert et al. (52) used TMS mapping to show that one hour after a single physiotherapy training session aimed at improving dexterity of the affected hand, the motor output map of the paretic abductor pollicis brevis was significantly enlarged and motor function was improved. One day later, these effects were partially reversed. Animal and motor learning studies (15,26) have shown that plastic changes begin almost immediately after a stroke. Studies, as yet, have not defined the timecourse of cortical plasticity related to locomotor therapy. The challenge is to better understand this process so that interventions are timely and appropriate to promote recovery.

We have limited knowledge of the recovery pattern after severe strokes because rehabilitation-related research studies focus on recovery after mild or moderate strokes.

Even the most widely used animal models fail to mimic the pathogenesis and clinical features of severe ischemic strokes (53). Clinically, we know that recovery from severe strokes takes more time (54), as expected from the patterns and timecourse of recovery (4,7–9,11), and that factors such as age and caregiver support affect not only recovery but also decisions made by rehabilitation personnel regarding recovery potential. Older patients do recover, but age alone is a weak predictor of functional recovery and its impact may be overestimated (55), predicting only 3% of the variance in the Functional Independent Measure score at discharge. Other factors such as the level of consciousness (sleepiness, attention problems) and possibly other comorbidities also affect recovery (56,57). Although persons with very severe stroke may rarely attain functional independence, they can benefit enormously from rehabilitation to reach their maximal functional level to facilitate transfers, to rise from a chair, and to walk with assistance, and may be able to return to their homes with the help of a caregiver (58).

There is little in the literature to guide the rehabilitation approach for persons with severe strokes. Will they benefit most from a regular intensive approach initiated as early as possible and as intense as tolerated, or should special parameters, such as a later and more gradual approach to intensity over time, apply? We also are only beginning to understand the effects of pain and fatigue (59), the depression that affects a very large proportion of stroke victims, apathy (60), psychological barriers, and perceptions that the "system" has given up on them (53) on the recovery potential. We also know little about the impact of cognitive impairments, such as of anticipatory processes and motor planning, on locomotor recovery (53,61).

After reviewing studies reporting neural correlates of recovery in persons with severe stroke, Sterr and Conforto (53) concluded that there was evidence that contralesional areas and augmented activity of networks not normally minimally or even active at all in healthy brains were related to recovery and limited behavioral gains. Severity of motor impairments thus influences patterns of rewiring after stroke, along with other factors such as age, brain status before stroke, and intensity and timing of rehabilitative interventions. To date, rehabilitation interventions have not taken into account the heterogeneity of mechanisms underlying the stroke and how these mechanisms may affect brain processes and behavioral and psychological factors that underlie recovery.

One can also question whether more effective, task-specific therapy, provided early and with sufficient intensity, could limit the development of disturbed motor control processes associated with spasticity, excessive coactivation, and paresis during walking (62). Furthermore, kinematic and kinetic studies have demonstrated that functional improvements in balance and gait or lower-extremity function can occur without the restoration of "normal" motor control, indicating that behavioral compensation strategies for impaired motor control are an important part of the "recovery" of function after stroke (62–75). One can ask whether these behavioral compensations, which reflect learned skills designed to overcome motor control impairments, are part of the recovery process that is triggered when restoration of "normal" function is not possible.

WALKING SPEED AS A MARKER OF RECOVERY AFTER STROKE

Walking speed has been shown to be a robust indicator of walking capacity (76). Supporting the validity of walking speed as a measure of locomotor recovery is its positive correlation with motor recovery (74,77,78), static muscle strength of the lower extremity (79,80), and the size of the "push-off" plantar flexor moment (70), with balance (80) and the use of walking aids (81) and its negative correlation to spasticity of the plantar flexors (68). Faster walking speeds are also indicative of the quality of the lower-extremity movements (73,82). Moreover, the reliability of the clinical measurement of walking speed has been established for test–retest and between-observer measurements (81–83), whereas repeated measurements of the simple, timed walking test over five and ten meters have been shown to be a responsive measure of walking performance in acute stroke (84). Gait speed, however, is not always the outcome of choice throughout the range of recovery. When subjects walk very slowly or need the support of a person, clinical outcomes such as the Barthel (10) ambulation subscale or the Fugl-Meyer (6) leg subscore may be more sensitive than walking speed (73). Nevertheless, chronicling the full extent of walking recovery may require measures more demanding than gait speed alone (85).

Importantly, Perry et al. (86) related the level of walking speed attained by persons after stroke to their capacity to participate in the community. Thus, to be able to be independent in the community, the stroke survivor must be able to walk at about 80 cm/s, but this speed is too slow to cross wide streets in large cities (87). At the end of their rehabilitation phase, relatively few persons with stroke walk at this speed (1,2,20,23,83). After stroke, persons lack what has become known as "walking competency" (23). Those reintegrating into the community after stroke walk at average speeds that are insufficient to cross the street safely, especially wide intersections, or have insufficient endurance and strength to walk distances necessary to accomplish basic and instrumental activities of daily living. They may be unable to negotiate curbs, to maintain balance and stability while turning the head or reacting to unexpected perturbations, and lack anticipatory strategies to avoid or accommodate obstacles (89). Moreover, they often are fearful and have cognitive impairments affecting decision making while walking (87,88). Desrosiers et al. (90) also found disability measures of the lower extremity, including gait speed, to be highly correlated to handicap situations as measured by the Life-H outcome measure in persons after stroke, thus emphasizing the importance of mobility to promote social participation.

Schmid et al. (91) stratified gait speed after stroke into the following clinically meaningful ambulation classes based on the Perry et al. (86) study: household ambulation (<40 cm/s),

limited community ambulation (40–80 cm/s), and full community ambulation (>80 cm/s). In subacute stroke survivors with mild or moderate deficits who participated in a randomized, clinical trial of stroke rehabilitation, they (91) found that a gait speed gain leading to a transition to a higher class of ambulation results in better function and quality of life, especially for household ambulators, thus suggesting that an outcome assessment based on transitions between gait speed classifications yields potentially meaningful indicators of clinical benefit. Such transitions in gait speed classification according to the Perry et al. (86) criteria were chosen as the primary outcome measure in the phase III Locomotor Experience Applied Post Stroke (LEAPS) trial (21).

As mentioned earlier, the patterns of recovery—and in particular, walking recovery—after stroke have essentially been defined by serial assessments made with clinical measures that detect little change beyond three months after stroke. When using walking speed as a marker of functional recovery, however, Richards et al. (74) found that walking speed continued to increase up to 12 to 18 months after stroke and that the increase in speed was related to increases in both cadence and stride length, thus redefining the timecourse of recovery. The recovery of gait speed, however, remained limited when compared to the gait speed of healthy, elderly persons asked to walk slowly, with the mean level of gait speed recovery attaining about 50% of the slow speed of the healthy subjects at 12 to 18 months after stroke (74). The latter study documented recovery in a cohort of patients with an ischemic stroke caused by a middle cerebral artery infarct who participated in a randomized, controlled trial comparing three physical therapy interventions (1,92).

Kollen et al. (83) documented the recovery of walking speed in a prospective cohort longitudinal study of 101 persons with acute stroke who participated in a clinical trial designed to study the effects of augmented therapy (20). None of the participants were able to walk unassisted in the first week after stroke. The mean interval between stroke onset and the first unassisted walk was 4.8 ± 2.9 weeks. They followed the subjects for 52 weeks, and not all of the subjects progressed to unassisted walking; however, comfortable walking speed was measured in 85 and fast walking speed in 81 participants. The mean comfortable walking speed progressively increased from 3.7 to 63.5 cm/s at 1 year after stroke, whereas the mean maximum speed increased from 7.1 to 85.1 cm/s, thus confirming the progressive increase in gait speed up to 1 year after stroke. Moreover, they found a systematic difference between comfortable and fast walking speeds. Regression analyses applied cross-sectionally and longitudinally demonstrated that the relation between comfortable and maximum walking speed does not change over time after stroke. Maximum speed was estimated to be 1.32 times that of comfortable walking speed (83). This is an important finding because it makes it possible to estimate the maximum speed a subject can attain, without actually measuring it, to predict, for instance, the capacity to cross a wide street.

The works of Richards et al. (73) and Kollen et al. (83) have clearly shown that gait speed continues to increase beyond six months after stroke when clinical measures may fail to show further functional recovery. The following section reports the extension of the Richards et al. (74) study of recovery in gait movements and muscle activations accompanying changes in gait speed in the 11 subjects that remained in the study 2 years after stroke (93).

RECOVERY, FROM STROKE ONSET TO TWO YEARS AFTER STROKE, OF WALKING SPEED AND ITS RELATION TO MOVEMENTS AND MUSCLE ACTIVATIONS OF THE LOWER EXTREMITY

Table 19.1 gives selected subject characteristics for 11 patients with complete data followed from baseline to 2 years after stroke. At 6 weeks after stroke, 23 of the 27 patients recruited into the study remained, and of these, 18 were able to walk, 15 with one-arm support for balance or independently, whereas 3 required maximal bilateral arm support to walk 4 m (73). Of the five patients who did not walk at six weeks after stroke, one refused to be evaluated and four others were unable to walk, even with maximal bilateral support. Two years after stroke, all of the patients remaining in the study could walk independently.

Figure 19.1 illustrates the recovery of gait speed over time in comparison to values obtained in healthy subjects walking slowly. At 6 weeks after stroke, the gait speed of two patients (cases 113 and 211) fell within the confidence limits of the healthy controls, and a third (case 206) was close. The mean gait speed was 31.8 ± 19.9 cm/s (mean, ± 1 SD, n = 11). Two years after stroke, all the patients walked faster and six attained normal confidence limits. The mean speed almost doubled, rising to 62.8 ± 19.1 cm/s (n = 11), a speed that is still much below the 104.3 ± 19.3 cm/s free speed of healthy subjects walking under similar laboratory conditions.

Recovery, as defined by comparison to healthy values, in the ankle movements and muscle activations that accompanied these changes in gait speed are shown in Figure 19.2. In most cases, the movement and activation profiles differ markedly from normal values at six weeks after stroke and are closer to normal two years after stroke. Interestingly, the movement profiles (top row) appear to show better recovery than the muscle activation profiles, particularly the TS (middle row). As previously mentioned, the mean speed approximately doubles during this time frame, and this increase in speed is related to both an increase in stride length (59–88 cm) and faster cadence (61–85 steps/min).

To examine more closely the relationship between gait speed and the patterns of movements and muscle activations with recovery, the 11 patients 2 years after stroke were divided into 2 groups: a slow-walking group (n = 5) and a fast-walking group (n = 6). The walking speed of patients in the fast group attained or surpassed the confidence limits of the healthy controls walking slowly (Figure 19.1).

TABLE 19.1 Selected Characteristics of the Subjects Evaluated at Baseline One Week After Stroke and Two Years After Stroke. These Subjects Participated in a Randomized Controlled Trial That Evaluated the Effects of an Intensive Task-Oriented Gait Training Program

			FUGL-MEYER LEG MOTOR SUBSCORE (MAXIMUM SCORE = 34)			BALANCE SCALE (MAXIMUM SCORE = 56)	
PATIENT NUMBER	AGE (YEARS)	GENDER/ AFFECTED SIDE	B	6 WEEKS	2 YEARS	6 WEEKS	2 YEARS
206	82	W/L	30	23	NA	22	NA
207	69	M/L	22	25	32	43	51
113	66	M/L	14	30	31	52	54
211	65	W/L	19	28	31	52	NA
201	60	M/R	21	31	33	55	56
104	63	W/R	9	30	29	54	55
204	77	M/R	19	26	29	39	52
101	61	W/L	5	24	28	23	51
208	63	W/L	16	16	26	14	48
109	56	M/R	6	20	NA	40	NA
107	48	M/R	4	10	12	42	51
Mean ± 1 SD (n = 11)	64.6 ± 9.3	W:5/R:5	15 ± 8.3	23.9 ± 6.5	27.9 ± 6.3	39.6 ± 14.2	52.3 ± 2.6

Abbreviations: B, baseline; L, left; M, men; NA, not available; R, right; W, women.
Source: From Refs. (1,92).

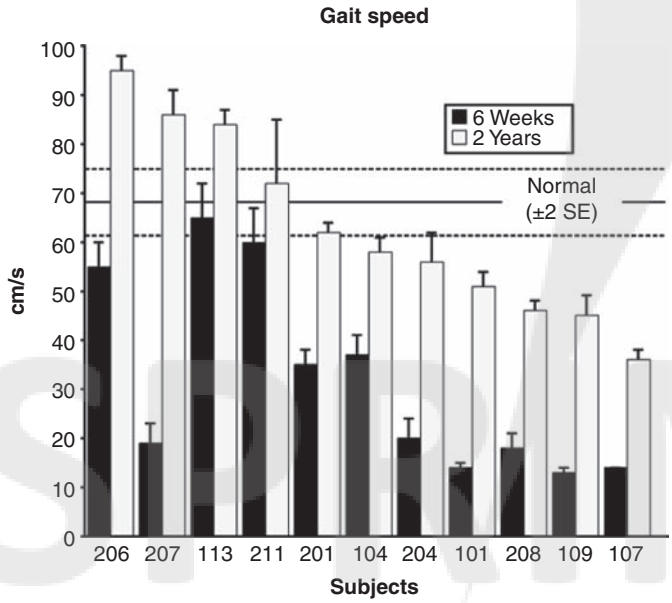


FIGURE 19.1 Bar graph representing changes in gait speed between 6 weeks and 2 years after stroke for 11 subjects with hemiparesis (case numbers given on x-axis). Horizontal lines indicate mean and confidence limits of gait speed obtained in a group (n = 10) of healthy subjects (aged 58 ± 5.6 yrs.) walking at 75% of their usual cadence (mean speed 68.3 ± 6.7 cm/s; ±2 SE, n = 8).

As shown in Figure 19.3, the movement and muscle activation profiles during gait of the fast group (H-N) tend to be more similar (except for the HAMST activations, which remain abnormal) to the profiles derived from the healthy subjects. Given the role of the TS in the generation of power to generate walking speed (71,72,94), one would expect more marked changes in the profiles (shape and amplitude) of the TS "push-off" activation bursts of the patients in the fast group.

To further examine the recovery (*recovery* is used in the general sense and refers to return in the capacity to activate the muscle) in the muscle activation profiles over time, the areas under functionally important activation bursts were compared (Figure 19.4). As expected from the profiles shown in Figures 19.2 and 19.3, the "push-off" activation burst in the TS does not change over time in this group of patients. In contrast, the TA activation burst that is related to foot lift at swing phase initiation (60%–80% of the gait cycle) shows recovery up to 2 years after stroke. The recovery in this burst is representative of recovery in the two other TA activation bursts (0%–16% and 84%–100% of the gait cycle) that were correlated with the 60% to 80% gait cycle activation burst ($r = 0.89$ and 0.86, respectively, $P < .01$). The QUAD also improves over time, but later than the TA, with the largest change occurring between 6 months and 1 year after stroke in the late swing activation burst (84%–100% of the gait cycle)

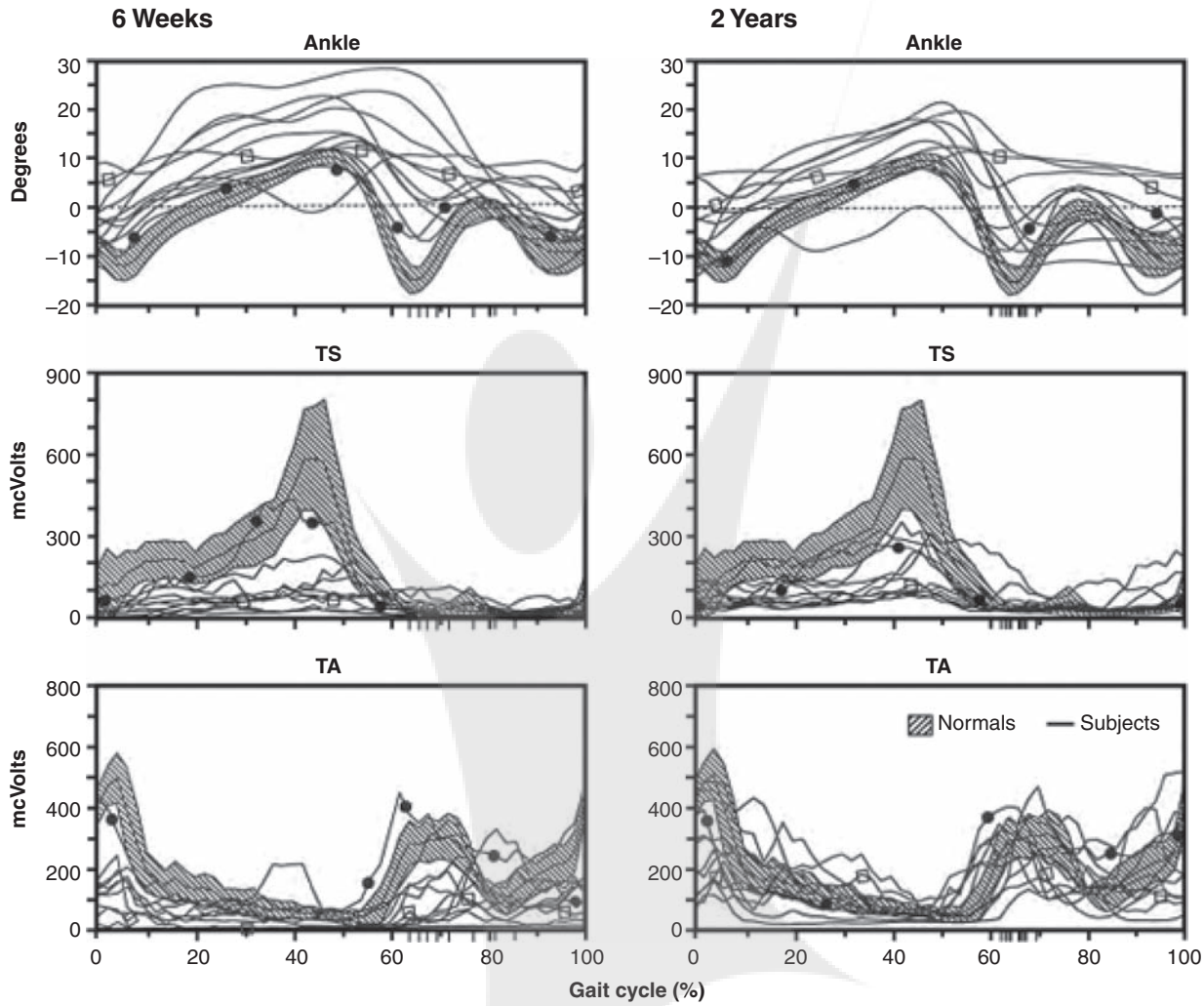


FIGURE 19.2 Profiles of ankle movements (obtained with a TRIAX electrogoniometer) and activations (surface EMG; rectified and time averaged; time constant 20 ms) of the triceps surae (TS) and tibialis anterior (TA) muscles during gait of 11 subjects at 6 weeks and 2 years after stroke in comparison with normal values (mean ±2 SE, n = 8). The patients who walked slowest (case 109: open squares) and fastest (case 113: filled circles) at 6 weeks are indicated.

that corresponds to knee extension preparatory to weight acceptance. Comparison of the magnitude of the activation bursts (TA, TS, and QUAD) in the patients with healthy values (Figure 19.4D) emphasizes the poor recovery of the TS two years after stroke.

Pearson correlation coefficients (Table 19.2) were calculated to further probe the interaction among the muscle activation bursts and gait speed during recovery, defined as the magnitude of change from baseline to two years after stroke. Recovery in the TA bursts (0%–16% and 84%–100%) was significantly associated (r = 0.74 and 0.64, respectively) with change in the TS (20%–50%). Recovery in the QUAD, mainly a knee extensor, was most highly correlated (r = 0.77, $P < .01$) with recovery in the ankle extensors (TS). Recovery of gait speed, in contrast, had a closer association with recovery in the TA (60%–80%: r = 0.60, $P < .01$) than with the two extensor muscle groups.

In summary, these data describe the longitudinal recovery of gait in a cohort of patients with a middle cerebral artery ischemic stroke (1). One week after stroke, their Fugl-Meyer leg subscores (6) varied from 4 to 30, indicating a wide range of impairment, and this was later reflected by the variable gait recovery. Although the mean gait speed at 6 weeks after stroke of about 30 cm/s doubled to a near-normal slow gait speed 2 years after stroke, some patients attained a relatively good walking pattern, whereas others were left with a very abnormal pattern. These results also show a clear relationship between gait speed and the quality of gait movements and muscle activations two years after stroke, confirming the findings of our earlier study (73) and in agreement with Wade et al. (82).

Recovery of activation profiles was not uniform among the muscles. The TA recovers consistently over time, whereas the QUAD recovers little until about one year after

stroke, and the TS was particularly resistant to change. The apparent resistance of the TS to recovery is a surprising and important result because of the importance of this muscle as a generator of propulsive force for walking and the emphasis put on the re-learning of "push-off" in gait rehabilitation approaches (71,95,96). One can ask whether the TS is more resistant to change for physiological reasons or, alternatively, if rehabilitation strategies are inadequate to provide the appropriate input to evoke recovery in this muscle. In this context, Colborne et al. (97) demonstrated that computer-assisted biofeedback (ankle position or EMG biofeedback) was more effective than conventional therapy in inducing improved force impulses of the plantar flexors at "push-off." Furthermore, in a subgroup of 25 subjects after stroke, participating in an RCT, who received task-oriented gait training, Richards et al. (2) found that an improved "pushoff" plantar flexor A2 power burst (see Figures 19.3 and 19.7 for illustrations of the muscle activations and power bursts) in late stance explained about 25% of the variance in the change in gait speed posttherapy.

Nevertheless, the close association between gait speed and recovery in the TA two years after stroke confirms and

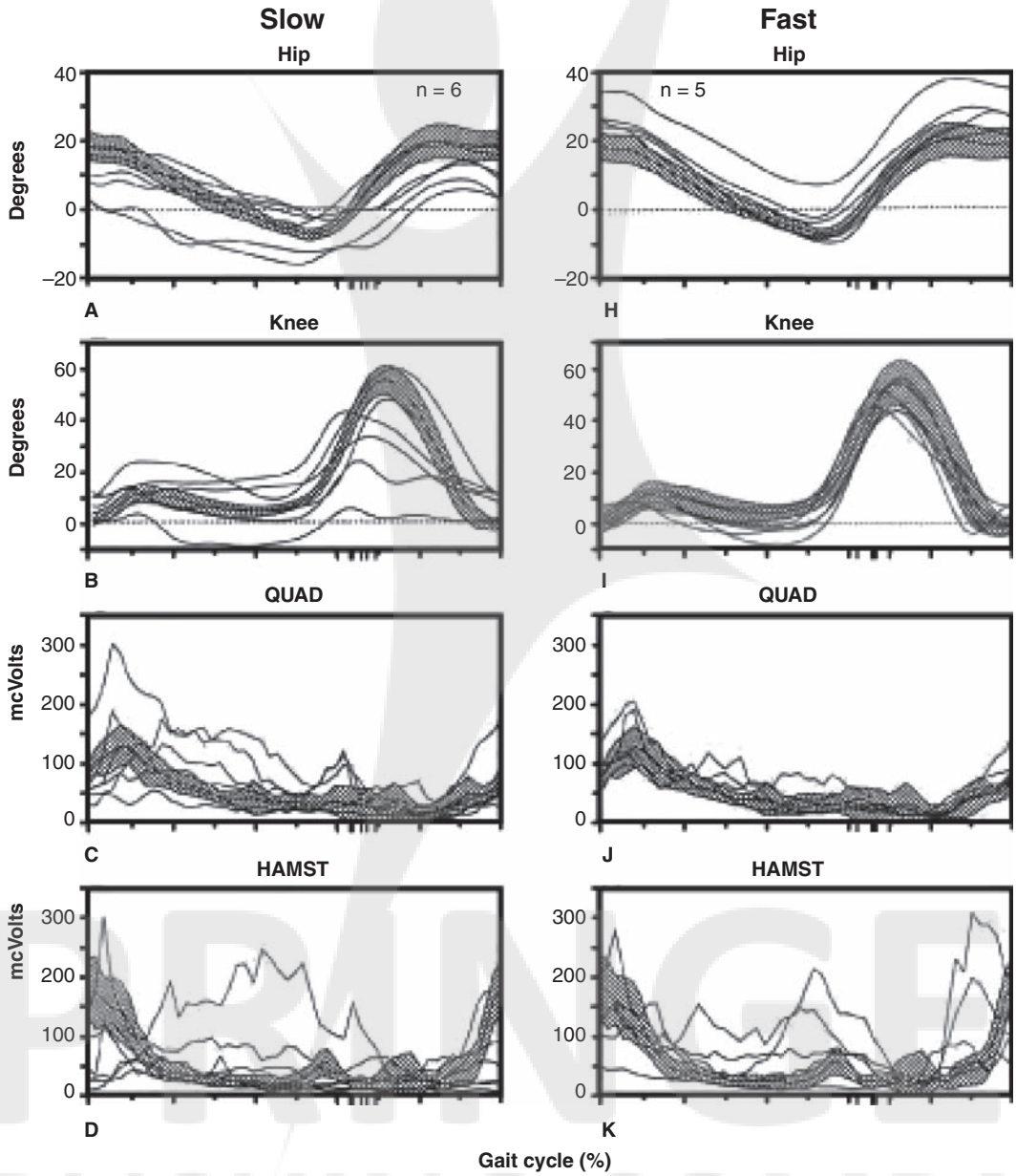


FIGURE 19.3 Comparison of the profiles of hip, knee, and ankle movements and activations (see Figure 19.2 text) of the quadriceps (QUAD), hamstrings (HAMST), triceps surae (TS), and tibialis anterior (TA) muscles during the gait cycle of a group of slow-walking (A–G) and a group of faster-walking (H–N) subjects at two years after stroke with normal values. Thin lines represent the profiles of individual subjects. Shaded area gives mean and confidence limits for healthy controls (n = 8). Additional vertical lines on x-axis indicate end-of-stance phase, which ranged from 62% to 69% and from 60% to 67% of the gait cycle for the slow and fast groups, respectively. (*Continued*)

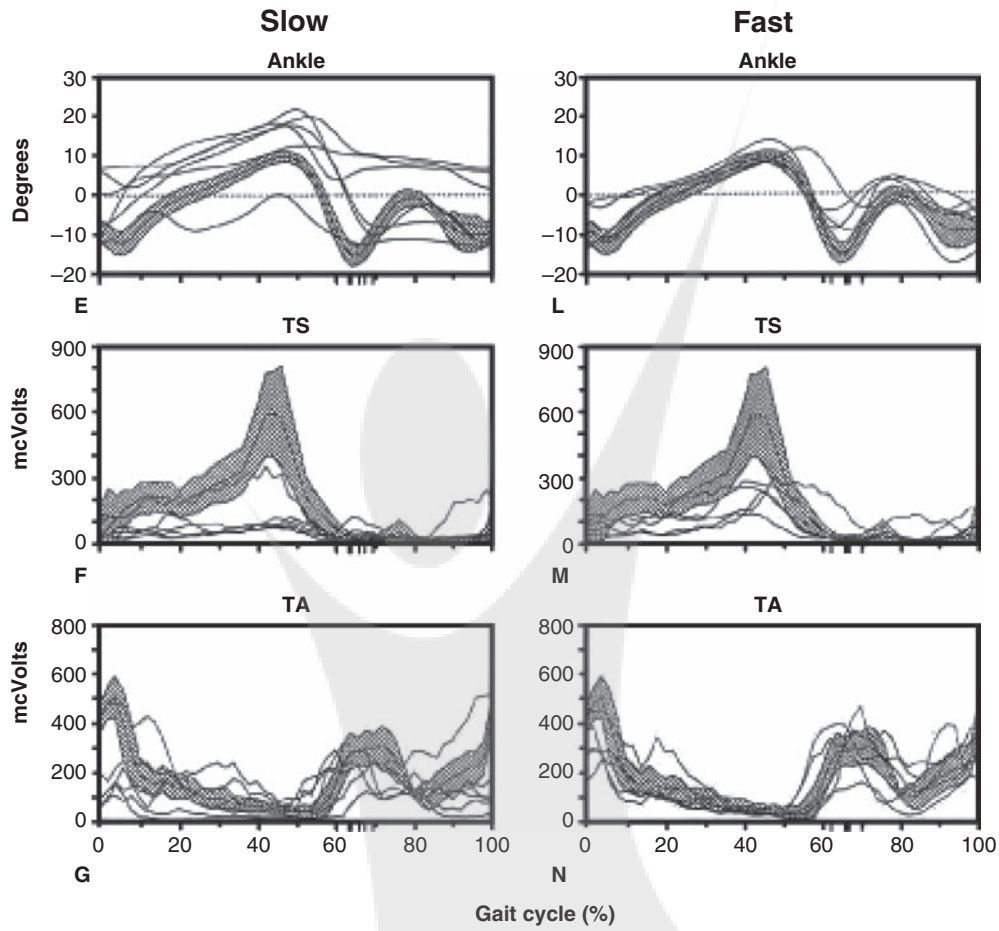


FIGURE 19.3 (*Continued*)

extends earlier findings (74) and suggests that the TA may be an important muscle to target in therapy given its recovery potential and association with gait speed recovery. Could it be that the TA is more easily controlled by voluntary drive (98) after stroke, whereas the TS is under control of the subcortical postural system and less accessible to voluntary drive after a lesion of the corticospinal tract? Clearly, these questions provide ample motivation for continued research in this area.

These changes in muscle activations during gait associated with recovery over time in persons after stroke may appear to be in opposition to previous reports (99–101) to the effect that recovery of gait is not associated with changes in the temporal patterning of muscle activations obtained with surface electrodes. These studies, however, only considered the timing of the muscle activations by defining "on" or "off" bursts during the gait cycle and did not take into consideration the amplitude of the muscle activations. Moreover, they did not imply that the timing of the muscle activations during gait was not perturbed after stroke, but rather that the pattern did not change over time or after therapy (100,101). Den Otter et al. (102) attributed the apparent robustness of neuromuscular timing characteristics in the context of varying task demands to differences in the control of the timing and amplitude of EMG bursts during locomotion. In particular, timing is understood to be determined mainly by central pattern generators, whereas amplitude is understood to be largely dependent on reflex loops (103,104).

Because paresis is a primary contributor to poststroke gait impairment (62), different methods have been devised to quantify the muscle activations during gait so that both the timing and the amplitude of the activation (EMG) bursts, which reflect the intensity of the contraction, are taken into account (62,105,106). The EMG analysis method depicted in Figure 19.4 allows the comparison of the muscle activations of the subjects after stroke with normal data in key functional activation bursts during the gait cycle. The area under these bursts represents both the timing and the amplitude of the activation bursts and assumes that the variability in EMG records as a result of factors such as electrode position, skin contact, and subcutaneous tissue are similar in the subjects after stroke and the healthy controls walking at slow speed to minimize differences in amplitude related to faster walking speeds (94). Den Otter et al. (102) argued that recovery-related changes in lower-extremity muscle activity during gait after stroke were primarily related to

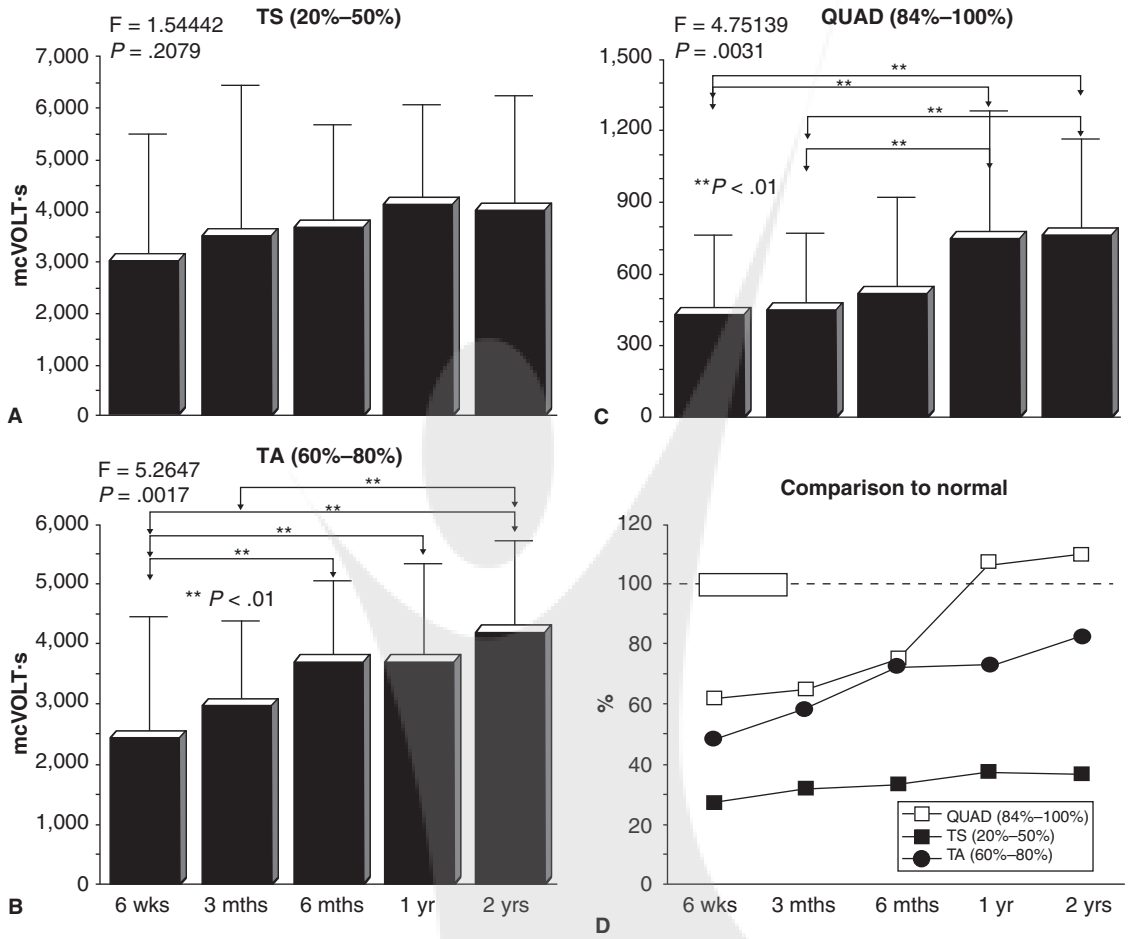


FIGURE 19.4 Bar graphs A–C, depicting recovery over time of selected muscle activation bursts of the triceps surae (TS), tibialis anterior (TA), and quadriceps (QUAD) muscles of 11 patients whose muscle activation profiles were depicted in Figure 19.3. Values in A–C give mean 1 SD. The area under specific activation bursts was used in comparisons. Three activation bursts were defined for the TA (0%–16%, 60%–80%, and 84%–100%). These bursts are related to footfall control after foot contact, toe lift at swing phase initiation, and foot lift preparatory to foot contact at the end of the cycle. Activation bursts related to functional events in the gait cycle were also defined for the other muscles: TS (20%–50%) and QUAD (84%–100%). An analysis of variance for repeated measures and the Scheffe post hoc test were used to compare changes over time (x-axis). Line graph in D compares recovery of the activation bursts (in % of values obtained in healthy subjects) in the three muscles. Statistical differences are indicated by asterisks (**$P < .01$) and horizontal lines above bars in A–C.

TABLE 19.2 Pearson Correlation Coefficients (r) Between Recovery (Change From Baseline to 2 Years After Stroke) in Gait Speed and Muscle Activation Burst That Are Functionally Important During the Gait Cycle in Persons With Chronic Stroke (n = 11)

	GAIT SPEED	TS (20%–50%)	TA (0%–16%)	TA (60%–80%)	TA (84%–100%)	QUAD (84%–100%)
Gait speed	1	0.27	0.53	0.60[a]	0.20	0.22
TS (20%–50%)		1	0.74[a]	0.59	0.64[b]	0.77[a]
TA (0%–16%)			1	0.89[a]	0.79[a]	0.49
TA (60%–80%)				1	0.86[a]	0.43
TA (84%–100%)					1	0.41
QUAD (84%–100%)						1

[a]$P < .01$; [b]$P < .05$.

Abbreviations: QUAD, quadriceps; TA, tibialis anterior; TS, triceps surae.

the potential force output of muscles and, therefore, that increases in strength may be expressed as changes in the amplitude of muscle activity within relatively stable timing schemes.

MAGNITUDE OF REHABILITATION-RELATED CHANGES IN WALKING SPEED

To examine how changes in balance and motor function relate to changes in gait speed after rehabilitation, Berg balance scores (BBS), FML subscores, and gait speed at baseline, after rehabilitation, and at follow-up, were reviewed for 62 persons with subacute stroke who participated in an RCT that compared the efficacy of 2 task-oriented physical therapy (PT) programs to promote gait recovery (2). Because the therapeutic effects of both approaches were found to be equivalent, the subjects were pooled for these secondary analyses. They received a total of about 38 hours of task-oriented physical therapy over 2 months that was provided in two in-patient rehabilitation settings. Of the 62 patients who entered the study, complete data were available for 50 patients at follow-up 3 months later.

Figure 19.5A illustrates the more than doubling of gait speed after therapy (27 ± 15 to 61 ± 38 cm/s) and the continued increase, by an additional 8 cm/s to 69 ± 38 cm/s, at follow-up 3 months later. The total change from baseline 50.4 ± 18.3 days after stroke onset to follow-up about 5 months later was 41.99 ± 31.54 cm/s. This is a large change in relation to other studies that will be discussed at the end of this section. It is evident from the standard deviations, however, that there is much variability in the magnitude of the change in gait speed among the subjects. From baseline to postrehabilitation (Figure 19.5B), only 30 subjects increased their gait speed to greater than or equal to 16 cm/s, recognized as the minimal clinically important difference (MCID) (107). At follow-up (Figure 19.5D), 13 subjects had further increases in gait speed greater than the MCID, but most had very small or no change.

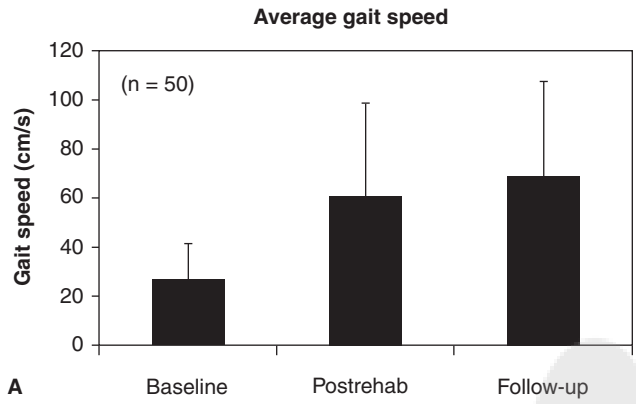
As expected, motor impairment (Figure 19.5E) of the lower extremity, as measured by the FML subscore, and balance, as measured by the BBS (Figure 19.5F), were significantly correlated ($P < .000$) with walking speed at baseline, and explained 36% and 30%, respectively, of the variance in gait speed. Importantly, the time after stroke when the inpatient rehabilitation program was initiated (subjects received undocumented rehabilitation services in the acute care setting before being admitted to the rehabilitation setting) was negatively correlated ($r = –0.39$, $P < .002$) with changes in gait speed from baseline to postrehabilitation (Figure 19.5G).

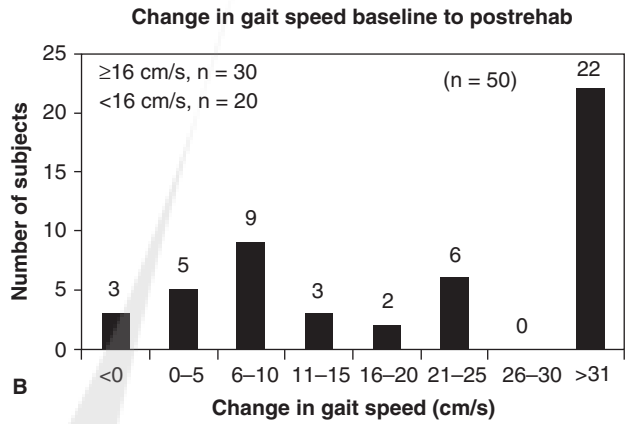
In this cohort of subjects, gait speed at baseline was significantly correlated with gait speed after rehabilitation ($r = 0.62$, $P < .0001$, $R^2 = 0.40$), indicating that about 40% of the change in gait speed from baseline can be explained by the initial gait speed. Also, the side of the hemiparesis had no significant effect on the change in gait speed with therapy ($P > .05$).

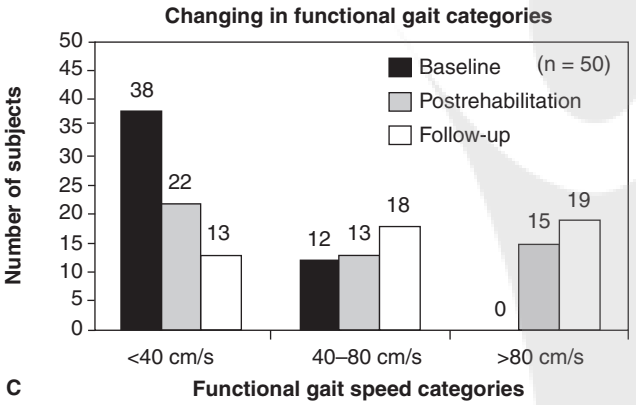
To further probe why some subjects improved more than others and why some continued to improve during the follow-up period, whereas others did not, further analyses focused on whether or not subjects changed functional gait speed category after two months of rehabilitation (21,91). Figure 19.5C shows the number of subjects in each functional gait speed category at the three time points. This analysis revealed that, at baseline among the 50 subjects, 38 had severe and 12 moderate gait impairment (21). After rehabilitation, 22 of the subjects in the severe category had "leaped" into another category, whereas 16 remained in the severe category. To better understand what characterized those who "leaped" as opposed to those who did not, gait speed, FML subscores, and BBS were compared as a group (Figure 19.6) and individually (Table 19.3).

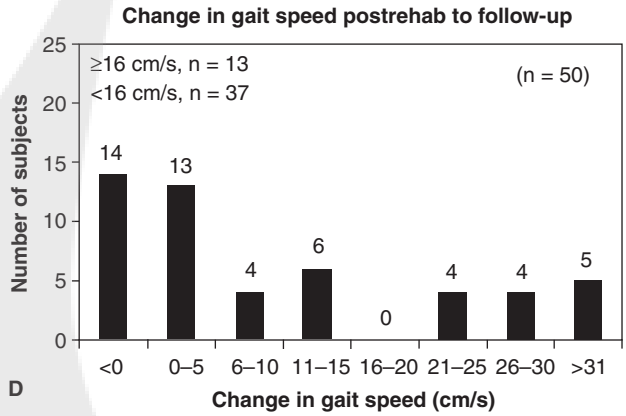
For the subjects with severe gait impairment (left column, Figure 19.6), the much faster gait speed ($P < .001$) in the subjects *that changed* category was associated with a higher BBS ($P < .05$) and FML ($P < .01$) at baseline and also after rehabilitation. At follow-up, the faster gait speed ($P < .001$) was associated with a higher FML ($P < .001$) but a similar BBS. The subjects in the group with a moderate gait speed impairment at baseline (right column, Figure 19.6) *that changed* category had a similar gait speed and BBS to those who did not, but a higher FML ($P < .001$). After rehabilitation, those *that changed* category had a much faster gait speed ($P < .001$) that was associated with higher FML ($P < .001$) and a trend in BBS ($P = .06$). At follow-up, the faster gait speed ($P < .001$) in the group *that changed* category was associated with a higher FML ($P = .05$) but a similar BBS, likely as a result of the ceiling effect with this measure. These results suggest that motor control is more discriminant than balance between the groups, but the ceiling effect of the BBS may be a confounding factor.

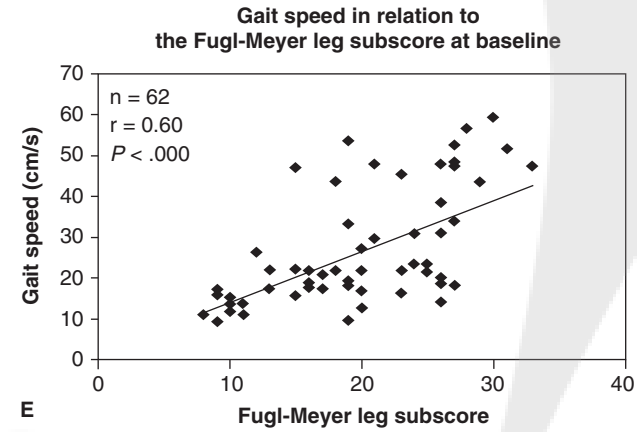
To further examine the association of BBS and FML scores with improvements in gait speed that allowed some subjects to "leap" category, a further analysis was made of individual scores by establishing threshold scores for the BBS and FML to distinguish the subjects. For the BBS, a threshold of less than 45 was selected because in elderly persons, the relative risk of falling is 2.7 times more likely in those with a BBS score of less than 45 and is associated with the need for a cane (112). For the FML, a threshold of 25 was used based on our previous work on recovery of gait speed in the first month after stroke (1). This analysis (Table 19.3) revealed that after therapy in the group with a severe gait impairment *that did not change* category (n = 22), 12 and 20 subjects, respectively, had BBS or FML scores below threshold, and 10 had both scores below threshold. In contrast, among *those that changed* category (n = 16), only one had BBS, two FML, and none both scores below threshold. In the moderate gait speed impairment group, of the six subjects *that did not change* category, two had BBS, four FML, and two both scores below threshold. In contrast, none of the subjects had either score below threshold in the group *that changed*

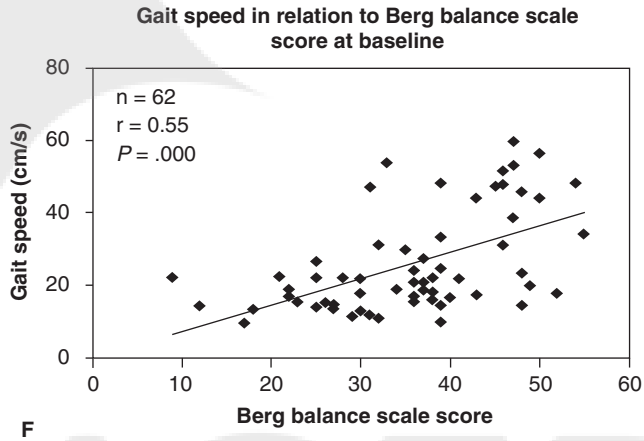












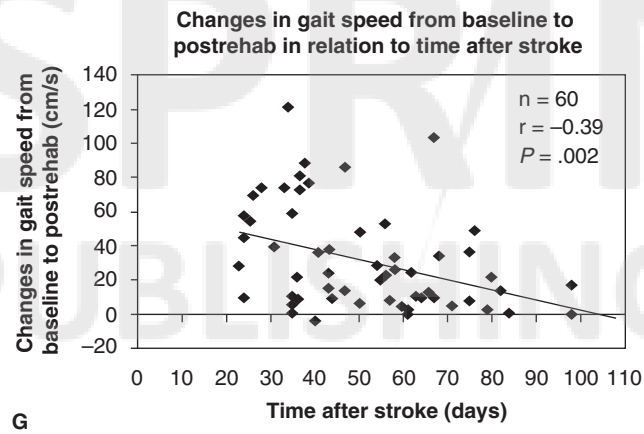


FIGURE 19.5 A series of graphs illustrating changes in gait speed in a cohort of subjects with subacute stroke who participated in an RCT. The size of the changes in gait speed are illustrated in A, B, and D, whereas C shows the number of subjects in gait categories at baseline, after therapy, and at follow-up. Selected correlations are illustrated in E–G.

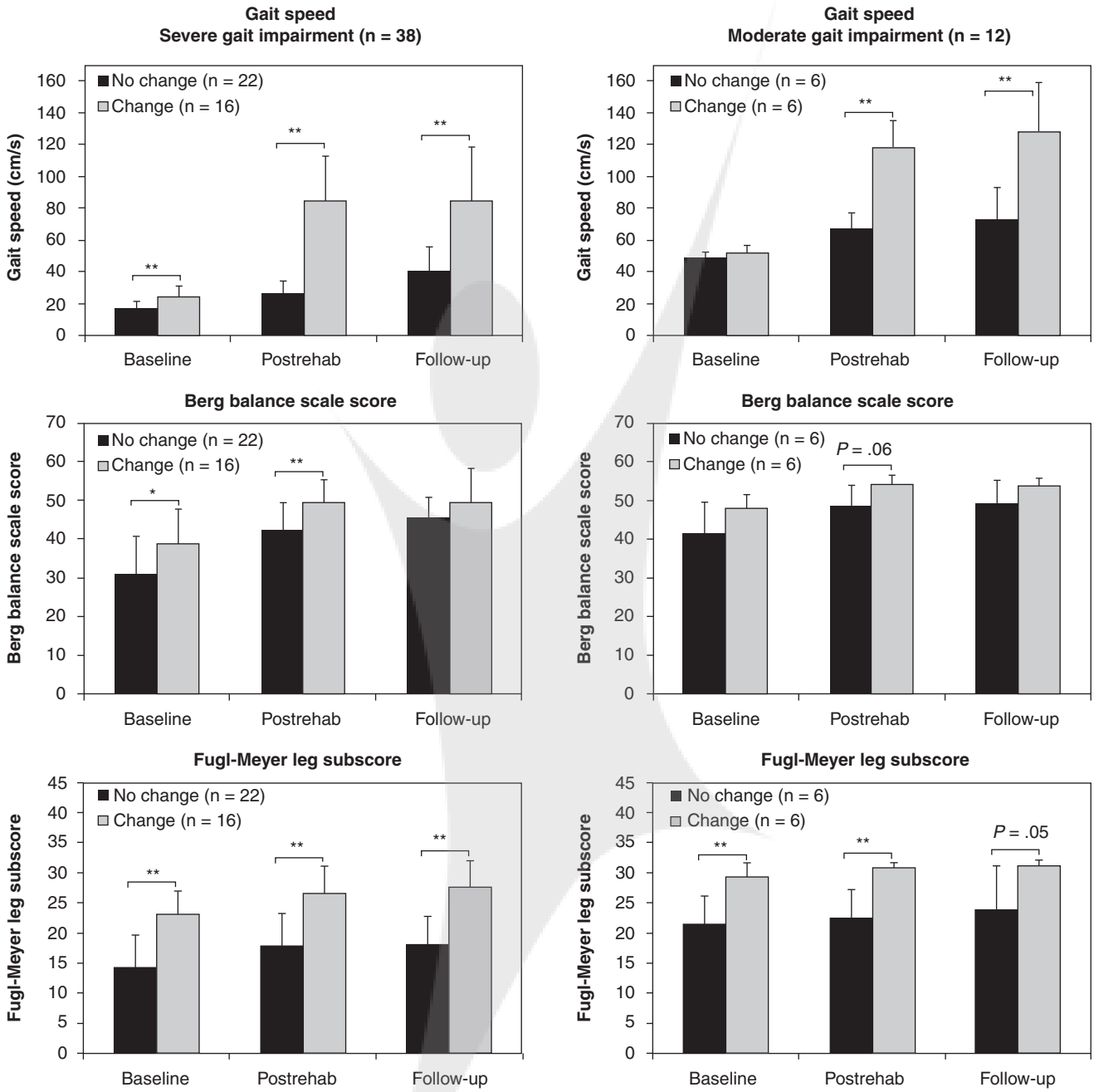


FIGURE 19.6 Bar graphs illustrating gait speed, the Berg Balance Score, and the Fugl-Meyer leg subscore in the subjects who changed or did not change functional gait category after therapy. Results for subjects in the severe gait speed impairment category (n = 38) are shown on the left, whereas those in the moderate gait impairment category (n = 12) are shown on the right of the figure. Statistical differences are indicated by asterisks (*$P < .05$, **$P < .01$) and horizontal lines above bars.

category. Thus, this analysis showed that, among subjects in the severe gait impairment category at baseline, those who attained the set thresholds for BBS and FML were likely to have improvements in gait speed allowing them to change functional category. In contrast, the fact that 20 of 22 subjects in the group who did not change category had FML scores less than 25, whereas 12 of 22 had BBS scores less than 45, suggests that the FML score may be more critical.

Despite the small number (n = 12) of subjects in the moderate gait impairment category at baseline, differences in the mean BBS and FML scores were found between those who changed category after rehabilitation and those who did not. In those who did not change category, two subjects did not attain both thresholds, and four did not attain only the FML threshold, possibly pointing to impairment as the limiting factor as with the subjects in the severe gait impairment

TABLE 19.3 Comparison of the Number of Subjects in the Severe and Moderate Gait Impairment Categories Who Attained the Berg Balance Scale (BBS) and the Fugl-Meyer Leg (FML) Subscore Threshold Among the Subjects Who Changed or Did Not Change Gait Category After Therapy

THRESHOLDS FOR BBS AND FML SUBSCORE AFTER THERAPY	SEVERE GAIT IMPAIRMENT (n = 38)		MODERATE GAIT IMPAIRMENT (n = 12)	
	NO CHANGE (n = 22)	CHANGE (n = 16)	NO CHANGE (n = 6)	CHANGE (n = 6)
BBS < 45	12	1	2	0
FML < 25	20	2/15	4	0
BBS < 45 and FML < 25	10	0	2	0

group. Such a finding is reasonable because it suggests that a certain level of motor recovery is necessary before independent gait that requires more balance control than walking with assistance or a cane can be attained (112). Nevertheless, these data clearly demonstrate the importance of recovering a threshold of motor and balance control before a change in functional gait speed can be reached. The high correlations between the BBS (r = 0.65, $P < .000$, n = 50) and FML (r = 0.71, $P < .000$, n = 50) after therapy and the change in gait speed from baseline to after therapy support this assertion. The suggested threshold values may be clinically important as predictors of gait outcome.

To complete this section, the magnitude of changes in gait speed in selected gait intervention studies are discussed in relation to the results of the Richards et al. (2) study. The subjects received 38 ± 12 (n = 60) hours of task-oriented physical therapy on the basis of 1 hour/day/5 days/week for 8 weeks, when possible. In a subset (see Figure 19.5) of subjects (n = 50), the baseline measures taken 59.1 ± 8.8 days after stroke were: (a) FML: 19.7 ± 7.0, (b) BBS: 36.6 ± 10.5, and (c) gait speed: 26.9 ± 14.6 cm/s. The change in gait speed from baseline to after intervention was 33.9 ± 31 cm/s and from baseline to follow-up 3 months later was 42.0 ± 31.5 cm/s, corresponding to about 5 months after stroke for these subjects. The magnitude of change is much larger than that reported in recent studies involving BWSTT (21,106,108,109), which report a change in gait speed varying from 13 to 27 cm/s (posttherapy-baseline) and 15 to 24 at follow-up (follow-up-baseline). Others report gains of 14 cm/s after task-oriented circuit training (23) or 25 cm/s at follow-up after a home program designed to improve strength, balance, and gait (21). Bowden et al. (108) divided 27 subjects with chronic stroke (22.9 ± 17 months after stroke) into responders (n = 18) and nonresponders (n = 9) after BWSTT. The responders, who had an intital FML of 24.7 ± 3.7 and a baseline gait speed of 52 ± 18 cm/s, gained 27 ± 12 cm/s after 12 weeks of an intervention consisting of BWSTT plus overground walking provided 3×/week for 12 weeks.

Although it is difficult to compare subjects included in different studies, the FML and gait speed at baseline provide an indication of stroke severity. In these studies, the FML baseline mean scores varied from 23.1 to 28.7 (21,106,108,109), whereas the BBS was 42 in the Salbach et al. (23) study that did not report the FML. Baseline gait speed varied from 37 to 50 cm/s, a strong indication that the majority of the subjects were less impaired at baseline than the subjects described in Figure 19.5. Moreover, the interventions were started later after stroke, suggesting that much of the early gait recovery (1,83) had already taken place, so that the gains in gait speed would be expected to be smaller. Thus, the earlier intitiation of the intervention (2) likely explains a large part of the relatively large change in gait speed after therapy. There is an urgent need to better understand the importance of specific motor control and balance threshold levels necessary to surpass before further recovery can proceed and also how to foster maintenance of gains once the intervention ends to ensure continued improvements at follow-up and the persistence of those improvements thereafter.

MUSCLE GROUPS CONTRIBUTING TO THE GENERATION OF ENERGY FOR FORWARD PROPULSION, THEIR RELATIVE CONTRIBUTIONS TO WALKING SPEED, AND STRATEGIES USED BY PERSONS WITH HEMIPARESIS

Kinetic analyses such as moment of force and power profiles over the gait cycle help to understand *why* a subject has a given movement pattern and gait speed. The reader is referred to Winter (94) and Olney et al. (70) for details of the equipment, data, and formulae required to calculate joint moments (a *moment* is defined as the turning effect of a force about any point) and power (the *power* generated by a moment is the product of the moment acting at an axis and the angular velocity of the rigid body about that axis). The method of calculating muscle power is such that power generation (above zero on the y-axis) indicates that the power burst is achieved by a concentric contraction (at least for muscles crossing a single joint), thus further helping understand the force deficit. Work is the integral of power, with concentric and eccentric contractions producing positive and negative work, respectively. Since the seminal work of Winter (94), the contributions of the major muscle groups of the lower extremity contributing to the work of walking have become well known. The three major bursts

of energy generation and the propulsive force for forward progression come from the hip extensors in early stance (H1 in Figure 19.7), the plantar flexors at "pushoff" (A2 in Figure 19.7), and the hip flexors at "pull-off" (H3 in Figure 19.7) in late stance and early swing. The knee extensors in early stance (K2) produce a small amount of positive work. Most of the absorption is provided by the ankle plantar flexors (A1), the hip flexors (H2), the knee extensors (K1 and K3), and the knee flexors (K4).

Winter (94) further showed in healthy subjects that faster walking speeds were related to larger power generation bursts, particularly of the ankle plantar flexors at push-off (A2) that contributed most (about 75%) of the propulsive force, with the H3 hip flexor burst and the H1 hip extensor burst contributing most of the remainder. The contribution of the knee to the propulsive force was considered to be minimal. Many studies have since confirmed the influence of speed on energy generation (110,111,113). A study (113)

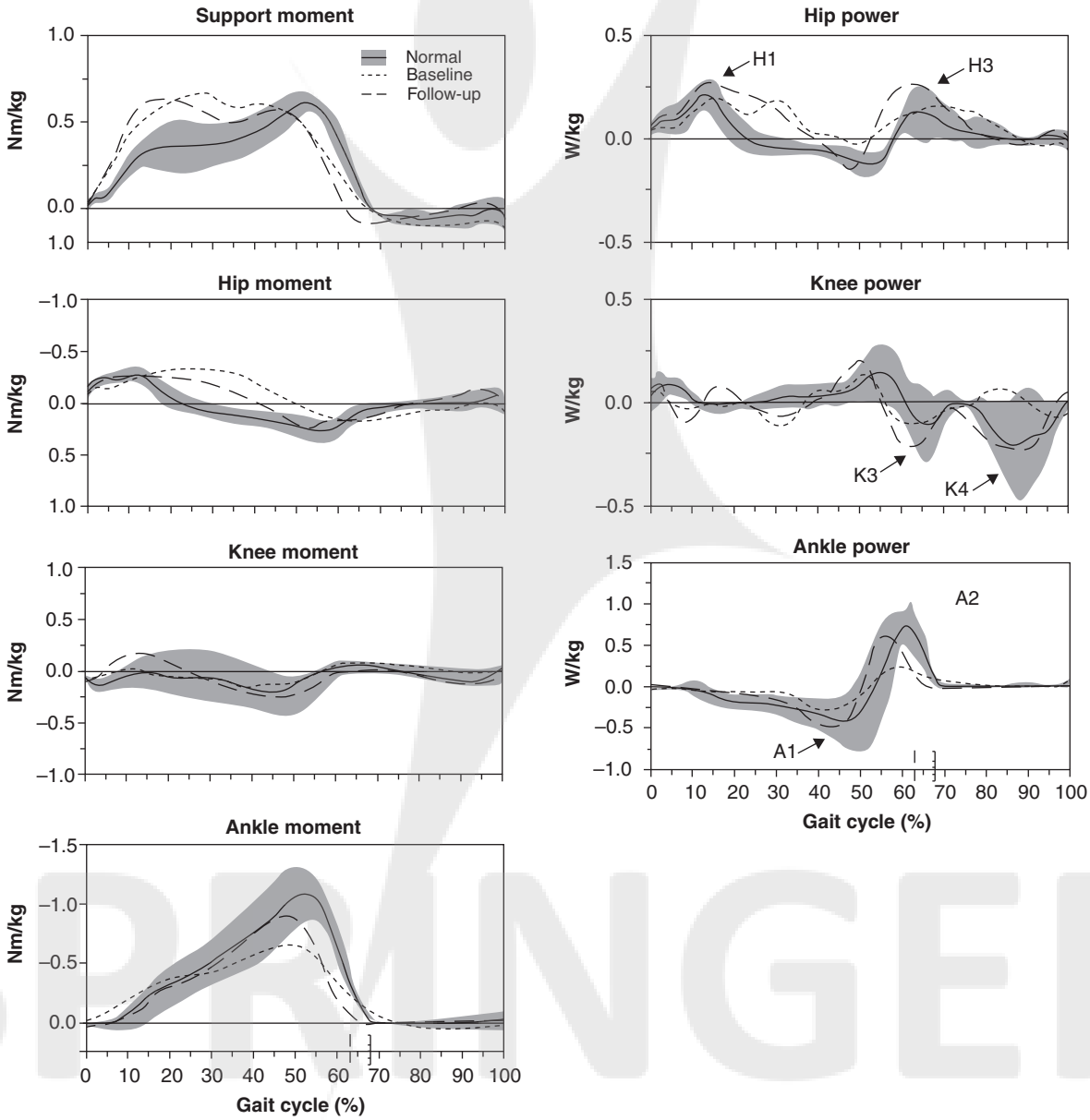


FIGURE 19.7 Comparison of the mean moment and power profiles for 19 subjects with subacute stroke who participated in the Richards et al. trial (2) before and after 2 months of task-oriented therapy with values obtained in healthy elderly controls walking slowly (59.7 cm/s, n = 5). Profile of moments and power (y-axis) are given in relation to the gait cycle in percent (x-axis). Mean baseline values for the subjects (dotted line) are compared to mean posttherapy values (interrupted line). Profiles in healthy controls represent mean 2 SD. The mean gait speed in the persons with stroke rose from 42 cm/s to 68 cm/s after therapy. Hip (H1 and H3) and ankle (A2) power generation and knee (K3 and K4) and ankle (A1) power absorption bursts are indicated.

that examined the effects of three metronome-induced cadences (60, 80, and 120 steps/min) on energy generation and absorption in healthy subjects found that the mean relative contribution of the ankle to mechanical energy generation was about 60% at the slowest cadence and fell to about 44% at the fastest cadence. In contrast, the 24% contribution of the hip at the slowest cadence rose to about 38% at the fastest cadence, whereas that of the knee increased from 16% to 19%. These findings indicate a large contribution from the hip muscles to the modulation of walking speed, whereas the ankle muscles are relatively insensitive to changes in speed—findings that are in agreement with previous studies (107,110,111,113). The variability, however, suggested that individual subjects likely used different strategies.

Do Persons With Stroke Employ the Same Kinetic Strategies to Produce Gait Speed as Healthy Subjects?

A stroke results in a walking disability because locomotor control is impaired. Although the impairment may be associated with different types of disturbed motor control (62,67–69,105), the net result is a diminished capacity of the lower-extremity muscles to act on the skeletal levers to produce rotational force at the hip, knee, and ankle. The impaired force output, in turn, results in altered power generation and absorption and can result in intralimb and interlimb compensatory gait patterns in which stronger muscle groups attempt to counter deficiencies by generating more than their normal work (70,71,96). In the first study examining the capacity for power generation in persons with chronic stroke, Olney et al. (70) divided a group of 30 subjects into slow (25 cm/s, SD = 5 cm/s, n = 10), intermediate (41 cm/s, SD = 8 cm/s, n = 10), and fast walkers (63 cm/s, SD = 8 cm/s, n = 10). Each subgroup comprised 10 subjects for a total of 30. They reported that in all three groups, the mean A2 power burst was smaller than that of healthy controls and, furthermore, that its magnitude was related to walking speed. The H3 power burst, in contrast, tended to be larger than in healthy controls, suggesting that persons with stroke compensate for a poor "push-off" burst by pulling off more at the hip. Not unexpectedly, given that walking is a bipedal task, they also reported that even if the power-generating capacity of the less-affected lower extremity differed from healthy values, the less-affected side performed a greater proportion of the positive work than the affected side at all speeds, approximately in a 60:40 ratio. From simulations, Higginson et al. (115) have shown that the contributions of individual muscles to the support moment in midstance of a person with stroke differ from those of neurologically healthy older subjects. The slower walking speed of persons with stroke, although no doubt a factor, cannot explain these differences in kinetic strategies, because persons with stroke walking at similar speeds may use quite different power combinations (65,114).

Data obtained from subgroups of the same cohort of patients that participated in the RCT (2) described in the previous section are used to illustrate the concepts relating to power generation and the production of gait speed. Figure 19.7 gives a comparison of the mean moment and power profiles produced by the affected side of 19 persons with stroke before (1.4 ± 0.5 months after stroke onset) and about 2 months after task-oriented gait training with values obtained in 5 healthy elderly persons walking at about 60% of their free gait speed (59 ± 7 cm/s). When comparisons are made with power profiles obtained from healthy subjects walking at free speed, the magnitude of the differences between the subjects with hemiparesis and the healthy subjects are much larger. As illustrated by the hip and ankle power profiles, the A2 ankle "push-off" power burst and the H1 hip extensor burst in early stance and the H3 hip "pull-off" burst in late stance and early swing phase increased after therapy. This increased power generation at the hip and ankle was associated with a mean increase in gait speed of 26 cm/s (42–68 cm/s). In this group of patients (n = 19), Richards et al. (72) found the peak of the A2 and H3 power bursts to be significantly correlated to gait speed ($r = 0.62$, $P < .01$, $r = 0.85$, $P < .01$, respectively) after stroke. At the end of the RCT, Richards et al. (2) reported a near-doubling of gait speed after therapy and reported that, in 25 of these subjects with prekinetic and postkinetic gait analyses, the increased gait speed was associated ($r = 0.52$, $P = .003$, $n = 25$) with an increase in the A2 ankle power generation burst of the affected leg.

The Relationship of Bilateral Ankle and Hip Power Bursts to Gait Speed

To further explore the choice of kinetic strategies used by persons with hemiparesis, bilateral kinetic analyses were made in a subgroup of 21 patients who participated in the RCT (Table 19.4) before and after task-oriented gait therapy for 2 months (2). Because we were particularly interested in the trade-off between a "push-off" (A2) or a "pull-off" (H3) strategy to create gait speed (dependent variable), the following variables (A2 peak power and H3 peak power on both the *affected* and *less affected* sides) were entered in the stepwise regression analyses, one on the baseline and the second on the posttherapy values (Table 19.5).

The regression analysis on the *baseline* values revealed that the peak A2 and H3 power bursts on the *affected* side explained as much as 84% (R^2) of the variance in gait speed in these subacute subjects who had an average gait speed of 40 cm/s. The results of the second stepwise regression analysis using the same bilateral kinetic variables *after therapy* (Table 19.5), however, show that the contribution of the *less-affected* side becomes important, with the H3 on the *less-affected* side replacing the *affected* H3 peak obtained in the baseline analysis. The A2 peak on the *affected* side and the H3 peak on the *less-affected* side thus explain about 82% of the variance in gait speed that had improved to an average of 58 cm/s after therapy. These results confirm the importance

TABLE 19.4 Selected Subject Characteristics of Slow and Fast Walkers. Subjects Walking ≥70 cm/s After Therapy Were Considered to Be Fast Walkers, Whereas Those Walking <70 cm/s Were Slow Walkers. These Subjects Participated in a Randomized Controlled Trial Evaluating the Effects of Task-Oriented Gait Training. Measures of Strength Were Obtained With a Hand-Held Dynamometer

	SLOW WALKERS (n = 13)	FAST WALKERS (n = 8)
Age (years)	67 ± 12	56 ± 11
Ashworth scale	2.4 ± 1.4	1.1 ± 1.1
Fugl-Meyer leg motor subscore	21.3 ± 6.1[a]	26.8 ± 3.5
Barthel ambulation subscore	20 ± 9.6	18 ± 8.5
Isometric hip flexor strength (Nm)	34 ± 23	48 ± 30
Isometric ankle plantar flexor strength (Nm)	16 ± 6	19 ± 6
Gait speed (cm/s)	28 ± 13[a]	52 ± 19
Change in gait speed with therapy (cm/s)	12 ± 12[a]	34 ± 20

[a]$P < .05$.

Source: From Ref. (2). Richards CL, Malouin F, Bravo G, Dumas F, Wood-Dauphinee S. The role of technology in task-oriented training in persons with subacute stroke: a randomized controlled trial. *Neurorehabil Neural Repair*. 2004;18:199–211.

of the ankle A2 power burst both before and after therapy and demonstrate an interlimb strategy to gain speed after therapy.

Because the trade-off between hip and ankle power generators during walking is highly dependent on walking speed (94,107,110), comparisons of results in patients with different walking speeds are difficult. For example, in a group of subjects with chronic stroke who followed an 8- to 10-week training program, Parvataneni et al. (114) found that the mean gait speed increased from a mean of 69 ± 31 cm/s to 83 ± 33 cm/s (n = 28). When the change in gait speed was regressed on the chosen predictor variables of change in positive work, the first variable selected was the affected H1, which alone accounted for 66% of the variation in change of gait speed. A2 was the second variable selected, which, together with the affected H1, accounted for 75% of the variation in gait speed. A second model, which included only the affected and less-affected H1, accounted for 74.3% of the variation in gait speed. These models resulting from the regression analyses confirm that subjects with hemiparesis increase their gait speed with a combination of H1, H3, and A2 work on the affected side and H1 and H3 on the less-affected side (114). Clinically, this suggests that the gait speed of subjects with similar characteristics could be increased with appropriate changes in a combination of these positive work variables during gait.

Changes in Hip and Ankle Power With Recovery

To further examine the relationship of changes in the A2 and H3 peak power bursts bilaterally with gait speed, the 21 subjects were divided into fast (≥70 cm/s after therapy) and slow (≤69 cm/s after therapy) walkers (Table 19.4). Figure 19.8 illustrates the relationship between changes (posttherapy minus pretherapy values) in the H3 and A2 peak power bursts bilaterally in the two groups.

TABLE 19.5 Stepwise Regression Analyses of the Relationship Between Peak A2 and H3 Power Bursts on the Affected and Less-Affected Sides of 21 Persons With Stroke While Walking at Comfortable Speed, With Gait Speed Before Therapy (Baseline) in the First Model and With Gait Speed After Therapy in the Second Model

	R	R SQUARE	ADJ R SQUARE	STD ERROR
Model at baseline				
1. A2, affected side	0.812	0.660	0.637	11.65
2. A2, affected side	0.917	0.841	0.818	8.26
H3, affected side				
Model after therapy				
1. A2, affected side	0.846	0.716	0.697	14.61
2. A2, affected side	0.907	0.822	0.797	11.97
H3, less-affected side				

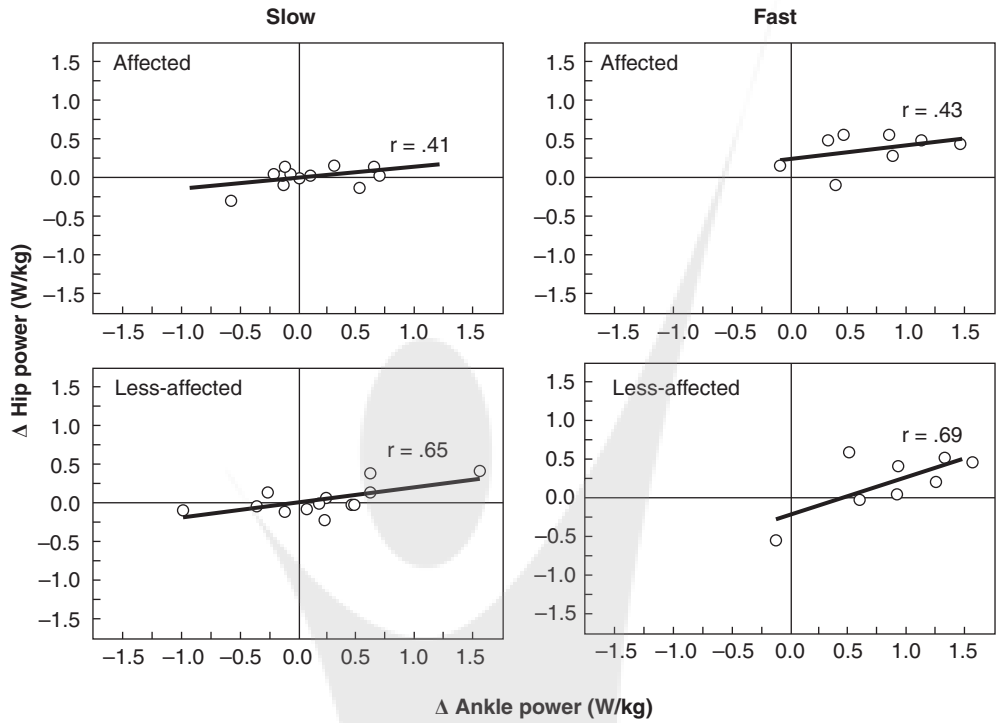


FIGURE 19.8 Concomitant change (after therapy minus baseline values), defined as recovery, in the A2 ankle power burst (x-axis) and the H3 hip power burst on the affected and less-affected sides of the group of slow (n = 13) and fast walkers (n = 8) described in Table 19.4. Correlations obtained with Pearson correlation coefficients.

In the group of fast walkers, the points cluster mainly in the upper right quadrants for both the affected and less-affected sides, indicating an increase in both the H3 and A2 power bursts. In one subject, the hip power decreased after therapy, whereas in another the ankle power decreased. Among the slow walkers, the points tend to cluster more near the intersection point of the quadrants, indicating that the changes are smaller. On the affected side, two subjects had concomitant decreases in the A2 and H3 bursts, whereas five had little change in the A2 burst. Only three had concomitant increases in both the hip and ankle powers. This graphical representation emphasizes the very small, lack of, or even negative changes in the power-producing capacity of the ankle plantar flexors and hip flexors on the affected side despite two months of task-oriented gait training. The magnitude of the correlations between change in the ankle plantar flexors and the hip flexors once again demonstrates the variability in kinetic strategies used to walk. The similar correlations for both the affected and less affected sides in the slow and fast walkers may be related to a matching of the sense of effort (116).

One can also question whether persons after stroke are capable of tapping into their full dynamic strength potential during walking. Milot et al. (116,117) have used a muscular utilization ratio (MUR) that relates the net moment produced during gait to the muscle's maximal capacity to quantify the level of effort in key muscle groups used by healthy persons and persons with chronic stroke during walking. When compared to a group of healthy individuals (117), they found the MUR values to be higher in the persons with hemiparesis, that the weakest paretic muscle groups had the highest level of effort during gait, and that persons with chronic stroke walking at self-selected and maximal speeds increase their MURs with gait speed. Thus, in a group of persons with stroke walking at a relatively fast mean self-selected speed (73 ± 27 cm/s, n = 17), the peak MURs on the affected side were 64%, 46%, and 33%, for the plantar flexors, hip flexors, and hip extensors, respectively. These values rose to 77%, 72%, and 58% at the maximal speed (126 ± 39 cm/s). Thus, the plantar flexors were the most used muscle group at self-selected speed, whereas at maximal speed, although the MUR value of all three muscle groups increased, that of the hip muscles increased more than the ankle. Thus, the analysis of the MURs concurs with that of the positive work generated at different speeds (113) during walking, with both showing the contribution of the plantar flexors to remain relatively constant at self-selected and maximal speeds, whereas the use of the hip muscles is increased at maximal speed.

In a subsequent study, Milot et al. (118) examined the effects of increased plantar flexor and hip flexor muscle strength following an isokinetic strengthening program on the levels of effort (MURs) during gait of a group of 24 persons with chronic stroke walking at both self-selected and maximal speeds. They observed a reduction in MUR ratios of 12% to 17% in the affected plantar flexors and

hip flexors and strength gains that were associated with a significant but small increase in gait speeds after training. Thus, as the subjects became stronger, they apparently favored a reduction in the levels of effort during walking instead of substantially increasing their gait speed. A logical extension of this work would be to test whether the decreased level of effort leads to better functional endurance during walking.

Interestingly, both healthy individuals and persons with stroke have similar MUR values for the muscle groups between sides at both self-selected and maximal speeds (117). This observation of similar levels of effort on the affected and less-affected sides, despite a more pronounced weakness of the affected distal muscles, led to the interpretation that the asymmetrical gait pattern of persons with hemiparesis could represent a means of preserving a similar, perceived sense of effort between the affected and less-affected sides. Simon and Ferris (119), building on work suggesting that healthy individuals use a sense of effort more than proprioceptive feedback to gauge force production in the upper limbs, recently demonstrated a similar mechanism in the control of asymmetrical force in the lower limbs in healthy subjects, providing evidence that the limb force asymmetry was related to neural factors rather than differences in mechanical capabilities between the limbs.

SUMMARY

This chapter has examined patterns of locomotor recovery after stroke as determined by different methods of evaluation. The use of clinical measures or the attainment of benchmarks, such as discharge from rehabilitation or the ability to walk with help or unassisted, provides an assessment of recovery of function that can be used to evaluate change related to therapy and in the planning of care programs. Such measures do not, however, assess change in biomechanical or neural variables related to locomotor control in relation to normal values. When an increase in gait speed is used as a surrogate for recovery, the poor recovery of the majority of stroke survivors, even after two months of therapy, becomes very obvious. Only the minority attain gait speeds that allow them to ambulate freely in the community (86,91), and it is those who walk at speeds less than 40 cm/s who benefit most, as reflected by a change in category (91). Nevertheless, few are able to cross busy streets in large cities (23,87). It is also important to realize that gait speed can continue to increase up to two years after stroke without formal therapy after discharge from rehabilitation, and that persons with chronic stroke can increase their gait speed with task-oriented circuit training (22,23).

These results also showed that gait speed at therapy initiation—at least in the subacute state when therapy in the rehabilitation center was started—predicts about 40% of the variance in gait speed after 2 months of task-oriented therapy. As expected, the change in the slowest walkers, who were likely the most severely affected, was small. The time of therapy initiation was also related to the recovery of gait speed, even though therapy was delayed because of constraints related to transfer from an acute hospital. Although the axiom "the earlier, the better" is used to describe the optimal time of therapy initiation, little is known about the optimal time, and further studies are indicated to guide therapy. In this group of stroke survivors, the recovery in gait speed was similar in persons with right and left hemiparesis. Again, these findings have to be confirmed in groups of persons with different severities, times of therapy initiation, and types of therapy.

As suggested in this chapter, it would also be beneficial if clinicians had access to full biomechanical gait evaluations (kinematics and kinetics) to guide their therapy selection in individual cases. Knowledge of the kinetics (muscle activations, muscle moments, and powers) helps understand "why" a subject walks with a given movement pattern and walking speed and provides clues for the choice of therapy. For example, the salient aspect of the disturbed motor control in an individual may be paresis, excessive muscle coactivation, spasticity, or hypoextensibility of the muscles because of nonneural factors (62,67–69); each of these requires different therapeutic approaches. Understanding the moments and powers acting at the joints to produce propulsive force mediating walking speed helps pinpoint not only the individual power-producing strategies but also the therapeutic targets for improvement (65,70,78,95).

Although the movement profiles of hip, knee, and ankle during the gait cycle tend to improve with increasing gait speed, they will only rarely return to "normal." Moreover, these abnormal gait movements are associated with patterns of muscle activations that differ in both timing and amplitude from normal values. Comparison of functionally important activation bursts in the TS, TA, and QUAD muscles over time with normal values revealed that the TA showed the most recovery and the TS the least. The late change in the QUAD also suggested that muscles may have different temporal patterns of recovery. Although these findings were obtained in a small number of subjects and must be confirmed in other longitudinal studies of recovery, they are intriguing and worthy of further study. The lack of recovery in the TS is particularly worrisome because of the role of that muscle in propulsion and the emphasis placed on it in locomotor therapy. In contrast, these findings suggest that the TA has an untapped and poorly understood potential in locomotor recovery.

Comparisons of the power and work profiles during gait in persons after stroke with normal values have revealed that persons after stroke tend to compensate for a poor power generation at the ankle by increasing the generation of power at the hip and that, with therapy, they may choose to produce gait speed by adopting a strategy that depends on the hip of the less-affected leg. Although variable, these compensatory power-generating strategies again point to poor recovery in the ankle "push-off" power-generating burst and the use of compensatory strategies involving the hip power generators to increase walking speed.

RESEARCH FRONTIERS

Sense of Effort and Force-Scaling

As persons with chronic stroke became stronger, they apparently favor a reduction in the levels of effort during walking instead of substantially increasing their gait speed (116). This finding opens a new area of inquiry into the mechanisms controlling the symmetry of effort at self-selected walking speeds. These investigators (117) have also shown that normalizing joint moments during gait to the maximum joint moment capabilities led to similar effort levels in the affected and less-affected limbs of persons with chronic stroke during walking. Thus, it seems that sense of effort is an important factor in determining lower-limb muscle activations in persons with hemiparesis. Force-matching studies (119,120) thus suggest that, in addition to strengthening the affected lower-extremity muscles, rehabilitation approaches should also address the impaired force-scaling ability. Simon et al. (121) advocate that symmetry-based resistance has the potential to improve both force-scaling ability and limb strength because subjects can learn to scale muscle activations more appropriately to achieve a desired force outcome. This would enable persons with stroke to better match paretic limb forces to task requirements during activities of daily living.

Functional Cognition and Walking Competency

Even though up to 65% of stroke survivors have new onset or worsening of cognitive deficits after stroke (122–125) that interfere with functional recovery and the potential benefits of rehabilitation (123,125,126) and lead to falls (127), the rehabilitation of cognitive deficits and, in particular, the impact of cognitive deficits on walking competency have been largely ignored. Members of the rehabilitation theme of the Canadian Stroke Network have identified cognitive deficits as a priority area for research (128), and recognizing the need, the National Institute of Neurological Disorders and Stroke (NINDS) and the Canadian Stroke Network have joined together to establish criteria for systematic study of cognitive deficits associated with stroke (129). In a recent paper devoted to conceptualizing functional cognition in stroke, Donavan et al. (123) defined *functional cognition* "as the ability to accomplish everyday activities that rely heavily on cognitive abilities." Walking competency (23) implies that, in addition to the physical capacity to walk fast enough to cross streets and far enough to be able to walk about in the community, a person also has the planning abilities to navigate among others and to find his or her way, as well as to make locomotor adjustments to meet the demands of the changing environment.

There is a growing body of literature from both the aging and clinical populations that examines the role of cognition in locomotion. The main approach to study of the interaction between cognitive processing and motor behavior is the dual task paradigm. Thus, Plumer-D'Amato et al. (130) have shown that, in persons with stroke living in the community, speech produced more gait interference than memory and visuospatial tasks and that, even though the participants were mobility impaired, they prioritized the cognitive tasks. Future research is needed to determine if dual task training can help reduce gait decrements in dual task situations. In this regard, the use of virtual reality paradigms provides the opportunity to combine physical locomotor training on the treadmill with cognitive training that is goal directed and motivating for persons with chronic stroke (131).

Studies are also needed to better understand the importance of *self-efficacy*, defined as a judgment of one's ability to organize and execute given types of performances (132), in the success of locomotor training programs. For example, Salbach et al. (133,134) found that enhancing balance self-efficacy in addition to functional walking capacity, when compared to enhancing functional walking capacity alone, may lead to greater improvement, not only in perceived health status, but also in physical function. Much work is needed to better elucidate the interaction between cognitive function and walking competency, as well as the development of adequate rehabilitation programs to target impaired cognitive function in persons with stroke.

Mental Practice as an Adjunct to Physical Practice

Another alternative for locomotor retraining in patients with severe motor impairment is the use of mental practice through motor imagery (135). Using transcranial magnetic stimulation, Pascual-Leone and colleagues (136) reported that mental practice produced representational changes in the brain comparable to those yielded by physical practice. Moreover, they found that subjects who had mentally practiced a one-handed piano exercise for five sessions and then added only one physical session reached the same level of performance as those who practiced physically for five sessions. The latter findings suggest that part of the behavioral improvement seen in the mental practice group may be latent, waiting to be expressed after minimal physical practice. Mental practice in subjects who cannot walk or with limited walking capacity could thus have a preparatory effect on the task, hence increasing the efficiency of subsequent physical training (136). The priming effects of mental practice have been extended to movements of the lower limbs in a PET study (137). Indeed, after five days of intense mental practice of a foot movement sequence, subjects were able to complete the sequences of foot movements faster, both mentally and physically. In addition, similar dynamic changes during both modalities (imagination and execution) were observed, hence demonstrating that learning a sequential motor task through motor imagery practice produces cerebral changes similar to those observed after physical practice of the same task (137). Combining physical and mental practice has also been found to promote the learning of a foot movement sequence after stroke (138).

To date, positive effects of mental practice on gait speed and step length have been reported after stroke in a series of patients with chronic stroke (139–141). Two recent

well-controlled trials (142,143) compared physical practice (physical therapy or treadmill training) alone or combined with mental practice and reported larger gains in gait speed with the addition of mental practice.

To conclude, results to date suggest that mental practice has potential as an adjunct to physical practice to promote the recovery of mobility tasks and walking ability after chronic stroke. Future studies should try to better control the nature and the dose of concomitant physical practice in both experimental and control groups so as to tease out the effects directly related to motor imagery. It is also essential to monitor adherence of the patients to the intervention by means of training strategies that favor vivid images that can be verified. The temporal congruence of imagined and physically executed movements is another way to monitor motor imagery. Patients should be trained in motor imagery to ensure that they are able to engage in motor imagery. To be able to attribute therapeutic effects to motor imagery, it is also essential to evaluate the motor imagery capacity of the patient prior to and during the intervention.

For patients who have difficulty or are unable to engage in motor imagery, action observation remains an interesting alternative for developing their walking capacity (144,145). This suggestion is based on findings that, like the imagination, the execution and the observation of a movement are controlled by more or less the same brain areas (146–148). Indeed, mirror neurons in the premotor cortex and the inferior parietal cortex discharge not only during the performance of a goal-directed movement, but also while observing the movements performed by another person. Thus, when a person sees an action performed by someone else, neurons representing that action are activated in the observer's premotor cortex so that, automatically, motor representations involved in the execution of that action are activated. Hence, observing an action directly activates the motor commands needed for performing that action.

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20

Task-Oriented Training to Promote Upper Extremity Recovery

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Task-oriented training has emerged as the dominant approach to motor restoration for stroke-induced motor impairments. Results from recent phase III randomized clinical trials (RCT) provide evidence that more intensive therapy and practice of functional tasks are far superior to the current standard of care (1,2). This updated chapter provides the background for the emergence of a task-oriented/task-specific approach to promote functional recovery after stroke. The first section, "Emergence of Task-Oriented Training for Neurorehabilitation" includes recent views on the restitution–substitution continuum of recovery. To move beyond a simplistic interpretation of task-oriented training, the section, "Criterion-Based Task-Oriented Training: What Are the Active Ingredients?" highlights recent evidence concerning the "active ingredients" for effective therapy approaches to promote motor learning and functional recovery. The section "Constraint-Induced Movement Therapy: A Special Class of Task-Oriented Training?" presents the argument that constraint-induced movement therapy is a special class of task-oriented approaches. In the section "Motor Control and Learning Considerations," we draw from the extensive foundations in the behavioral sciences of motor control and learning to consider the "pharmacokinetics" of training, including practice schedules, practice time and intensity of training, the organization of training, and the contents of training. Importantly, we include consideration of motor severity, timing of training, and dosing. In the section "Considerations From the Neuroscience Perspective," we review the behavioral signals driving neural plasticity in the context of rehabilitation. In the section "Emerging Innovative Approaches to Upper Limb Rehabilitation" two examples are provided of emerging innovative approaches to upper limb rehabilitation. The first is a multimodal combination intervention using noninvasive brain stimulation combined with physical therapy. The second example is a fully defined evidence-based hybrid combination of skill-based/impairment-mitigating motor skill training with embedded motivational enhancements that we define as the Accelerated Skill Acquisition Program (ASAP). Finally, the section "Research Frontiers" provides a revised and expanded overview of four related research frontiers in neurorehabilitation including an expanded section on predictive models.

EMERGENCE OF TASK-ORIENTED TRAINING FOR NEUROREHABILITATION

The 2006 National Institutes of Health, National Institute for Neurological Disorders, and Stroke (NINDS) Stroke Progress Review Group summarized what it considered to be the most significant of scientific accomplishments since its last published guidelines in 2001. In particular, the workgroup concluded that *task-oriented training* had emerged as the dominant approach to motor restoration. Other highlighted findings, including the delivery schedule of training, motivation, and characteristics of treatment participants (e.g., severity of motor deficits and co-existing sensory or cognitive impairments), continue to be active areas of research. Further, the panel identified that clinical trials in this area proved more challenging than previously anticipated, with variables in dosing, timing, and duration adding to their inherent complexity and resolving the question of whether the training paradigm matters (3).

In 2012, NINDS released its report from the Stroke Research Priorities Meeting pertaining to the top scientific research opportunities from workgroups on stroke prevention, treatment, and recovery research (4). For recovery, the report defined two priorities: (a) translational research using neural interface devices for stroke and other neurologic disorders, and (b) translational research targeting early recovery after stroke in humans (4). In October 2013, NIH established StrokeNet, a network of 25 regional research centers working with nearby satellite facilities around the country, each with teams of researchers representing every medical specialty needed for stroke care, to address the three prongs of stroke research: prevention, treatment, and rehabilitation/recovery. The network concept evolved from an NINDS planning effort in which stroke experts were asked what is most needed to reduce death and disability caused by stroke in the United States. They called for a nationwide stroke network that would allow for a more seamless transition between early safety and efficacy trials and phase II and III clinical trials.

There continues to be a substantial number of small-scale, preclinical feasibility studies pertaining to task-oriented approaches for upper extremity recovery. These

kinds of studies, if well designed, are important, particularly if they have a strong scientific foundation (conceptual and theoretical) for the kinds of translational research that could leverage the opportunity enabled by StrokeNet. The translational work that will be hosted by StrokeNet in the next five years will likely infuse new energy into the clinical research enterprise by promoting more basic work as well as the clinical translation of task-oriented approaches across different care settings (5,6).

What Is Task-Oriented Training?

Task-oriented training is now prevalent within the field of neurorehabilitation but continues to lack clear criteria, that is, there is considerable variability in the literature as to what constitutes a task-oriented training approach. From a disablement/enablement perspective, such as the World Health Organization's International Classification of Disability and Functioning (7), task-oriented training is described best as a top–down approach to rehabilitation (see top–down model) (8). This approach is one that addresses activity limitations, rather than the specific and isolated remediation of impairments (9–12) or specific movement kinematics (i.e., body functions/structures). In the literature, this top–down approach has been referred to as a "motor learning" or "movement science" approach to rehabilitation (13), "task-specific training" (9), "task-related training" (14–17), "functional task practice" (18), or "goal-directed training" (19–21). Task-oriented training is based on integrated models of motor control, motor learning, and behavioral neuroscience, where active participation and skill acquisition are critical components of recovery. Consistent with a patient-centered perspective of motor control, the manner in which voluntary movement is elicited after a stroke represents the best efforts to achieve "functional task goals" given the constraints imposed by the stroke-induced impairments, the personal attributes, the environment, and the demands of the task (22–25). With these assumptions, and considering this conceptual framework, the patient is viewed as an ***active problem solver***, and ***rehabilitation is focused on the acquisition of skills*** for performance of meaningful and relevant tasks. Although task-oriented training approaches highlight the importance of repetition and task specificity, they sometimes downplay the achievement of skilled movement in the service of functional tasks. A subtle but important point is that *the pursuit of skilled movement*, rather than merely functional actions (i.e., activities of daily living [ADL]), is both relatively demanding and engaging and invokes natural goal-directed advantages—that of seeking skilled performance rather than simply task accomplishment. These activities therefore are distinct from rote or exercise-based movements that can be abstract and without a preconceived and task-based functional goal (10,26–28).

It should be obvious from this discussion that a precise and evidence-based definition of task-oriented training is essential to stimulate further advances in neurorehabilitation. There is, however, a clear distinction between task-oriented training approaches and the more traditional bottom–up neuromuscular reeducation approaches that dominated neurorehabilitation well into the 1980s.

How Is Task-Oriented Training Different From Neuromuscular Reeducation?

When one reviews a magnificent compendium of work that characterizes rehabilitative efforts to improve movement among patients with central nervous system deficits and that is housed within the landmark Northwestern University Special Therapeutic Exercise Project (NUSTEP) volume (29), one is struck by the outstanding efforts set forth among a dedicated group of clinicians, whose collective treatment formulations were derived from elements of fundamental neurophysiology. The emergence of such "approaches" as advocated, for example, by Brunnstrom, Bobath, Rood, Knott, and Doman-Delgado were sincere efforts to guide practice by encouraging clinicians to treat patient impairments using specific directives. These efforts at "neuromuscular reeducation" were appreciated by physical and occupational therapists because they provided some of the initial foundations and translation of the science for implementation of clinical practice. Many of these techniques are still in use. However, even with their births and subsequent evolution, their collective value has been hampered by a series of concerns, the significance of which becomes more meaningful with the development of more sophisticated assessment tools and with advances in scientific exploration. Among these concerns is the fact that the bases for most "neuromuscular reeducation techniques" never were externally validated. That is, the relevance and verification of observations extracted from animal preparations (often using anesthetized animal preparations) were not confirmed in a convincing fashion among human subjects before the formulations of specific techniques were disseminated. Second, very few outcome measures existed, and those that did lacked confirmatory validation until subjected to study and refinement that did not begin until the mid-1980s. Moreover, many procedures permitted the use of compensatory behaviors rather than optimizing function within the context of maximal utilization of the impaired neuromuscular substrate. Last, much of the emphasis of neuromuscular reeducation was focused on the impairment level of disablement (i.e., "body functions/structures" in the ICF framework) without considering adequately the implications or relevance to voluntary participatory behaviors (i.e., "activity" in the ICF framework) or the importance of changes in life roles or health-related quality of life (i.e., "participation" in the ICF framework).

One area of clinical activity that gained considerable popularity during the last three decades of the 20th century was biofeedback, especially electromyographic (EMG), position, and force feedback. These forms of biofeedback were particularly applicable to rehabilitation of patients with musculoskeletal or neuromuscular disorders. Force feedback continues to thrive in the form of posturography to improve balance, whereas an interface like virtual reality is listed as a contemporary form of feedback (30). EMG biofeedback to

restore limb movements following stroke was the subject of considerable research during that 30-year interval. A recent PubMed search (May 10, 2014) cross-referencing the terms stroke and biofeedback identified 376 articles of which only 88 were published prior to 2000. However, a consistent direction followed by these studies highlighted the importance of knowledge of results (usually postresponse information about performance relative to the goal) to improve movement. In addition, the working hypothesis for training was dependent upon the neuromuscular reeducation principles previously discussed. For example, feedback about muscle activity was provided to reduce hyperactivity in "spastic" muscles. This was thought to be necessary prior to recruitment of antagonist muscles and was to progress in a proximal to distal direction. These concepts had been extracted from studies using animal models but without comprehensive clinical validation prior to implementation. Moreover, efforts to delineate the most critical elements or procedures to succeed in rehabilitative biofeedback applications did not systematically explore optimal provision of this training or integrate feedback forms within task reacquisition. As a result, emphasis was placed on altering impairment status without substantial consideration of: (a) activity or participatory changes, (b) integration of training within tasks deemed important to the user, or (c) quantification of outcomes using kinematic and kinetic measures to determine the extent to which outcomes could be classified along the restitution–substitution continuum. Even more contemporary work that examines functional magnetic resonance imaging (fMRI) changes with biofeedback training for improved ambulation (31), video gaming (32), or neurofeedback in combination with EMG biofeedback, (33) has thus far focused on the relationship of changes in impairments to measures of cortical reorganization. These studies could be more substantive if they also included outcome measures pertaining to the activity or participatory domains of the ICF model.

From this contemporary biofeedback work and other examples such as rehabilitation robotics, it is evident that a more traditional focus on the impairment/body structure domain of the ICF is important for providing insight pertaining to the restitution–substitution continuum of motor control (34). On the other hand, it has been argued that a change in function (e.g., better hand use) measured at the activity level of the ICF (e.g., using Action Research Arm Test [ARAT] (35)) may reflect adaptation of the movement behavior through a substitution–compensation mechanism rather than a restitution/–recovery mechanism. However, Krakauer and colleagues argue that if we do not measure the kinematics of the movement (36), or use some valid measure at the impairment level (e.g., Fugl-Meyer Motor Assessment), we cannot ascertain the mechanism of change in the behavior. Without such measures, we will not be able to develop new assessments or interventions that target specific mechanisms for motor control and learning (37). Maladaptive or "bad use" can occur when less optimal, unskilled solutions—ones that rely on compensatory strategies—are used (36,38–43). This can contribute to incipient declines after therapy ends and gains are not generalized (44). The hypothesis as yet untested is that if we do not understand how the movement problem was solved (i.e., restitution vs. substitution), we cannot optimize recovery. We will say more about this in the last section, Research Frontiers.

CRITERION-BASED TASK-ORIENTED TRAINING: WHAT ARE THE ACTIVE INGREDIENTS?

It is now fairly well accepted that ***behavioral demands*** and ***motor skill acquisition*** are critical drivers to cortical reorganization associated with positive functional outcomes following a stroke or stroke-like lesion in animals (45–48). In nondisabled adults, the kinematics of arm and hand movements have been shown to be uniquely constrained by the behavioral goals of the movement and the characteristics of the to-be-grasped object, such as spatial location and object shape and size (49–51). After stroke, there is evidence to suggest that the emergent movement kinematics are organized differently for real objects compared with simulated or artificial objects. Upper limb movement kinematics were more efficient when the goal-directed activity included reaching for a ringing telephone, compared to simulated contexts such as reaching for a stick (52) or no object (51). Thus, the fidelity of the task in the natural context seems to be a critical ingredient of effective task-oriented training programs. In addition, greater transfer of training to life activities might be anticipated from such task-oriented training, particularly given the focus on familiar everyday tasks, and transfer to unpracticed tasks might be possible given the focus on the development of problem-solving strategies.

It is well known that training programs that are designed to enforce the ***practice of problem solving*** usually are more effective for learning than those that are drill-like and enforce mere repetition of the previous solution to the movement problem (53,54). Taken together, and compiled from perspectives including brain, cognitive, and the social sciences, we propose a minimum of three active ingredients thought to be critical for an effective task-oriented training program. The program must:

1. **Be challenging** enough to require new learning and engagement with attention to solve the motor problem (48).
2. **Be progressive and optimally adapted** such that over practice, the task-demand is optimally adapted to the patient's capability and the environmental context. It must not be too simple or repetitive to not challenge and not too difficult to cause a failure of skill acquisition or a low sense of competence (55,56). Extending the environmental context outside the laboratory or clinic is an important aspect of an optimally adapted patient-centered program. This reinforces the "real-life" benefits through a virtuous cycle that becomes self-sustaining.
3. **Solicit active participation** to engage a "particular type of repetition" that Bernstein referred to as "problem-solving" (57).

It should be noted that these three criteria (i.e., challenging, progressive and optimally adapted, and active participation) are likely not independent but rather overlap and are complimentary in nature. Equally relevant to these criteria is the growing awareness of protocols that directly address the three fundamental psychological needs—autonomy, competence, and social-relatedness. Of importance, there is mounting evidence that when these needs are considered in the context of instructions or expectations, they benefit the motor learning and the rehabilitation process (58).

CONSTRAINT-INDUCED MOVEMENT THERAPY: A SPECIAL CLASS OF TASK-ORIENTED TRAINING?

During the last decade and a half, a class of intervention studies that has addressed the suboptimal recovery of upper extremity function, and for which there is mounting evidence, is the family of forced-use and constraint-induced movement therapy protocols (59–66). Along with the publication of the EXCITE trial results (1,67,68), there have been numerous small (69,70) and larger-scale (65) studies showing efficacious results for constraint-induced movement therapy in restoring motor function in patients with upper extremity motor impairments. A modified protocol was shown to be effective in outpatient (60), clinic (62), and home settings (61), and even feasible in the acute in-patient setting (71).

Constraint-induced movement therapy protocols combine the use of a constraint (restraint mitt worn on the less-affected limb) and training of the affected arm and hand. The restraint device can be thought to exert an indirect effect on paretic limb use by preventing compensatory use of the less-affected limb for some tasks, whereas the task-specific training with the paretic limb can be thought to exert a direct effect on paretic limb use. Several studies of constraint-induced movement therapy used a training duration of 14 days (2 weeks), in which 10 of those days included six hours per day of supervised in-laboratory task practice training with the participant's less-affected upper extremity placed in a protective safety mitt for a goal of 90% of their waking hours (64,65,72,73). One study compared the effectiveness of a six-hour per day training protocol to one half as long (three hours per day) and found that though the shorter training period produced significant and functionally relevant treatment effects, the longer training protocol produced even greater efficacy in young adolescent participants (73). Because the two groups had equivalent restraint use times, Sterr and colleagues suggest that the major factor contributing to the gains in upper extremity function comes from the massed practice that occurs during training. In essence, task-oriented training may exert a greater influence on recovery than the restraint when overcoming the effects of learned-nonuse, but this hypothesis is controversial with other findings using a modified protocol showing that reduced levels of training relative to mitt use are also effective (60,74,75).

In addition to mitt use, two distinct training procedures were employed with these participants as they practiced functional task activities: shaping or adaptive task practice (ATP) and standard task practice (TP). The former is a training method based on the principles of behavioral training (76–78) that also can be described in terms of motor learning derived from adaptive or part-task practice (79–82). In this approach, a motor or behavioral objective (task goal) is approached in small steps, by successive approximation (i.e., parts of the task), by making the task more difficult in accordance with a participant's motor capabilities, or by progressively increasing the speed of performance. Each functional activity is practiced for a set of 10 trials, and explicit positive feedback is provided regarding the participant's performance with each trial. Standard task practice (TP) is less structured (e.g., the tasks are not set up to be carried out as individual trials of discrete movements); they involve functionally-based activities performed continuously for a period of 15 to 20 minutes (e.g., wrapping a present, writing a letter). In successive periods of TP, the spatial requirements of the activity or other parameters (such as duration) can be changed to require more demanding control of limb segments for task completion. Global feedback about overall performance is provided at the end of the 15- to 20-minute period. For the majority of signature protocol CIMT studies, the training tasks are selected for each participant using the following criteria: (a) specific joint movements that exhibit the most pronounced deficits, (b) joint movements that trainers believe have the greatest potential for improvement, and (c) participant preference among tasks that have similar potential for producing specific improvements.

For the EXCITE trial, a large bank of tasks was created for each type of training procedure. Additional tasks could be submitted and added to the bank of approved tasks only after receiving approval from the EXCITE Training Core. The task bank consisted of 71 adaptive task practice (ATP) activities (e.g., ring toss, nuts and bolts, pouring from mug) and 42 TP activities (e.g., setting table, dusting, eating with chopsticks). All practice items were considered "task oriented" and were items from a broad range of everyday activities including: food preparation, dining, cleaning, home maintenance, laundry, office, recreational, and instrumental activities of daily living.

Published CIMT protocol descriptions have included shaping procedures to progress task difficulty, the provision of optimal challenge, and multifaceted approaches to encourage active participation (e.g., behavioral contract, constraint mitt). Taub and colleagues suggested that a key to the optimal outcomes with CIMT resides in the use of a comprehensive transfer package—a set of techniques to facilitate transfer of therapeutic gains from the laboratory to the life situation (83). Earlier work investigated the long-term effects of the "transfer package" to facilitate actual use of the trained affected arm in activities of daily living (44). One group received 4.5 hours of intensive task training and 0.5 hours of transfer package whereas the control group received 5.0 hours of intensive task training per day during 10 consecutive workdays. As expected, both groups showed increase in arm function after intervention, but at

the six-month follow-up, only the transfer package group showed continued increase in arm function compared to the control group.

To date there are no systematic "head to head" comparisons of these models that could determine if any one of them is superior. Accordingly, we suggest that CIMT be considered a special class of task-oriented training. The most important difference is that forced-use/CIMT protocols tend to negate other approaches for training, such as bimanual task practice (84). Further, there is no formal attention to impairment mitigation (e.g., strengthening, range of motion), use is promoted to a greater degree than skill, and personal social–cognitive factors such as perceptions, expectations, and motivations are lacking. Although disentangling the individual contributions to arm and hand improvements of constraint (i.e., mitt use) and task practice embedded in CIMT protocols are not possible at this time, there is emerging support for the effectiveness of task-oriented upper limb training in the subacute phase following stroke, particularly in those individuals who suffered their first-ever stroke that resulted in mild to moderate unilateral upper limb paresis.

In a majority of clinical trials during the subacute phase, and one case study, participants who received task-oriented training, without using a constraint, demonstrated significant improvements in upper limb motor impairment and in activity limitations immediately after intervention (16,85–87). However, significant between-group differences in favor of task-oriented training were most apparent when long-term upper limb outcomes were evaluated many months following the intervention (85). One interpretation of these findings is that in the subacute phase, there has been less opportunity (less time) for robust learned-nonuse strategies to dominate, and patients in this phase are less likely to benefit from an approach that emphasizes the reversal of learned-nonuse compared to one that emphasizes motor relearning through skill acquisition, problem solving, and self management. On the other hand, data from the EXCITE Trial provide a unique opportunity to compare an identical intervention (constraint-induced movement therapy) delivered by the same clinicians to participants within three to twelve months after stroke or exactly one year later to their enrollment date. Whether or not the delayed CIMT participants received other interventions during the year in which they were awaiting the provision of CIMT did not seem to matter. All those individuals improved equally after they received the constraint training and actually reached the same point of recovery using the Wolf Motor Function Test (88,89) as an outcome measure, but the rate of improvement following the two-week CIMT intervention was significantly greater in the subacute participants (68). Whereas the findings are restricted to stroke survivors with mild to moderate upper extremity impairment, the results suggest at least two key observations: (a) recovery can occur more than one year following stroke; and (b) the rate of that recovery appears more substantial when CIMT was delivered in a subacute population. The latter finding may be because of less profound learned nonuse, a greater substrate for functional plasticity earlier following stroke, or a combination of these and other factors.

MOTOR CONTROL AND LEARNING CONSIDERATIONS

There is a significant body of work from movement and psychological science that deals with the behavioral aspects of motor control and learning in nondisabled populations. Such knowledge can provide important direction to the implementation of task-oriented training to promote upper extremity recovery (90,91).

Massed Versus Distributed Practice Schedules

In the motor learning literature, the term "massed" practice is defined as a set of practice trials in which the performance–rest ratio is high and the proportion of rest between practice attempts is relatively shorter than the amount of time spent practicing. In contrast, "distributed" practice refers to a set of practice trials in which the performance–rest ratio is low and the rest time between trials is longer than the amount of time spent practicing (81). Although there are no direct comparisons (massed vs. distributed) in the neurorehabilitation literature, there is a long history of this debate in the motor learning literature (92).

The effectiveness for motor learning of various task performance and rest schedules seems to depend on the nature of the tasks that are practiced. For discrete tasks, such as tossing a ball or fastening a button, reducing the rest time (i.e., massed practice) has little or no influence on learning, and in some cases less rest may even be beneficial. However, for continuous tasks, such as handwriting, fatigue-like states are more apt to build up within a performance bout, suggesting that massed practice would be undesirable. The majority of the laboratory findings in nondisabled populations would support this notion—less rest between performance epochs degrades performance and has a detrimental effect on earning.

In the clinical literature, especially that used to describe the signature CIMT protocol, the term "massed practice" has been used to mean high intensity training conducted, for example, daily using a schedule up to six hours per day in the laboratory one-on-one with a "trainer." Though there is no doubt that the saying, "practice makes perfect" bears some truth and there is ample evidence to support the notion that "practice" is the most important variable for motor learning, conventional wisdom suggests that the design of that practice (schedule, duration), and the contents of practice (task-specificity) are equally important factors to consider when attempting to optimize the effectiveness of task-oriented training.

A concentrated "massed practice" schedule may be impractical to implement in today's health care environment. On the other hand, a more distributed schedule, though a departure from the signature CIMT massed schedule, is

closer to that prescribed in more recent reports that have used a modified CIMT protocol (74,75,93). Finally, such a distributed schedule is attractive from a practical perspective, both to the patient and clinic. Clinics consider a therapy visit to be approximately 45 minutes to an hour, and customary out-patient therapy for stroke ranges from two to three times per week for up to 10 weeks. Together, there is considerable practical and empirical support for implementing a task-specific practice program using these more distributed training schedules for upper extremity neurorehabilitation. This idea is consistent with recent work on memory consolidation and memory modification (reconsolidation) in which the off-line learning between practice bouts across days may represent a bridge between early and late procedural learning that underlies efficient skill acquisition (94).

Practice Time or Intensity of Training

Practice time, or the amount of time engaged with specific tasks, appears to be a major factor contributing to the effectiveness of constraint-induced movement therapy. However, in general, in clinical practice and even for published protocols, a precise quantification of task-specific practice usually is no more explicit than the length of stay or the total minutes or hours of each particular therapy delivered (95,96). The considerable outcomes and effectiveness research surrounding constraint-induced movement therapy seldom have focused on an explicit characterization of the intervention itself, including the very nature of the repetitions inherent to task practice. The signature CIMT protocol calls for a minimum of six hours per day of supervised training; however, from a task-oriented training perspective, the metric that is of interest is the amount of actual time practicing and time on task with the more impaired limb. We undertook a secondary analysis of time on task for one of the seven sites from the EXCITE RCT (96).

This retrospective analysis of a 2-week (range 11 to 16 days) administration of the signature CIT protocol revealed that on average, participants tolerated approximately four hours of actual task-specific practice per day or 62% of in-laboratory time. Further, we showed that there was 100% compliance with the specified 6-hour minimum supervised in-laboratory time averaged across the 10 days. The significant correlation between Mean Daily Practice Time (time on task) and in-laboratory time in the context of the large between-subject ranges for practice time prompts the question concerning the impact of training time and outcomes. For example, do participants who have longer training times benefit more from constraint-induced movement therapy than those with shorter training times? Although outside the scope of our single-site "time-on-task" project, a subsequent analysis was performed on the entire EXCITE database to address this (97).

In fact, when all participants enrolled into the EXCITE Trial and those who underwent 10 days of CIMT (n = 169) were examined for change scores on a primary outcome measure, the Wolf Motor Function Test (98,99), there was no apparent relationship between the intensity of training and outcome until the nature of the training was included in the analysis (97). Apparently, spending an excessive amount of training time in ATP training, which, arguably implements a "problem-solving" approach, yielded greater improvements with less overall practice time among those participants classified in the higher functional level, compared to other EXCITE participants. The lack of an overall intensity-to-outcome relationship along with the more detailed subgroup analysis suggests that total time spent practicing is less important than the nature of how tasks are practiced. As such, task-specificity may be more important than intensity of training (99,100).

From our single-site analysis, there was considerable variability (2.83–5.04 hours per day) across participants in mean daily practice time and the proportion of TP and ATP that constituted practice time. However, this variability did not appear to depend on functional level. In fact, two of the three in the low functional group were among the lowest for the entire group in Practice Time (22% and 23% below the mean), whereas the other had the third highest overall practice time at 20% above the mean. Instead, independent of functional level, it appears that those who engaged in more total practice time also engaged in more time on ATP/Shaping. However, this was not the case between total practice time and TP time. Therefore, other factors besides motor capability were more important in determining the time on task practice and the relative proportion of ATP and TP engaged in by any given participant. Individual subject motor capability and motivational and behavioral factors likely influenced important training parameters, such as task progression, training intensity, and choice of ATP/TP components. An understanding of these factors that are beyond training intensity, but relevant to the implementation of individualized patient-centered therapy programs, will be important for future developments in clinical practice (100,101).

Both the full-study and single-site EXCITE (96,97) analyses were limited to the temporal components of task-specific training, and the two classifications of tasks, ATP and TP, that represent only one of the active ingredients for efficacy of CIMT. The motor learning literature would suggest that there may be other critical elements of task-specific training that are important for the design of effective programs. We describe a few of these macro-level elements in the next sections.

Practice Schedules and Organization of Tasks

Random Versus Blocked Task Order Practice

The motor learning literature describes the contextual interference (CI) effect as an important and compelling variable for consideration in motor learning. For nondisabled learners, a practice schedule that promotes *interference* has been shown to be beneficial for skill learning (102–104). One way to manipulate interference during practice of multiple tasks

is to change the order in which tasks are practiced. For example, a random practice order in which tasks are practiced in a quasi-random order (i.e., C-A-B, A-B-C, B-C-A, where each letter represents a different task) is thought to introduce more interference than a blocked practice order in which each task is practiced repeatedly prior to switching to the next task (i.e., A-A-A, B-B-B, C-C-C).

Results from studies investigating the effects of practice order on motor learning typically show that if the total number of trials is the same for each group, the random practice order group shows enhanced motor learning compared with a blocked practice order group. However, there are exceptions to this random practice order benefit (105). This phenomenon is known as the CI effect (106,107). The CI effect elicited under random practice (i.e., high-interference) conditions has been explained in part by the additional planning and parameter specification that is required when different tasks are being practiced within the same session. For random order practice, every trial necessitates parameter specification and action planning. Both processes now are thought to implement a stronger memory representation of the practiced tasks (108–112). This enhanced processing related to the CI effect may in part take the form of increased cortical motor activity.

Recently, explorations into the neural bases of motor learning employ an imaging technique called transcranial magnetic stimulation (TMS). TMS is a technique that can introduce a transient perturbation to modulate cortical motor activity by means of noninvasive stimulation of the human brain (113). Single-pulse TMS was used *during* practice in healthy nondisabled participants as an identical external perturbation during both blocked and random practice (114). The TMS perturbation centered over primary motor cortex during encoding selectively disrupted motor learning under random, but not blocked practice conditions. More recently, Kantak and colleagues used low-frequency repetitive TMS (rTMS) *after* practice, over dorsolateral–prefrontal (DLPFC) or primary motor cortex (MI), during offline consolidation of a visuospatial movement pattern. Nondisabled participants practiced under constant or variable order conditions and were tested one day later for retention performance. Interference to DLPFC, but not to MI, after *variable* practice attenuated motor learning, whereas interference to MI, but not to DLPFC, after *constant* practice attenuated motor learning (115). Kantak and Winstein (2012) suggested a model of the learning-performance distinction and memory processes that can be used to explain these two sets of findings and to suggest additional testable hypotheses concerning the neural bases for motor learning.

Functional magnetic resonance imaging (fMRI) studies (116), together with recent TMS studies (114,115) exploring the neural bases of the CI effect, provide compelling support for the hypothesis that active information processing is greater under variable or random order practice compared to that under blocked or constant order practice. This observation suggests that task practice conditions used to invoke preparatory processing, might offer an important "active" ingredient to the design of effective task-oriented training programs for stroke neurorehabilitation. Recently, Schweighofer and colleagues (117) used a computational model of motor memory that contains a common fast process and multiple slow processes to predict and explain a set of counterintuitive CI effect results in participants at least three months after stroke. Nondisabled participants exhibited the usual CI effect with no forgetting from immediate to delayed retention in the random condition, but forgetting in the blocked condition. In contrast, the participants with at least three months stroke duration exhibited no forgetting in the random practice condition, but only marginal forgetting in the blocked condition (i.e., less forgetting than the control group). However, in poststroke participants, the integrity of visuospatial working memory (associated with the fast process) modulated long-term retention after blocked schedule training—that is, participants with poor visuospatial working memory exhibited little forgetting at 24 hours. This suggests that greater understanding of the neural bases for encoding and consolidation processes in the stroke brain will be important for future advances in this area.

Task Specificity and the Contents of Training

There is no doubt that behavioral experience can enhance function after brain injury. Studies of the effects of enriched environments show that rats exposed to complex housing environments before and/or after injury typically have improved functional outcomes compared to animals in standard housing (118,119). Further, general exercise, such as wheel running, which influences neuronal circuitry of brain and spinal cord when initiated before and after injury, is associated with activity-dependent plasticity. A landmark study conducted more than a decade ago showed that physical exercise has a direct, positive impact on enriching the blood supply (i.e., angiogenesis) to a brain region that is engaged by the exercise (120), but physical exercise by itself generated no changes in the elaboration of brain connections. In models of injury, exercise is beneficial for restoring plasticity-related proteins after spinal cord injury (121,122), increasing axonal regeneration in sensory neurons (123) and protecting from damage caused by cerebral ischemia (124). However, there is no evidence that the running rat or hamster has better memories, faster or more competent thinking, or stronger, more refined, and more flexible control of its actions because it spent considerable time on the running wheel. It seems that for the latter benefits to occur, for fundamental processes including remembering, reasoning, and fine motor control, *new experiences and learning* are a necessary and critical driver.

In support of this idea, considerable work using animal models of stroke suggest that functional brain remodeling may be critically contingent upon the behavioral demands of the training and the acquisition of motor skills associated with learning a novel task (48,125). Animals trained in skilled upper limb tasks show differential changes in the functional reorganization of the motor cortex compared

either to animals that had the unaffected limb restrained but received no additional training (126) or to animals that received an identical intensity of training in unskilled upper limb movement tasks that demanded less movement precision (48,127). The adult animals that were exposed to motor skill training demonstrated enlargement of the motor cortex representation of the wrist and digits, whereas comparable changes in functional reorganization of the cortical maps were not found in the animals that undertook repetitive unskilled upper limb activities. Thus, although exercise can be beneficial in some ways, learning motor skills results in neuronal structural and functional plasticity in the motor cortex and cerebellum that is not found with simple exercise or repetition of previously learned skills (125,127–130).

Maldonado and colleagues used a unilateral ischemic lesion model and asked if exercise could be used as a positive modulator of motor skill "relearning" in young and older rats. Motor skill training consisted of daily practice of the impaired forelimb in a tray-reaching task (task-specific training). Exercised rats had free access to running wheels for six hours per day. In the young adult rats (task-specific training group), motor skill training significantly enhanced skilled reaching recovery compared to controls (no activity or exercise groups). However, exercise did not significantly enhance performance when administered alone or in combination with task-specific training. Further, there was no major benefit of exercise in older rats, and no effects of exercise in a measure of coordinated forelimb placement or in immunocytochemical measures of several plasticity-related proteins (BDNF, NMDAR-1, spinophilin, MAP-2) in the motor cortex. Thus, the Maldonado et al.'s results support the importance of task-specific training over general exercise, either alone or combined, for improving skilled reaching after unilateral ischemic lesions of the sensorimotor cortex in rats (125).

Recently, researchers in Denmark showed that a single bout of exercise improves motor memory for a visuomotor accuracy-tracking task. Using a clever design in which 48 young nondisabled participants were allocated randomly into 3 groups, Roig and colleagues (131) investigated whether a single bout of intense aerobic exercise could improve motor memory and motor skill learning. They also explored if the timing of the exercise bout in relation to the timing of the practice had any impact on the acquisition and retention of a motor skill. Participants practiced a visuomotor task either before or after a bout of intense cycling exercise or after rest. Visuomotor skill acquisition was assessed during practice and retention was measured at 1 hour, 24 hours, and 7 days after practice. There were no differences in the rate of motor skill acquisition between the groups. In contrast, both exercise groups showed significantly better retention at 24 hours and 7 days after practice compared to the rest-only control group. In addition, the positive effects of acute exercise on motor memory are maximized when exercise is performed immediately after practice, during the early stages of memory consolidation. These results highlight the benefits of one bout of intense exercise performed immediately before or after practicing a motor task and that the timing of exercise in relation to practice is possibly an important factor regulating the effects of acute exercise on long-term motor memory.

Pak and Patten (132) conducted a comprehensive review of the impact of strengthening exercises on function (not skill). Most relevant to task-oriented training is that power training when combined with functional training can improve upper extremity movement accuracy more so than functional training alone (41). A combination of the two also can lead to improvements irrespective of the order in which they are provided (133). When examining the respective roles of functional task practice and power training, the former was found to increase upper extremity compensatory patterns whereas the latter led to more normal movement patterns (41). However, power training led to more normal movement patterns. If provided first, power training may enhance the benefits of repetitive task practice.

In noninjured humans, learning-associated activation of the primary motor cortex was found to be greater than the activation associated with simple repetitive motor use (134,135). Investigations of CIMT showed both increased use of the affected upper limb and changes in cortical activation after training (136–140). However, the specific contribution of task-oriented training compared with the "forced-use" associated with the constraint of the nonparetic limb cannot be determined without a control group (141).

Nelles and colleagues conducted a small RCT and compared the effects of upper limb task-oriented training and a similar intensity of passive movements and muscle-stretching activities in 10 subacute stroke participants (47). The task-oriented training group showed a trend toward diminished motor impairments (UL Fugl-Meyer) and significantly increased activation in several sensori–motor regions of the brain (bilateral parietal, premotor, contralateral precentral, and postcentral areas). In contrast, the control participants did not exhibit comparable changes in the fMRI BOLD signal response. Similar results were obtained in a study that used computer-aided training of finger tracking in 10 chronic stroke participants. Here the researchers found a significant shift in activation from the unaffected to the affected hemisphere in the primary sensory and motor areas and premotor cortices after training, as well as associated improvements in manual dexterity compared to pretraining (142). This same group compared the effects of two weeks of computer-aided training of finger tracking to repetitive simple finger movements in 20 mildly impaired chronic stroke participants (143). Surprisingly, they found no differences between the two training groups in the performance of clinical tests, including the Box and Block and Jebsen–Taylor hand function test. However, both groups showed improvements on these tests compared with pretraining levels. Similar findings prevailed for the fMRI activation results, with no consistent patterns or trends.

Compared to the animal studies, those in humans are less conclusive about the relative effects of the contents of training on cortical plasticity and associated upper limb functional recovery after stroke. However, there are several additional variables that deserve consideration, especially the *severity* of motor deficits of participants.

Severity of Motor Deficits

Two studies in particular highlight the importance of matching the task-specific training program to the severity of motor deficits of participants. Salbach and colleagues reported on the efficacy of a task-oriented intervention in enhancing competence in walking in people after stroke (144). This was a two-center observer-blinded, stratified, block-randomized controlled trial with 91 patients (44 experimental, 47 control) who exhibited a residual walking deficit within one year of first or recurrent stroke. All participants could walk at baseline, though some much slower than others.

The experimental intervention consisted of a task-oriented training program administered during three 90-minute sessions per week for 6 weeks. The task-oriented training consisted of functional tasks designed to strengthen the lower extremities and enhance walking balance, speed, and distance. The control intervention consisted of task-oriented upper limb practice of functional, unilateral, and bilateral tasks chosen to improve gross and fine manual dexterity. A baseline six-minute walk test was not different between groups (experimental 209 m, control 204 m), but the change in the task-specific training group was significantly greater (40 ± 72 m) compared to the control (5 ± 66 m) group. More importantly, though participants with mild, moderate, or severe walking deficits at baseline improved on average (36 ± 96 m, 55 ± 56 m, and 18 ± 23 m, respectively), the best responders to the task-oriented training program for walking were those who presented with moderate walking deficits at baseline.

Two years later, this same group published the results of the task-oriented intervention on arm function in people with stroke using the control group (n = 47) data from the same RCT described above (145). They reported that the 27 hours of upper extremity task-oriented training distributed over 6 weeks did not improve voluntary movement or manual dexterity of the affected arm. However, a closer look at the baseline upper limb motor deficit of the "control" group provided a reasonable explanation for these negative findings. Indeed, these results were not surprising when considering the heterogeneous sample that was selected based on walking impairment, rather than arm impairment. Sixteen percent of the patients had no distal (wrist/fingers) movement capability. It is well known that if no hand dexterity is apparent by six weeks after stroke, the likelihood of achieving hand function at six months is poor (146).

An international panel supported with funding from the Canadian Stroke Network has been working for the past three years to develop an algorithm for progressing poststroke upper extremity rehabilitation along with best outcome measures at each decision point of the algorithm. The group concurs that if no hand function is achieved by 12 weeks after the stroke, the likelihood for such gains to be made subsequently is poor (146,147).

Timing of Task-Oriented Training

Evidence from animal studies suggests that timing of training may play a critical role in its effectiveness in restoring or improving performance, enhancing the survival and neural reorganization of the surviving perilesional tissue, and establishing effective neural reorganization of the contralesional hemisphere (148–150). Although postlesion intensive training that commenced too early has been shown to have deleterious effects in animals (151–153), a modified CIMT protocol commenced within the first two weeks following stroke in humans was shown to be safe (71). In animal models, a delay in training results in poorer behavioral recovery and poorer preservation of penumbral areas representing the distal forelimbs (149,154). In an oft cited review, Murphy and Corbett (155) point to evidence from animal models that suggest that a time-limited window of neuroplasticity opens following a stroke, during which the greatest gains in recovery are made. They suggest that understanding how to optimally engage and modify surviving neuronal networks could lead to new response strategies that compensate for tissue lost to injury. In humans, the optimal therapeutic window after stroke for rehabilitation of the upper limb remains to be established (156). Further, the recent NINDS priority program for translational research targeting early recovery after stroke in humans suggests that more work is needed (4).

Regardless of severity, there is preliminary evidence to suggest that earlier, more aggressive therapy results in better upper limb outcomes (157,158). It is likely that the therapeutic window for rehabilitation might depend upon the severity of the stroke, as well as the presence of other comorbidities (159). Imaging studies provide evidence of ongoing cortical reorganization of motor systems for several months after stroke (160). Improvements in function have been observed from clinical measures in the first three to six months after stroke, after which relatively less change may be seen if no further intervention is undertaken (161). As mentioned earlier, changes in cortical activation and improvements in affected upper limb function have been reported with training in chronic stroke participants (137–139); however, there are several compelling arguments for introducing a task-oriented approach earlier after a stroke, during the immediate outpatient interval, especially for those who exhibit a mild to moderate upper limb impairment (i.e., enough residual capacity to benefit from therapy).

Although the exact proportion of stroke survivors who are mildly to moderately impaired is not known, conservative estimates range between 5% and 30%. These are individuals who return to the community but with significant disablement (162). The paucity of dose-equivalent designs in the stroke upper extremity clinical trial literature, and

the recent EXCITE trial (1), highlight an important need in this area (163,164). Unlike the EXCITE trial design, a task-oriented intervention that targets the immediate postacute period provides several advantages for the patient with a mild to moderate motor deficit. This timing is considered optimal for several reasons:

1. It enables a supportive interaction between processes associated with experience-dependent and injury-induced cortical reorganization that are known to influence functional recovery (165,166)
2. It is possible that earlier intervention may allow for more optimal cortical reorganization and potentially less use of behavioral compensatory strategies (149,167)
3. It may attenuate the detrimental effects of maladaptive compensatory strategies (e.g., learned nonuse) currently promoted during inpatient rehabilitation (168) that may with time be reinforced and become more difficult for the patient and clinician to reverse (11)
4. It is not so early as to be overly aggressive during a more vulnerable period both physiologically and psychologically (165,169)
5. The outpatient environment is a more practical setting for a distributed, relatively high dose of upper extremity task-specific training, especially given the already dwindling acute inpatient length of stay (164). Indeed, recently, Lang and colleagues showed that affected upper extremity use is minimal during the inpatient rehabilitation stay in patients with mild to moderate acute hemiparesis (170)

Dosing of Task-Oriented Training

The 2005 AHA/ASA-endorsed Clinical Practice Guidelines (171) reviewed the evidence for therapy intensity and duration. Though the heterogeneity of the studies combined with borderline results in many trials limited the specificity and strength of any conclusions overall, the trials supported the general concept that rehabilitation can improve functional outcomes, particularly in patients with lesser degrees of impairment. There is weak evidence for a dose–response relationship between intensity of the rehabilitation intervention and functional outcomes. For example, Sterr and colleagues demonstrated that in a 2-group randomized trial of 15 adults with chronic hemiparesis, the group receiving 6 hours of CIMT daily over 2 weeks improved significantly at 1 month on the WMFT and MAL than the group receiving 3 hours delivered daily over the same period (70). Despite limitations of these individual studies, the conclusions among several systematic reviews are fairly consistent: greater intensity produces slightly better outcomes (172,173). Kwakkel (173) reported a small but statistically significant intensity effect relationship in the rehabilitation of stroke patients. The literature specific to upper extremity treatment is mixed. Other than EXCITE, there are no multicenter trials of dosing of task-oriented training in the literature.

The very early constraint-induced movement therapy (VECTORS) phase II single center, single-blind RCT (71) begins within 14 days of stroke onset during acute inpatient rehabilitation. VECTORS compared traditional upper extremity therapy with dose-matched and high-intensity CIMT protocols. The primary endpoint was the total ARAT score on the more affected side at 90 days after stroke onset. As expected, all groups improved with time on the total ARAT score. Of particular importance, the high-dose CIMT group had significantly worse scores at Day 90 compared to the other two groups. No significant differences were found between the dose-matched CIMT and control groups at Day 90. ADC maps revealed no evidence of new neuronal damage. A dose–response relationship was observed, where a *higher dose* of CIMT was associated with *less motor recovery*. Given the importance of longer-term outcomes for rehabilitation, the implications of these results should be taken cautiously until more distal time points at six months and one year are reported.

For our currently running phase III stroke rehabilitation trial, Interdisciplinary Comprehensive Arm Rehabilitation Evaluation (ICARE), we chose a distributed dose of 30 hours of training for scientific and pragmatic reasons (174). We included a comparison control group, an observation only, usual and customary (UCC) outpatient therapy. We expect considerable variation in the UCC dose both by site and across the five-year monitoring period. These observation data will be important in the end from a policy standpoint and should be useful to estimate the cost if more prescriptive practice guidelines were to be implemented, especially if a higher dose can be shown to produce better outcomes. Pilot data from a multisite outpatient survey suggests that 30 hours distributed over 10 weeks would be on the higher side of what is commonly prescribed, but still practical in that it would allow patients to participate in other concurrent therapy services (e.g., physical therapy and speech therapy). Thirty hours is 33% more than what we used in our single site phase II trial that commenced during inpatient rehabilitation and extending to outpatient (20 hours distributed over 4–6 weeks) (85). It is 50% of that used for EXCITE (60 hours over 2 weeks) during the 3- to-9-month postoutpatient period (1), twice that used by Page and colleagues (75) (15 hours over 10 weeks, 30-minute sessions, 3 times per week) in a phase I acute trial of mCIT, and 55% of that prescribed in the home-based RCT of a multifaceted therapeutic exercise program (54 hours over 12 weeks) in subacute stroke (175). Therefore, the 30-hour dose is well within the range of previous intervention trials shown to be effective and is practical for the outpatient environment. Yet, it is likely higher than the usual average dose that is prescribed for this patient group.

The only head-to-head comparison—a single center, single-blind phase I RCT, dose optimization for stroke evaluation (DOSE)—is currently enrolling participants (ClinicalTrials.gov Identifier: NCT01749358). This study will enroll and adaptively randomize 60 individuals who are no less than six months in stroke duration and who meet inclusion criteria into one of four dose groups (0-, 15-, 30-, and 60-hours) of a principle-based, theoretically defensible ASAP for upper extremity recovery. Frequency is four times

per week, one week per month for three months in a train–wait–train paradigm. Follow-up assessments will be performed monthly up to 10 months after randomization. At the time of this writing, DOSE has enrolled approximately 50% of its target.

CONSIDERATIONS FROM THE NEUROSCIENCE PERSPECTIVE

In 2008, Kleim and Jones (176) reviewed a growing body of neuroscience research that used a variety of models of learning, neurologic disease, and trauma from the perspective of basic neuroscientists but in a manner intended to be useful for the development of more effective clinical rehabilitation interventions. Because neural plasticity is believed to be the basis for both motor learning in the intact brain and relearning in the damaged brain that occurs through physical rehabilitation, the recent advances in understanding experience-dependent neural plasticity can inform the application of task-oriented training interventions. Kleim and Jones argue that the "qualities and constraints of experience dependent neural plasticity are likely to be of major relevance to rehabilitation efforts in humans with brain damage." Recently, an interactive e-book, *Neural Plasticity: Foundation for Neurorehabilitation* (177) provides an updated and more fully developed expose of neural plasticity (especially good for students interested in the translation of neural plasticity to effective therapy programs). This e-book goes beyond a simple literature review (there are many excellent review articles and book chapters on this topic) and begins to integrate and apply the important principles of neural plasticity so as to inform therapeutic paradigms. To be clear, the book is not a handbook on how to treat people with brain injury. For our purposes, we review the seven behavioral signals driving neural plasticity as outlined in this e-book. For each behavioral signal, we consider a literal translation as it pertains to the promotion of upper extremity recovery and, where appropriate, include current behavioral perspectives and translational studies in stroke rehabilitation.

Behavioral Signal 1: Use It or Lose It

Failure to drive specific brain functions can lead to functional degradation. Behavioral signal 1 suggests that any intervention that encourages or promotes "use" of the paretic limb would be appropriate. Task-oriented training, CIMT, bilateral arm training, and functional task practice are just a few programs from the clinical evidence-based literature that would qualify for application of Behavioral Signal 1 (see "What is Task-Oriented Training," above, and "Emerging Innovative Approaches," below, for details). Recently, to better understand the interaction between arm function and use in humans after stroke, Schweighofer and colleagues used a computational approach to develop a first-order dynamical model of stroke recovery with longitudinal data from participants receiving constraint-induced movement therapy in the EXCITE clinical trial (178). Of most import, by comparing the model parameters before and after CIMT intervention in participants receiving the intervention one year after randomization, they found that therapy increased the parameter that controls the effect of arm function on use. Increase in this parameter, which can be thought of as the confidence to use the arm for a given level of function, lead to an increase in spontaneous use after therapy compared to before therapy.

Behavioral Signal 2: Specificity

The nature of the training experience dictates the nature of the plasticity. Behavioral signal 2 implies that *specificity* of training is important. Indeed, *specificity* effects are one of the oldest and most common findings in learning and memory research (179). Later in the twentieth century, work in the transfer of skills again supported a specificity effect, with the general finding that transfer of training was small unless the skills were essentially identical to one another (180). Similarly, a specificity effect was found in experiments in which participants learned a task during practice and then performed it under similar or changed conditions in a transfer test (181). As predicted by the specificity effect, performance was usually most effective when the transfer conditions matched those conditions that were available during the practice session. Therefore, there is considerable evidence suggesting that motor skills are represented in memory in a highly specialized way (182). Although the memory representation might be specific, recent behavioral findings from an examination of individuals with chronic hemiparesis suggests otherwise. In a small-scale study (n = 11), Schaefer and colleagues (183) tested whether training on one motor task (i.e., feeding task) would transfer to untrained tasks that were either spatiotemporally similar (i.e., sorting) or different (i.e., dressing) in individuals with chronic hemiparesis after stroke. Interestingly, after five days of supervised massed practice of a feeding task, performance of all three tasks improved significantly after training. Further, the amount of improvement in the untrained tasks was comparable but not dependent on the degree of similarity to the trained task. Given the small sample, these results are clearly not definitive, but rather they are suggestive that the effects of upper extremity task-specific training can transfer to other untrained tasks in individuals with chronic mild-to-moderate hemiparesis. One possible mechanism for this transfer effect may be attributed to a more general phenomenon such as improved self-efficacy or confidence to use the limb that comes with task success during training. Understanding how these social–cognitive factors modulate motor learning and transfer will be important for future research (58).

Taken together, the literature regarding specificity of training (see also "Task-Specificity and Contents of Training" section) shows that although general exercise and strengthening programs are thought to be effective when combined with task-oriented or task-specific training programs, the direct benefits are usually expressed at the system level (i.e., physiology, musculoskeletal) and not at the level of the specific task or skill that is being trained. Recent work has begun

to examine the degree to which practice on one task actually transfers in meaningful ways to another task.

Behavioral Signal 3: Intensity Matters

Induction of plasticity requires sufficient training intensity. Behavioral signal 3 implies that the dose, frequency, and duration of training are important parameters in the design of any effective task-oriented training program. Intensity is usually defined as an exceptionally great concentration, power, or force. In the field of physics, it is the amount or degree of strength of electricity, light, heat, or sound per unit area or volume. In earlier sections (see "Practice Time or Intensity of Training," and "Practice Schedules and Organization of Tasks"), we reviewed the studies that have manipulated the "intensity" of training by varying parameters of dose, frequency, and duration. There is considerable evidence to support this idea, but explicit guidelines for what constitutes a "sufficient" level of intensity is sorely lacking. The so-called "pharmacokinetics" includes "dosing of training" and has been identified as both a challenge and an important unmet need in the design of clinical trials in rehabilitation (see "Research Frontiers," below, for more discussion). The importance of "therapy dose" in neurorehabilitation is reflected in a recent trend for clinical trials of complex interventions to include at least one dose-equivalent control group in the design (184,185). In translating from animal models (155,186) to human clinical practice, Krakauer and colleagues suggest that there will need to be a substantial increase in the intensity and dosage of treatments offered in the first month after stroke with an emphasis on impairment (187).

Behavioral Signal 4: Repetition Matters

Induction of plasticity requires sufficient repetition. Behavioral signal 4 suggests that repeated attempts to solve the motor problem benefits plasticity and learning. There is considerable evidence for this idea that comes from the motor learning literature and is reviewed earlier (see "Motor Control and Learning Considerations," above). What is less understood is how the organization of those repetitions (e.g., massed vs. distributed) should be structured for the best outcomes. What is clear from the evidence to date is that mere repetition of simple tasks that are well within the capability of the performer will most certainly not induce neural plasticity or learning (48). It is likely that Bernstein's observation that "practice is repetition without repetition" is profound and fundamental to advancing understanding in this area of study (57).

Behavioral Signal 5: Time Matters

Different forms of plasticity occur at different times during training. Behavioral Signal 5 implies that timing of an intense, task-oriented training program is an important factor. Most of the clinical research up until recently has been conducted in the chronic phase of stroke recovery. The reason for this choice is complicated and multifaceted (e.g., confounded by spontaneous recovery and safety concerns related to glutamatergic toxicity from animal studies) but also an unfortunate one, especially in the light of more recent studies in both human and animal models suggesting that an earlier time frame would likely have a greater impact on important outcomes (148,149,154,155). In a provocative Point of View: Directions for Research piece, "Getting Neurorehabilitation Right: What can be learned from Animal Models?" (187) there is an impassioned plea for focused high-intensity interventions offered in the first month after stroke. This proposal is reflected in the recent NINDS priority program for translational research targeting early recovery after stroke in humans (4).

Behavioral Signal 6: Difficulty Matters

There is substantial evidence from the behavioral, computational, neuroscience, and social psychological literatures for the beneficial effects on motor skill learning of practice conditions in which the difficulty of the task matters (54,116,117,188–192). The level of task difficulty can be manipulated through practice schedules, contextual factors, dual tasking, and the actual task requirements (e.g., precision, magnitude, degrees of freedom). Perceived task difficulty can be manipulated through simple statements before practice that have been shown to increase confidence and impact motor learning (58). Various mechanisms have been suggested as the basis for this beneficial effect on learning including that which requires deeper information processing, working memory load, problem solving, and reward-induced consolidation.

Behavioral Signal 7: Salience Matters

The training experience must be sufficiently salient to induce plasticity. Behavioral signal 7 implies that the training must have the quality or state of being "salient." It must be prominent or stand out conspicuously or be noticeable. There has been considerable discussion about the nature of the recovery process from the patient's perspective (193–195). Barker and colleagues (194) reported that the single most important factor that contributed to upper limb recovery, from the perspective of the stroke survivor and through self-report, was "use of the arm in everyday tasks." From this observation, we suggest that a task-oriented training program which includes participant-selected meaningful tasks will likely be viewed as most salient in the context of the recovery process. In support of this notion, a recent qualitative study to identify themes and possible mechanisms of recovery of the hand suggested a therapeutic framework for continued rehabilitation and research that includes the patient's perspective (195). Finally, there is considerable evidence that self-controlled conditions of practice (e.g., self-controlled feedback) are better for learning than externally controlled conditions (192,196). Together, the behavioral evidence suggests that understanding salience

as defined by the patient or learner may be a fruitful direction for future work that seeks to drive positive plasticity and optimize recovery processes.

EMERGING INNOVATIVE APPROACHES TO UPPER LIMB REHABILITATION

In the Clinical Trials section of the 2006 Stroke Progress Review Group report, "multimodality combination interventions" were identified as an emergent research area. The most recent NINDS stroke priorities (4) specifically targeted "Translational research using neural interface devices for stroke and other neurologic disorders." The failure of the industry-sponsored multisite pivotal trial (phase III) of targeted subthreshold epidural cortical stimulation delivered concurrently with intensive rehabilitation therapy (197–200) warranted a critical appraisal. Plow and colleagues (201) summarized their concerns regarding cortical stimulation with the following comments: "it is important to determine the (a) location of peri-infarct representations by integrating multiple neuroanatomical and physiological techniques; (b) role of other mechanisms of stroke recovery; (c) viability of peri-infarct tissue and descending pathways; (d) lesion geometry to ensure no alteration/displacement of current density; and (e) applicability of lessons generated from noninvasive brain stimulation studies in humans. In terms of combining stimulation with rehabilitation, we should understand (a) the principle of homeostatic plasticity; (b) the effect of ongoing cortical activity and phases of learning; and (c) that subject-specific intervention may be necessary."

In the next section, we focus on the applicability of lessons generated from noninvasive brain stimulation studies in humans. Specifically, we describe research combining noninvasive stimulation with rehabilitation, which provides Class I evidence that time-locked rTMS before or after physical therapy improves measures of dexterity and force in the affected limb in patients with chronic deficits more than six months after stroke.

Multimodal Combination Intervention: Low-Frequency rTMS and Physical Therapy

Avenanti and colleagues demonstrated that low-frequency rTMS promotes use-dependent motor plasticity in chronic stroke using a cleverly designed randomized trial (202). Their aim was to investigate the long-term behavioral and neurophysiologic effects of combined time-locked rTMS and physical therapy intervention in chronic stroke patients with mild motor disabilities. Thirty patients were enrolled in a double-blind, randomized, single-center clinical trial. Participants received 10 daily sessions of 1 Hz rTMS over the intact motor cortex. In different groups, rTMS stimulation was either real or sham and was administered either immediately before or after physical therapy. Outcome measures included: dexterity, force, interhemispheric inhibition, and corticospinal excitability and were assessed for three months after the end of treatment to determine persistence of any effects. With regard to mechanism, they reported a treatment-induced cumulative rebalanced excitability in the two hemispheres and a reduction of inter-hemispheric inhibition in the groups that received real rTMS. Use-dependent improvements were detected in all groups. Improvements in trained abilities were small and transitory in the sham rTMS group (therapy only effect). They reported greater behavioral and neurophysiologic outcomes after real rTMS with the group receiving stimulation *before* physical therapy showing robust and stable improvements and the other group (i.e., rTMS *after* physical therapy) showing less persistence of the training effect over time. Their results suggest that priming motor networks with rTMS can promote effective use-dependent plasticity. These findings suggest that hypothesis-driven multimodal combination therapies using noninvasive brain stimulation that implement known mechanisms of neuroplasticity can be developed for future clinical use. Future work will need to determine if the present findings can be extended to stroke patients with moderate to severe motor impairments.

An Integrated Model: Accelerated Skill Acquisition Program

In this section, we introduce an integrated model of task-oriented training that proposes the infusion of contemporary motor learning research into neurorehabilitation practice (203). Neuroscientific evidence revealing the inherent plasticity of the brain (i.e., neuroplasticity) that allows new learning, adaptation, and compensation at multiple levels of the system, from early development well into old age, profoundly impacted conceptions of rehabilitation and recovery after stroke. In fact, this insight has heightened the relevance of the science of motor learning to physical therapy practice. Prior to the revolution in neuroscience, researchers in the field of motor learning had established a number of behavioral variables important for skill acquisition, chief among them being practice. The science of motor learning itself continues to evolve, providing new insights into the optimization of skill learning and its application to the complex process of neurorehabilitation. Throughout this section, we use the terms skill acquisition and learning, synonymously. Furthermore, we distinguish performance from learning. The learning–performance distinction (81,204) has relevance to physical therapy in that the concern is with the achievement of a sustainable or relatively permanent change in the capability for responding in contrast to a short-lasting temporary change. We now understand that some practice-related techniques such as drills and frequent feedback can have a performance-enhancing effect that boosts performance while available. Similarly, some practice-related interventions may appear to retard or slow performance gains when present, seen, for example, when tasks are ordered randomly (205) (see Behavioral Signal 6: Task Difficulty Matters above for more discussion). An assessment of learning and the associated memory processes is not reliable unless it is conducted at some time or context

that is removed from the practice period—during retention or transfer tests (185,206–208).

Neuroplasticity Heightens the Importance of Motor Learning

It took until the turn of the 21st century before studies that examined motor learning in patient populations began to appear in the literature (209,210). At about the same time, Nudo and colleagues published in 1996 the now seminal paper in the journal *Science*. In that study, using a primate model of stroke, they demonstrated the capability of the motor cortex to reorganize the digit representation area in response to postinjury motor training—but not as a consequence of spontaneous recovery, without training (126) (see Chapter 7). More importantly, Nudo and colleagues showed that cortical reorganization of the digit area was the direct result of the food-retrieval practice paradigm used to train the primates after the stroke lesion. In later work, Plautz and colleagues identified further that cortical reorganization was dependent on goal-directed, task-specific practice, likely the result of acquisition of a motor skill (i.e., motor learning) and not mere repetition of grasping movements from the easiest and largest food wells (48).

With the advent of new brain imaging technology, it is now well accepted that the learning of motor skills results in adaptive changes in the functional organization of the motor system (211,212). Attempts at skilled movements together with injury-induced plasticity (e.g., stroke or head injury) can influence the use of injury-affected musculature and subsequent reorganization of spared neuronal networks (213). Research over the last decade has provided considerable evidence that has advanced knowledge about how to shape plasticity to enhance recovery after injury (214,215).

Perspectives on Skill Acquisition, Sustainability and Generalizability

There is now sufficient evidence that the acquisition of a new motor skill requires progressive challenge, intensity, problem solving, sufficient motivation, and focused attention, especially in the early stages of learning (58,81,177 (chapter 2),216). We also know that skill-based learning involves active participation and requires a certain degree of voluntary neuromotor capability. Most motor skills involve procedural (implicit) memory and knowledge and require little attention once they are learned (190,217,218).

Recently, motivational factors involved in long-term behavioral engagement, including self-efficacy and support for fundamental psychological needs (competence, autonomy support, social-relatedness) (219–222), have been examined with respect to their role in motor performance and learning, as reflected in acquisition and retention of novel motor skills in clinical and nonclinical populations (58,223–225). For example, relative to a control group, older women learning a novel balance task and who were provided a single statement prior to beginning the task that "active people like you, with your experience, usually do very well on this task," retained learning, balanced longer, and had higher self-efficacy on a delayed test of learning (223). Individuals in inpatient stroke rehabilitation given feedback and encouragement of daily timed gait trials walked significantly faster both at discharge and three months later than those not provided with their times and encouragement (225).

In a manner not unlike the effects of exercise that will not be retained unless the exercise is continued, the concept of task-specific practice implies that without ongoing and progressive practice, movement skills will not be advanced (226). Task-specific practice may occur by deliberate and systematic set-aside sessions. It also may be induced transparently by responding to the demands of everyday activities (227), provided that those activities call for use of the more affected extremity. Because development and retention of movement skills over time require ongoing behavior, psychological science pertaining to behavior change or support (219,228,229) becomes highly relevant to those seeking to produce lasting effects in their clients. As such, another aspect of skill that will be important for sustaining gains and generalizing movement skills into everyday contexts (230) is a set of skills related to self-management of those gains and continued use in the natural environment (see "Behavioral Signal 7: Salience Matters" above for more discussion).

Infusing Contemporary Motor Learning Into Neurorehabilitation Practice

In essence, learning significantly underlies the recovery of function and the development of new skills after catastrophic or profound neurologic and other disabling disorders. Creating the conditions that optimize the processes of motor learning and relearning may have been the implicit intent of some rehabilitation and research programs. However, many lack a strong conceptual framework, have been narrow in focus, and have not included critical features to direct, sustain, and generalize effects into life activities and community participation.

The past decade has witnessed an explosion of different therapeutic interventions for stroke rehabilitation emergent from new insight about the brain–behavior relationship. Despite the varied intervention options, a significant percentage of individuals are unable to maintain and generalize the gains achieved in therapy to the natural environment after therapy ends (44,178,231). Though task-oriented training approaches highlight the importance of repetition and task specificity, they sometimes downplay the achievement of skilled movement in the service of functional tasks. Maladaptive or "bad use" can occur when less optimal, unskilled, solutions—ones that rely on compensatory strategies—are used (36,38–43). This can contribute to incipient declines after therapy ends and gains are not generalized.

The opportunity, therefore, is to integrate the known benefits of intense, challenging, and progressive task practice programs with those that optimize skill, transfer, generalization, and persistence of gains made in therapy to the natural environment. Recently, we suggested an

evidence-based solution—one in which the benefits of progressive, task-oriented training could be integrated with patient-centered strategies to facilitate translation of the therapeutic gains into skilled use in the home and community and in which the patient is empowered to incorporate the paretic limb into valued activities (185,232).

The Accelerated Skill Acquisition Program

We developed an evidence-based intervention, the ASAP, which integrates contemporary principles of motor learning (40,185,233,234). ASAP is a hybrid combination of task-specific and skill-based/impairment-mitigating training with embedded patient-centered motivational enhancements. Targeted task-specific training (skill) emerges as the single most important approach to intervention for the disabling consequences of stroke in mildly to moderately impaired participants. The fundamental problems that ASAP addresses are conceived as the learning or relearning of motor skills to optimally affect neural plasticity (177), as well as skills to self-direct posttraining activities (195). Development of skill is facilitated by the amelioration of impairments (e.g., muscle weakness, low self-efficacy) to enhance capacity (17,41,235). Attention to motor learning, motor control (e.g., goal-directed whole tasks with natural synergies) (81 (p. 382), 236), and basic exercise physiology (e.g., overload in terms of training load/intensity, speed) principles are very relevant (237). Social–cognitive psychological theories of motivation are applied in this intervention for immediate and particularly longer-term participant motivation. These assume that intrinsic sources of motivation, including perceptions of self-determination (choice, control, collaboration) and self-efficacy (confidence in one's capabilities) are key contributors of continued choice, effort, and persistence to use paretic limbs, which in turn, leads to mitigation of disability and of self-imposed participation restrictions. A note of historical interest, the ASAP intervention draws upon research from motor learning and several overlapping fields of study, and in fact incorporates principles of even more subfields of movement science (e.g., exercise physiology). As such, we do not consider ASAP as a motor learning approach per se (238).

Conceptual Framework: Integration of Skill, Capacity, and Motivation

In this section, we outline the conceptual framework for ASAP. A pathway from impairment reduction to functional capability to more general use of restored limbs in natural contexts often is implicit but less frequently operationalized in therapeutic practice. This conceptual model derives from the infusion of motor learning, neuroscience, and behavioral science described earlier (81,212,214,220), with the developing evidence base of neurorehabilitation as outlined in this chapter. Figure 20.1 illustrates the conceptual framework that skill (motor learning and self-management), capacity (impairment mitigation), and motivation (intrinsic drive) together form the fundamental components for effective

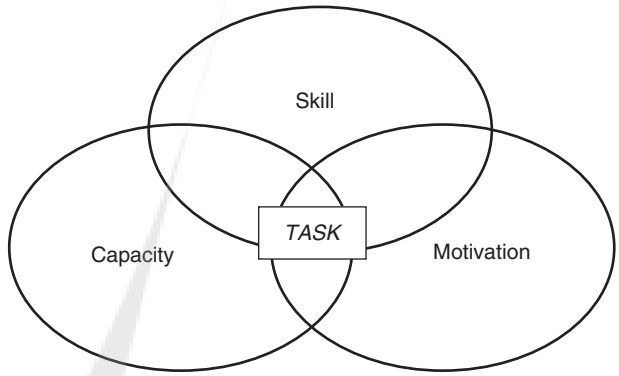

FIGURE 20.1 Conceptual framework for the Accelerated Skill Acquisition Program (ASAP). Activities to increase capacity, skill, and motivation were centered around meaningful tasks of the participant's choosing.

incorporation of impaired extremities into life activities. These three essential elements result in a set of eight nonexclusive principles that inform rehabilitation practice (Table 20.1). Activities to increase capacity, skills, and motivation are centered on specific tasks of the participant's choosing. Here the task is viewed as an important vehicle for the acquisition of skilled movements, a means to promote capacity building, and as a mechanism to foster the development of motivation for meaningful task engagement in the natural setting. Table 20.1 lists the principles of ASAP along with implementation examples.

As of this writing the ICARE phase III, randomized controlled trial (185) is currently underway. ICARE was developed to compare the effectiveness for paretic arm recovery of the investigational intervention, ASAP, with a dose-matched usual care group. It was designed with a relatively high dose of therapy in large part to ensure a reasonable test of the intervention that is dependent on sufficient practice for skill acquisition and generalizability beyond the clinic setting (i.e., 30 one-hour visits distributed over 10 weeks delivered in the outpatient setting). Primary outcomes from this trial are to be released during the first quarter of 2015. It is our expectation that the ASAP principles would apply across a diverse spectrum of disabling conditions to rehabilitation interventions for a number of different patient groups and are not unique to the case example of upper-extremity function in neurological conditions. Further refinement and testing of ASAP, and in varying populations and permutations, in well-conceived and sound clinical research is encouraged (5,239). The principle-based approach of ASAP relative to most protocol-driven approaches (e.g., CIMT) was undertaken to provide for a more flexible and customizable intervention, including innovative technologies for participants of varying clinical needs, severity levels, and personal preferences for therapeutic goals. The identification of multiple principles guiding dynamic clinical decisions means that in any given moment, some principles will be emphasized to the downplay of others. However, it is usually the case that therapeutic actions can satisfy one or more principles

TABLE 20.1 Principles of ASAP With Implementation Examples

ASAP PRINCIPLE	IMPLEMENTATION EXAMPLES
1. Ensure challenging and meaningful practice (48)	Demonstrate the challenge threshold (the performance threshold above which movement breaks down and is unsuccessful, and below which the task can be accomplished relatively successfully)
	Focus on skillful performance of important activity to participant
2. Address important (interfering) changeable impairments (235,278)	Focus on mitigating a particular area of weakness (e.g., wrist), pain, or interference with progress
3. Enhance motor capacity through overload and specificity (279)	Practice at a clearly intense level
	Provide task repetitions to physical limits
4. Preserve natural goal-directedness in movement organization (280)	Perform the natural task, practice with natural coordination demands
5. Avoid artificial task breakdowns when possible (281)	When feasible, practice the whole task in its functional entirety
	Break down the functional task when key to pinpointing or addressing the problem area
6. Assure active patient/participant involvement and opportunities for self-direction (228,229)	Encourage participant activity/response involving problem solving or task construction/determination
7. Balance immediate and future needs (55)	Participant problem solving (problem identification, solution generation, education, and action plan discussions focused on future, action plan extrapolations of session activities for home practice/recovery); focus is on knowledge and choices for the future
8. Drive task-specific self-confidence high through performance accomplishments (220)	Assess participant's task self-efficacy
	Demonstrate progress through clear measurement (timed performance, counts, repetitions, increased weight, etc.)
	Celebrate or attend to success

without contradicting others (203). It is expected that all of the principles will be supported over the course of a therapy session and especially over a multisession episode of care. The ability to take advantage of frequently occurring "teachable moments" is one strength of a principle-driven approach. Conversely, this abstraction and flexibility can be challenging for inexperienced clinicians but exciting to those seeking new challenges in their practice and high-quality interactions with their clients.

RESEARCH FRONTIERS

In this section, we briefly highlight four important research frontiers including: predictive models, mirror neuron system and the action observation network, quantification of the restitution–substitution continuum, and Attention and motor skill learning. Each topic is relevant to task-oriented approaches to promote recovery after stroke.

Predictive Models

This area is particularly challenging and identified by the NINDS Stroke Progress review group as one of the important unmet needs of the 2006 strategic planning process. Because poststroke recovery lasts several months, long-term outcomes must be considered to make informed decisions for individual patients. Two possible methods can be envisioned. First, the treatment modality and dose can be determined postdictively based on measured outcomes and iteratively. This method, however, is lengthy, costly, and may lead to sub-par outcomes because of the delays involved. Second, the treatment and dose can be determined predictively, based on a computational model of stroke recovery that predicts long-term outcomes. Predictive models, based on variants of the generalized linear model (GLM), are commonly used in clinical prediction rules. Several studies have employed such models with quantitative measures of anatomical and functional neural capacity (e.g., corticospinal tract) to determine functional potential in chronic stroke (240) or to determine the relationship between corticospinal tract injury and peduncular asymmetry (241). Recently, the predicting recovery potential (PREP) algorithm was developed for determining the recovery potential within the first 72 hours after stroke (147). Given that neural capacity largely determines potential for recovery and the choice of an appropriate rehabilitation strategy (242), patient specific models that include neural resources would be particularly appealing to optimize health care services.

However, because stroke recovery is a dynamic, time-varying, process, time should be included in predictive models. Although time can be added as a regressor in GLM models to predict recovery (243,244), GLMs are not well suited to model time-varying quantities. In addition,

because GLM models are nonmechanistic, parameters are empiric and generally have no true physical or physiological correspondence. In contrast, theory-driven and mechanistic dynamical, or state-space, models naturally encode time in differential equations that model "the change in states." Because of the multiplicity of plastic processes involved, upper extremity recovery is best modeled and predicted by dynamical state-space models that include both short and long time scales. On the one hand, change in performance during motor training occurs at a variety of time scales, some as short as 10s of seconds (245,246). We and others have shown that state-space models with short time scales can account for motor adaptation in stroke (247) and motor learning in poststroke individuals (117,148). On the other hand, recovery after stroke is characterized by a number of repair and plastic processes that happen at time scales of weeks to months. For instance, the initial performance changes after stroke are mostly because of "spontaneous recovery," which involves both reduction of the ischemic penumbra and brain reorganization (155), and are maximally expressed in the first four weeks after stroke, but continue until about six months (249). In addition, rehabilitation, consisting of thousands of practice movements over weeks, influences recovery (1,250–252). In previous work, we showed the existence of time-varying interactions between the amount of daily arm use and recovery of function via a dynamical model of stroke recovery in the two years following therapy (178,227,253). The model notably showed that learned nonuse, and its possible reversal, can be best framed in terms of interactions between motor learning and adaptive decision making (253,254). In addition, the model predicted that there is a threshold in function above which spontaneous use and function can spontaneously improve in a virtuous circle (253). We provided supporting data at the group-level for such a threshold (227). In these models of recovery, the main recovery time constant was several weeks. However, the time constant controlling the change in the decisions to learn one hand or the other was much smaller, and as a result, the model developed learned nonuse soon after stroke. Because it is unknown how fast learned nonuse actually develops after stroke, hand choice and kinematic data collected soon after stroke would lead to better parameter estimation, and hence, better predictions from these models.

Mirror Neuron System and Action Observation Network

A second exciting research frontier involves the *mirror neuron system* (255). Evidence for a human mirror neuron system and action observation network is mounting (256,257). However, there still is considerable controversy and confusion about the homologue to the primate mirror neuron system (258) as well as the purpose of the action observation network (259) in humans. Studies have been conducted to examine the sensitivity of the action observation network to physical and observational learning in humans (260). A provocative review suggested that the mirror neuron system might provide a useful circuitry to enhance recovery of the severely affected upper limb early after stroke (261). One of the first studies that provided empirical support for the use of action observation with intent to imitate in the context of stroke rehabilitation was published in 2007 (262). Recently, action observation was classified as one of several specific priming techniques to increase the excitability of the stroke-affected motor system and promote plastic reorganization in response to subsequent practice of physical activity (263). A small-scale study with eight chronic stroke patients provided evidence that a single session of action observation that was congruent with the practiced movement (i.e., voluntary thumb movement in a specific direction) enhanced motor memory more than practice alone or action observation of thumb movements that were incongruent to the practiced movement (264). However, a recent translational RCT found that observation-to-imitate plus practice for 15 days of treatment could add little to physical therapy benefits early after stroke (within 31 days) (265). Given the variable response to action observation in the stroke population, it will be important to understand how the stroke brain responds to action observation. Garrison and colleagues conducted the first fMRI investigation to determine if and how the motor system is modulated by action observation after stroke (266). Functional MRI was used to compare brain activity during right and left hand action observation in right-handed nondisabled matched participants (n = 12) and participants who were right-handed before left hemisphere stroke (n = 12). Action observation was found to activate specific motor plans in damaged motor circuits after stroke, and this activity was related to the motor capabilities to perform the same actions. Cortical motor activity during action observation may be relevant to motor learning and motor relearning in stroke rehabilitation. Harnessing the action observation network after stroke represents an exciting frontier for neurorehabilitation and a potentially important underutilized circuit for driving relevant recovery after stroke.

Quantification of the Restitution–Substitution Continuum

As discussed earlier in the first section, considerable attention has been directed toward defining the optimal outcome with reference to the rehabilitation process along the restitution–substitution continuum (36,37,187). Recently, a very reasonable argument has been put forward to the research community that to achieve restoration of upper extremity function in poststroke survivors requires intense therapy early after injury, but not too early (37,267). However, an unresolved but important issue that may impact the interpretation of outcomes following neurorehabilitation and, by extension, reimbursement decisions, is the need for a valid and unified distinction between compensation and restoration. A distinction between the two should be predicated upon objective data.

Recently, a collaborative group developed a quantification schema called the kinematic impairment measure (KIM).

KIM is a compellation of 43 kinematic measurements acquired simultaneously during reaching movements performed in the context of an adaptive mixed reality system for stroke survivors (268,269). KIM values are compiled for each variable and averaged across all of them to create a composite KIM score. The scoring system is based upon a binary where a "0" is an average value (and its variability) extracted from age-matched able-bodied participants and a "1" is the maximal deviation beyond the normal variance as measured from a patient with stroke. In this way, at least three objectives are achieved: (a) quantifying quality of movement; (b) assigning a specific metric that can serve as a model to distinguish compensatory/substitution from restorative behaviors; and (c) informing a clinician about which kinematic dimensions of movement need to be emphasized in the rehabilitation process, information specification that might not ordinarily be achieved through casual observation. This scheme, therefore, would define restoration as any value among the multiple kinematic measurements that falls within the variance derived from each kinematic measurement and compensation as any that does not. Hence, the collective components of the movement are reduced to a series of independent kinematic measurements, some of which may fall within the restorative range and some of which may not. Ultimately, the argument could be made that for a given functional task (e.g., goal-directed reaching movements), the average KIM score would be indicative of a compensatory behavior containing subcomponents that have both compensatory and restorative features. This KIM quantification scheme has shown promise as part of a mixed reality interactive neurorehabilitation system (270,271).

Attention and Motor Skill Learning

Finally, the area of *attention and motor skill learning* is an important one for motor retraining (272). There is considerable evidence that a simple manipulation of attentional focus can benefit motor learning (273–276). Instructional manipulations that focus attention on external cues are more effective for motor learning than those that direct attention on internal cues (i.e., the moving limb or pressure under the feet). Fasoli and colleagues tested this simple concept in an experiment dealing with functional reach actions in persons with and without cerebrovascular accident (277). One group was instructed to focus on the to-be-grasped object, and the other was instructed to focus on their arm movements. The results showed that both nondisabled and disabled groups performed the tasks more effectively (e.g., more effective movement kinematics) if given external rather than internal focus instructions. This finding suggests that participants with stroke and controls preplanned these functional actions to a greater extent and used more automatic control processes when they focused externally. The importance of this work for task-oriented training in rehabilitation is tremendous. It suggests that the nature of the instructions about attentional focus can impact the effectiveness of the training program and could be as important as the specific training paradigm for determining the most effective dose of training. For example, a task-oriented training program administered using instructions for an external focus of attention would be expected to achieve a clinically meaningful outcome with greater efficiency (e.g., shorter time, smaller dose) than one using instructions for an internal focus of attention. This area is clearly important for future developments and in conjunction with determining the pharmacokinetics of task-oriented training.

CONCLUSION

We find ourselves in a particularly exciting time for neurorehabilitation, repair, and recovery, with significant advances both in the basic and clinical sciences. In this chapter, we merely scratch the surface of the most relevant foundations including opportunities and limitations of the dominant approach to motor restoration, a task-oriented or task-specific approach. Contrary to current medical reimbursement models that support early acute and subacute stages of rehabilitation, substantial evidence supports the effectiveness of task-oriented training in the postsubacute and chronic stages of recovery. More work is needed to determine the best predictors of recovery and the nature of that recovery (restitution vs. substitution) so that therapies can be personalized for optimal recovery. Further, more work is needed in the area of clinical translation of task-oriented approaches across different care settings to maximize outreach and dissemination.

We are encouraged by how much is known, and at the same time, how little is known, for example, about the "pharmacokinetics" of training and how that training can be personalized to the individual's characteristics including social, cognitive, and neural factors. Building a strong theoretical foundation will be important for future advances in this exciting field of neurorehabilitation. We hope this updated chapter provides a beginning and impetus for these future advances in rehabilitation science.

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21

Neuromuscular Electrical Stimulation for Motor Restoration in Hemiplegia

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This chapter provides a comprehensive review of upper- and lower-limb clinical applications of neuromuscular electrical stimulation (NMES) specifically for the hemiparetic stroke survivor. NMES is the application of a low-level electrical current for the purpose of eliciting a contraction of muscle fibers that have been paralyzed secondary to an upper motor neuron injury such as stroke. NMES is applied in hemiplegia as either a therapy or an assistive device. In therapeutic applications, a regimen of NMES may produce a lasting effect that reduces motor impairment level and/or improves functional performance. A therapeutic effect is both measurable and sustained after the NMES device is turned off. An example of a therapeutic effect of NMES in hemiparesis is motor relearning, which is defined as "the recovery of previously learned motor skills that have been lost following localized damage to the central nervous system" (1). Another therapeutic application of NMES, the management of poststroke shoulder pain, is addressed in Chapter 30 ("Musculoskeletal Complications After Stroke"). Applications in which NMES is used as an assistive device to perform an upper- or lower-limb task are called functional electrical stimulation (FES) applications (2). Specific movement tasks may include grasping an object or stepping over an obstacle. An FES device is called a *neuroprosthesis*, and the measurable improvement in functional performance that occurs when the neuroprosthesis is being used is called the *neuroprosthetic effect*. In clinical practice, a neuroprosthesis may produce a neuroprosthetic effect, a therapeutic effect, or both.

This chapter is organized to first provide an overview of the basic neurophysiologic principles that underlie all NMES applications. These include principles of electrical activation of muscle, modulation of muscle contraction, and safe delivery of electrical current. Second, we describe basic NMES system components, which include the electrodes, neurostimulator, and controller. Third, we present an overview of therapeutic applications of NMES, limited to upper- and lower-limb poststroke motor relearning. Fourth, clinical poststroke neuroprosthetic applications for upper-limb activities of daily living (ADLs) and lower-limb mobility are reviewed. Lastly, we present a critical review of the stroke NMES literature and our perspective on promising research initiatives for future clinical NMES systems.

NEUROPHYSIOLOGY OF NMES

Principles of Electrical Activation of Muscle

When applied to a healthy, intact nerve, an electrical current can cause the initiation and propagation of action potentials (AP) within motor neurons that ultimately result in the contraction of muscle fibers. An NMES system uses a pair of electrodes to deliver an electrical current and create a localized electric field that depolarizes the axonal membranes of the motor neurons in closest proximity to the electrodes. If the magnitude of the depolarization reaches a critical threshold for any given neuron, an influx of extracellular sodium ions into the intracellular space is triggered, and an AP is generated (3). The AP propagates the length of the axon to the axonal terminal and, in the case of a motor neuron, triggers the release of neurotransmitter from synaptic vesicles into the neuromuscular junction that results in muscle fiber contraction. The so-called "all or none" phenomenon of an AP that is produced by natural physiologic means is identical to an NMES-initiated AP.

The stimulus threshold necessary to generate an AP in neural tissue is much lower than the threshold for activating muscle fibers directly (3). Therefore, what is often termed "muscle stimulation" is in reality the activation of motor neurons that innervate target muscles. That is why denervated or partially denervated muscles do not respond well to NMES and why stroke survivors who have a concomitant peripheral nerve injury, severe peripheral motor neuropathy, disease of the neuromuscular junction, and/or a congenital or acquired myopathy, may not be good candidates for NMES. The most common targets for NMES are peripheral nerves and motor points of the target muscles. Nerves and motor points closest to the stimulating electrodes are more likely to be activated than those farther away because the transmembrane potentials generated by the electrical current are greatest in the axons closest to the stimulus source. Therefore,

selectivity of stimulation is increased, and less current is required by placing the electrodes in closest proximity to the target neural tissue.

Under normal physiologic mechanisms, as more muscle force is needed, neurons with smaller diameter axons are recruited prior to neurons with larger diameter axons. With NMES, however, larger diameter axons are recruited preferentially before small diameter axons because large diameter axons have lower stimulus thresholds. This phenomenon is referred to as "reverse recruitment order." Nerve fiber recruitment order is important clinically because of the relationship between nerve fiber recruitment and activation of motor units. A *motor unit* is defined as a single neuronal cell body located in the anterior horn of the spinal cord, its motor axon, and all of the muscle fibers innervated by that axon. All muscle fibers of a single motor unit are of the same type (Type I or Type II muscle fibers), and all associated muscle fibers contract when a motor unit is activated. Larger diameter axons innervate Type II muscle fibers and are associated with larger motor units, whereas smaller diameter axons innervate Type I muscle fibers and are associated with smaller motor units. Thus, clinical NMES systems preferentially activate large diameter motor neurons that innervate larger motor units comprised primarily of Type II muscle fibers.

In most clinical NMES applications, the primary recruitment of Type I muscle fibers (physiologic recruitment order) would be preferable to the recruitment of Type II muscle fibers ("reverse recruitment" order) because of the physiologic characteristics that differentiate the two fiber types. Skeletal muscle contains "fast" and "slow" muscle fibers that are distinguished on the basis of their contraction kinetics. Slow-twitch, oxidative Type I muscle fibers generate lower forces, but are fatigue resistant, whereas fast-twitch glycolytic Type II muscle fibers generate higher forces but fatigue more rapidly (4). The primary activation of muscle fibers that are fatigue resistant is highly desirable, particularly in neuroprosthetic (FES) applications where functional movement tasks require sustained, repetitive muscle contraction. Recent research has explored the viability of selectively activating smaller diameter fibers by reshaping the extracellular voltage profile along the nerve, effectively reversing the recruitment order elicited by NMES (5,6), although these methods remain experimental and are not available for clinical use.

Unfortunately, disuse muscle atrophy, which is a common sequela of an upper motor neuron injury, is characterized by the conversion of fatigue-resistant Type I muscle fibers to fast-fatiguing Type II muscle fibers (7). Chronic NMES applied at stimulus frequencies of 10 to 12 Hz has been demonstrated to effectively reverse this natural conversion of muscle fibers and convert fast-fatiguing fibers to fatigue-resistant fibers to some degree (8). The ability of NMES to "reverse" Type I to Type II fiber conversion is proposed to be related to NMES-induced changes in the motor neuron firing patterns that control expression of specific contractile proteins and metabolic enzymes in muscle fibers (9). Because of muscle fiber conversion, many clinical NMES applications include a conditioning component that is intended to both increase and optimize the functioning of fatigue-resistant muscle fibers.

Modulation of Muscle Contraction

In NMES, electrical current usually is delivered as a train of pulses. The strength of a NMES-elicited muscle contraction may be modulated by varying three stimulus parameters of the applied electrical current: the stimulus pulse frequency, pulse amplitude, and pulse duration. A minimum stimulus pulse frequency (i.e., fusion frequency) is necessary to produce a "fused" muscle contraction and not simply a series of individual muscle "twitches." In general, a higher pulse frequency produces a stronger muscle contraction; however, the clinical trade-off of a higher pulse frequency is more rapid fatigue of the muscle fibers. The optimal pulse frequency for a muscle contraction is thus the minimum pulse frequency that generates a fused muscle response without discomfort given the muscle fiber type, degree of muscle conditioning, and electrode type used to deliver the stimulation (surface or implanted). The pulse frequency is determined experimentally for any given application. The strength of a muscle contraction also may be modulated by changing the magnitude of the electric charge per pulse by adjusting either the stimulus pulse amplitude or the pulse duration (10). A greater electric charge creates a larger electrical field that allows activation of more neurons, including those at a greater distance from the electrode, and thus activation of a greater total number of motor units. In most NMES applications, the stimulus pulse frequency is kept constant. Either the stimulus pulse amplitude is kept constant and the pulse duration is manipulated to optimize the strength of the muscle contraction, or the pulse duration is kept constant and pulse amplitude modulates contraction strength.

Muscle fatigue is defined as a decrease in the force-generating ability of a muscle that results from recent muscle activation (11). Muscle fatigue may limit the ability of a stroke survivor to use a neuroprosthesis with consistent performance for an extended period of time. As a result, research has focused on the variable relationship between stimulus pulse frequency patterns and muscle force generation as one way to mitigate muscle fatigue. Usually, NMES applications stimulate skeletal muscle using a constant pulse frequency. Binder-Macleod et al. (12) experimented with specific stimulus waveforms characterized by doublets, pulses separated by short interpulse intervals (5 ms). In a study of repetitive isometric activation of the quadriceps muscles of subjects with paralysis, Scott et al. (13) found that a variable stimulus pattern that combined constant-frequency pulses and doublets resulted in achieving a targeted isometric force 14% more frequently than the constant-frequency pulses alone and 18% more frequently than the doublets alone. In fatigued muscle, multiple studies have demonstrated that isometric (12,14) and nonisometric (15) muscle force generation is optimized when stimulus waveforms are characterized by doublets combined with constant-frequency pulses. These studies and others

(14,16–21) suggest that manipulating stimulus waveform characteristics may be a method to minimize skeletal muscle fatigue while optimizing performance in FES applications.

Safe Delivery of Electrical Current

Clinical NMES stimulators may be either current-regulated or voltage-regulated. *Current*, which is defined as the charge delivered per unit of time, is directly controlled using a current-regulated stimulator. Thus, the quantity of charge per stimulus pulse is chosen and can be maintained within safe limits given the material composition of the electrode. Current density (charge per unit area) thresholds determine if electrode corrosion or tissue damage occurs. In general, current-regulated stimulators must be used with implanted NMES electrode applications and current- or voltage-regulated stimulators can be used with surface NMES electrode applications. With a voltage-regulated stimulator, the magnitude of the current (and therefore, charge density) delivered to the tissue may be variable because it is dependent on the impedance (resistance) at the electrode–tissue interface, which can change over time. Per Ohm's Law, as resistance (impedance) increases, current decreases for a fixed voltage [I (current) = V (voltage)/R (resistance)]. The impedance at a surface electrode–tissue interface is much greater and more variable than impedance at an implanted electrode–tissue interface. Because the risk of tissue injury in any given patient is directly related to the magnitude of the charge density, one advantage of voltage-regulated stimulation is the decreased likelihood for tissue injury. If a surface electrode pulls away from the skin, the current delivered by the electrode will decrease because impedance has increased. However, the disadvantage of voltage-regulated stimulation is that it can result in inconsistent muscle contractions. A current-regulated stimulator can be used to provide more consistent muscle contractions as long as the electrodes are charged frequently to keep the electrode–skin impedance consistent.

SYSTEM COMPONENTS

Electrodes, Neurostimulator, and Controller

NMES systems generally consist of at least three components: electrodes, a neurostimulator, and a controller. Surface, percutaneous, or implanted electrodes deliver electrical current pulses to the neural tissue. The neurostimulator generates the current waveforms from a power supply. The controller regulates the stimulation in response to an input signal, switch, or preset program. With surface NMES systems, the electrodes, neurostimulator, and controller all are external to the body. With percutaneous NMES systems, an electrode is implanted into the muscle or near a nerve and a lead attached to the electrode exits the skin and connects to the neurostimulator and controller, both of which are external. With implanted NMES systems, the electrode, connecting lead wire, and neurostimulator all are fully implanted. An implanted neurostimulator generally receives both power and command instructions through a radio-frequency telemetry link to an external control unit.

Each NMES system, classified by electrode type, has specific features that should be considered when used for clinical or research purposes. A surface-electrode NMES system, although generally well tolerated in most patients, may pose a risk of tissue injury in patients with concomitant sensory and/or cognitive deficits. Thus, careful patient selection is required. Activation of cutaneous pain receptors, electrode positioning, limited selectivity of nerve and/or muscle fibers, insecure fixation on moving limbs, skin irritation, and undesirable cosmesis are common limitations of surface electrodes. The advantages of using surface electrodes to deliver NMES include easy application in clinical settings, low cost, noninvasiveness, and the commercial availability of surface neurostimulator units for home use. Percutaneous NMES systems are particularly useful in activating small, deep muscles such as the intrinsic muscles of the hand. Percutaneous electrodes are inserted through the skin into the target muscle and thus carry the risks of displacement or breakage, infection, and granuloma formation secondary to retained electrode fragments when the electrode is removed (22). The advantages of a percutaneous electrode include elimination of skin resistance, bypassing of cutaneous pain receptors, and greater muscle selectivity. Lastly, implanted electrodes are designed for longer-term use and are attached directly to muscle or nerve tissue via a surgical procedure. Epimysial electrodes are sutured directly to the epimysium or fascia of the target muscle (23). Epineural electrodes are sutured to connective tissue directly surrounding the nerve (24). Intramuscular electrodes are inserted at the motor points of the target muscles. Direct nerve stimulation is most commonly achieved via a nerve cuff electrode that encompasses the nerve trunk and requires approximately one-tenth of the current necessary for intramuscular stimulation (25).

For any NMES system to be used as a neuroprosthesis, there is the additional requirement of volitional control to carry out a specific functional task. A key component to the design of FES control systems, thus, is the correlation of user intent or the movement task desired to actual functional performance. Many clinical FES systems utilize an open loop control system in which the user regulates the stimulation based on feedback for necessary system modifications; this is limited to visual and/or proprioceptive input. Though closed loop control systems are not clinically available, such a system would allow continuous automatic real-time modification of the stimulation via feedback input. The optimal clinical FES system, given the nonlinearity and temporal variability of contractile muscle forces, would be a closed loop system modulated by sensor-derived feedback signals (26,27). An ideal FES control system would yield consistent and predictable response to internal time variations (e.g., fatigue, effort) as well as external perturbations to the system (e.g., changing muscle loads, resistance).

MOTOR RELEARNING

Basic Science and Theoretical Considerations

Goal-oriented active repetitive movement training of the paretic limb following injury to the brain has been demonstrated to enhance motor relearning in both research and clinical applications. Researchers have explored possible mechanisms for movement-associated motor relearning based on the known plasticity of the central nervous system. In an animal model, Asanuma and Keller showed that electrical stimulation of the somatosensory cortex alone or in conjunction with thalamic stimulation induced long-term potentiation (LTP) in the motor cortex (28). They hypothesized that proprioceptive and cutaneous afferent impulses associated with repetitive movement modify the excitability of specific motor neurons to facilitate motor relearning (29). Ke et al. (30) showed an association between exercise-induced upregulation of hippocampal brain neurotrophic factor (BDNF) and motor recovery following brain ischemia. Nonhuman primate research has demonstrated that after local damage to the motor cortex, goal-oriented, active repetitive movement training of the paretic limb shaped subsequent functional reorganization in the adjacent intact cortex, and the undamaged motor cortex played an important role in motor relearning. Specific types of behavioral experiences that induce long-term plasticity in motor maps were repetitive movements that entail the development of motor skills (31). That is, the motor tasks were new and therefore, "required" significant cognitive effort to learn and complete. Training to acquire new skills such as retrieving food pellets from a small well or a rotating well were associated with task-specific cortical reorganization. However, this was not the case with repetitive movement tasks that did not require new skill acquisition (i.e., motor tasks are already mastered and, therefore, are easy to carry out and require minimal to no cognitive effort) (32).

Because goal-oriented repetitive movement therapy facilitates motor relearning, electrical stimulation-mediated goal-oriented repetitive movement therapy also may facilitate motor relearning. There is evidence that electrical stimulation of the peripheral nerve is associated with concomitant physiologic changes in the brain. Electrical stimulation to a peripheral nerve has been associated with activation of both sensory and motor structures in the brain (33) and reduction of intracortical inhibition (34). Han et al. (35) demonstrated that NMES-mediated wrist extension elicited activation of the contralateral somatosensory cortex and bilateral supplementary motor areas using functional magnetic resonance imaging (fMRI). Smith et al. (36) used fMRI to demonstrate a dose–response relationship between selected NMES stimulation parameters and the hemodynamic responses in sensorimotor regions. Research supports that repetitive movement therapy mediated by NMES has the potential to facilitate motor relearning via cortical mechanisms (37). NMES can be used by stroke survivors with hemiparesis who do not have sufficient residual movement to take part in volitional, active repetitive movement therapy. Regardless of mechanism, the experimental and theoretical considerations suggest that the necessary prerequisites for NMES mediated motor relearning include repetition, novelty of activity, concurrent volitional effort, and high functional content.

Several forms of NMES systems are available clinically for poststroke motor relearning applications: cyclic NMES, electromyography (EMG)-triggered NMES, and neuroprostheses. Cyclic NMES systems contract paretic muscles at a set duty cycle for a preset time period without any input from the patient beyond turning the device on and off. The patient is a passive participant and is not required to invest cognitive effort in the form of either initiation of muscle contraction, interpretation of afferent signals, or functionality of motor task. EMG-triggered stimulation requires that the subject generate a detectable EMG signal by attempting volitional muscle contraction. The EMG signal is recorded by a surface electrode and that signal is used to turn on NMES for a preset duration. Thus, EMG-triggered NMES systems have the ability to couple motor intent to motor response. This technique may be applied to patients who can partially activate a paretic muscle but are unable to generate sufficient muscle contraction for adequate exercise or functional purposes. Alternative patient-initiated volitional triggers are being evaluated for clinical use. Mann et al. recently described an accelerometer-triggered NMES system, which also requires volitional muscle contraction but triggers in response to change in joint position (38). Whereas the patients who use cyclic NMES are passive participants, EMG-triggered NMES requires greater cognitive investment, which may theoretically result in greater therapeutic benefit (39). The third type of NMES system is a neuroprosthetic application that provides FES for completion of ADL and mobility tasks. Because repetitive movement training is performed in the context of meaningful, functional behavioral tasks, neuroprostheses have a theoretical advantage over both cyclic and EMG-triggered NMES systems for motor relearning. Neuroprosthetic applications are discussed in greater detail in a later section.

Contralaterally controlled functional electrical stimulation (CCFES) is an innovative research application of NMES (40,41). Upper-limb CCFES uses surface NMES to open the paretic hand in direct proportion to the degree of volitional movement of the unimpaired contralateral hand, which wears an instrumented glove (Figure 21.1). The rationale for using CCFES for poststroke motor relearning is that, as compared to cyclic NMES or EMG-triggered NMES, CCFES maximizes the degree of coupling between motor intention (central or presynaptic activity) and stimulated motor response (peripheral, or postsynaptic activity). The subject not only controls the onset and duration of the stimulation but also controls the intensity of stimulation and resultant degree of hand opening, potentially creating a stronger perception of restored motor control. In addition to enabling active repetitive goal-oriented movement and coupling motor intention to motor output and afferent feedback, the CCFES paradigm incorporates both bilateral symmetric

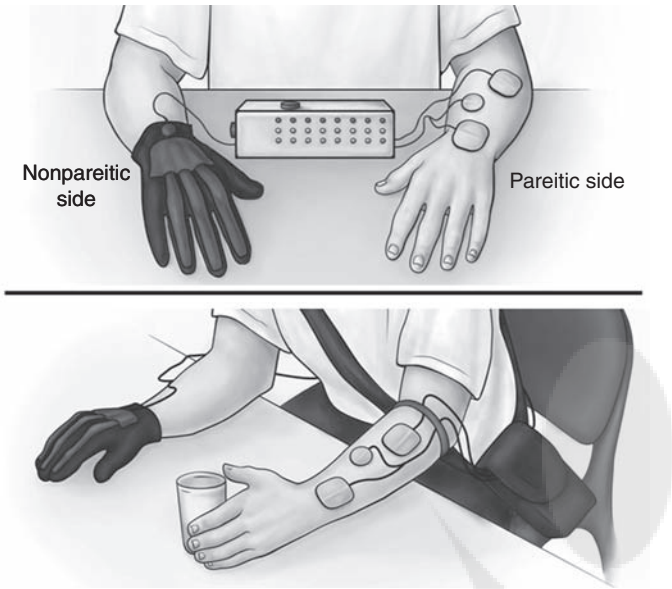

FIGURE 21.1 Contralaterally controlled FES system for repetitive intention-driven hand opening exercise and functional task-practice therapy after stroke.

Used with permission, Cleveland Functional Electrical Stimulation Center, Cleveland, Ohio.

movement and motor imagery, rehabilitation techniques that have been associated with improved motor recovery. CCFES also enables stroke survivors to practice functional tasks, similar to a neuroprosthesis.

Upper-Limb Applications

Multiple randomized clinical trials have evaluated the efficacy of cyclic NMES in enhancing upper-limb motor relearning (42–50) and demonstrated improvement in motor impairment. Rosewilliam et al. (47), recently found that acute stroke survivors (<6 weeks after stroke) with severe upper-extremity disability who received 6 weeks of surface NMES demonstrated significant improvement in wrist extensor and grip strength at end of treatment as compared to a control group, though arm function as measured by the action research arm test (ARAT) scores did not differ between groups. In a study by Lin et al. (48), stroke survivors who received 3 weeks of NMES and a control group both demonstrated gains in Fugl-Meyer (FMA) and Modified Ashworth scores (but not modified Barthel index) at end of treatment, though the gains in the NMES group were significantly better than the control group at 3 and 6 months after treatment. Improvement in activity limitations has been demonstrated as a secondary outcome in a subset of those studies that demonstrated an improvement in motor impairment (45,46,49,50). In various studies, NMES treatment groups have demonstrated significantly greater functional performance, as compared to a control group, on end-of-treatment ARAT score (45,50), object manipulation (49), Barthel index (49), and the functional independence measure (FIM) (37).

Several clinical trials have evaluated EMG-triggered NMES for upper-limb motor relearning (51–56). In general, these studies demonstrated improvement in motor impairment at end of treatment. In the few studies that evaluated activity limitations, improved outcomes were also noted (52,55,56). Kimberley et al. compared 3 weeks of EMG-triggered NMES to the extensor muscles of the forearm to sham NMES treatment in chronic stroke survivors (55). The EMG-triggered NMES group demonstrated significant improvements in measures of isometric finger extension strength, grasp, and release of objects (Box and Block Test and Jebsen Taylor Hand Function), and self-rated activity limitation (motor activity log). In addition, fMRI and a finger-tracking task demonstrated significantly increased cortical intensity in the contralesional somatosensory cortex from pretest to posttest following treatment. The participants receiving sham treatments failed to improve on any of the outcome measures except isometric finger extension strength. EMG-triggered NMES research also suggests that central mechanisms, evidenced by changes in assays such as reaction time (54), fMRI cortical activation patterns (55–57), and positron emission tomography (PET) scanning (58), may be associated with improved outcomes.

These studies suggest that EMG-triggered NMES reduces upper-limb motor impairment, possibly through central mechanisms, and that these changes may translate into improvements in activity limitations. However, a paradigm shift in the clinical application of NMES in stroke would require that one application (in this case, EMG-triggered) be clearly superior to standard of care treatment (cyclic and/or sensory stimulation). Two recent randomized controlled trials suggest that EMG-triggered NMES does not have a greater therapeutic effect on motor recovery than either cyclic NMES and/or sensory stimulation. DeKroon et al. (59) compared the efficacy of a six-week trial of upper-extremity surface EMG-triggered NMES versus cyclic NMES in chronic stroke and did not detect a significant difference with respect to improvement in motor function at end of treatment. Similarly, Chae et al. (60) compared the effect of surface EMG-triggered, cyclic NMES and sensory stimulation (placebo) on motor recovery in a randomized clinical trial (RCT) that enrolled 122 subacute stroke survivors. Although all three groups experienced significant improvements in FMA and arm motor ability test (AMAT) scores following eight weeks of treatment, EMG-triggered NMES and cyclic NMES were no more effective than sensory stimulation.

The therapeutic efficacy for NMES delivered via percutaneous electrodes has been evaluated specifically because pain tolerance and muscle specificity are limiting factors in some applications with surface electrodes (61). Chae et al. (62) randomized 26 chronic stroke survivors to either percutaneous NMES for hand opening or percutaneous sensory stimulation only. The percutaneous NMES group received six weeks of cyclic, EMG-triggered, or EMG-controlled

NMES depending on baseline motor status. There was no significant treatment or time × treatment effects for any of the outcomes (FMA, AMAT, delay, and termination of EMG activity) at end of treatment or at 1, 3, or 6 months follow-up. The authors concluded that percutaneous NMES (delivered as cyclic, EMG-triggered, or EMG-controlled) was no more effective than percutaneous sensory stimulation for the recovery of the hemiparetic upper limb among chronic stroke survivors.

Studies of the neuroprosthetic effect of a hand neuroprostheses for hemiplegic stroke survivors are reviewed later in this chapter. However, a motor relearning effect associated with the use of the upper-extremity neuroprosthesis, which is sustained and measurable after removal of the neuroprosthesis, has been evaluated (63–70). Two studies (63,64) parenthetically reported evidence of improved motor ability when the upper-extremity neuroprosthesis was turned off after a period of use. Alon et al. (65) evaluated the therapeutic effect of five weeks' use of a hybrid brace-NMES device that incorporated surface electrodes into a brace for hand grasp and release (Bioness H200) and found significant improvement in motor impairment and activity limitation. More recently, Page et al. (68) compared the effect of 30, 60, and 120 minutes of repetitive task-specific practice incorporating an upper-extremity neuroprosthesis in chronic stroke survivors over an 8-week treatment period and found significant increases in FMA, AMAT, and ARAT performance limited only to the 120-minute intervention group. A subsequent study (69) evaluated the retention of the upper-extremity gains in the treatment group and found no significant change in scores from end of treatment to 3 months after treatment. Improvement in motor impairment in eight chronic stroke survivors following eight weeks of upper-extremity neuroprosthesis use also was associated with an increase in cortical activation on fMRI (71). Lastly, the neuroprosthetic effect of an FES grasp-assist glove for use with task-oriented robotic stroke therapy for hand opening (72), a hybrid wrist splint with volitional electrical stimulation (73), and a fully implantable upper-extremity neuroprosthesis (74) have been described, though none has been studied in a controlled trial nor evaluated for a motor relearning effect.

Finally, a recent RCT (40) of subacute stroke survivors demonstrated that six weeks of CCFES produced greater improvement in voluntary finger extension angle, finger movement tracking error, FMA score, Box and Blocks test, and AMAT scores as compared to cyclic NMES. Maximum voluntary finger extension showed the largest treatment effect, with a mean group difference across the posttreatment time points of 28 degrees more finger extension for CCFES. Additional studies are planned to further evaluate the therapeutic effect of CCFES as a poststroke rehabilitation intervention.

In summary, although the strength of many of these NMES studies rests on a randomized study design, methodological limitations render results difficult to interpret, including inadequate blinding, unequal treatment intensity, inconsistent follow-up beyond end of treatment, inadequate accounting of dropouts, and failure to use intent-to-treat analysis. Nevertheless, the literature suggests that upper-extremity NMES is effective in enhancing poststroke motor impairment, although interval after stroke (44,45,49), baseline level of motor impairment, and NMES dose (50) may affect the potential for motor relearning. The effect of upper-extremity NMES on activity limitations is suggested by many studies, though not conclusive. In terms of motor relearning theory, EMG-triggered NMES would be expected to have a greater therapeutic effect than either cyclic or sensory stimulation. However, recent RCTs (59,60) did not demonstrate superiority of upper-extremity EMG-triggered NMES. Whereas sensory stimulation, cyclic NMES, and EMG-triggered NMES using surface electrodes remain therapeutic tools in the armamentarium of rehabilitation clinicians, these RCTs strongly challenge a prevailing clinical belief that EMG-triggered NMES provides greater therapeutic benefit in the stroke patient population. Clinical prescription of NMES for the upper extremity thus should be primarily driven by clinical considerations including residual motor function, ease of application and compliance, and patient preference without expectation that a specific mode of delivery will have greater benefit. Future NMES research for upper-extremity motor relearning should expand on exploratory studies that have combined various upper-extremity NMES therapies with other motor relearning strategies to enhance efficacy, including mental imagery (58), mirror therapy (75), robotics (76–78), botulinum toxin plus task practice (79), various forms of bilateral upper-extremity therapies (80,81), and noninvasive brain computer interfaces (82).

Lower-Limb Applications

Surface NMES lower-extremity applications have been shown to improve motor recovery in controlled clinical stroke trials. Surface NMES has been demonstrated to improve strength of paretic ankle dorsiflexors (83,84), ankle dorsiflexion moment (85,86), and EMG agonist activity (86) and decrease plantar flexion spasticity (83,84,87) and antagonist co-contraction (83,86). In a recent randomized trial, Sabut et al. (88) found that a hemiparetic treatment group that received 12 weeks of NMES to the dorsiflexors applied during a daily therapy session demonstrated greater improvements in plantar flexor spasticity, dorsiflexion strength, active and passive ankle range of motion, and lower-extremity FMA motor impairment score as compared to a control group. EMG-triggered NMES to enhance ankle strength, range of motion, and balance has been evaluated for stroke survivors with residual dorsiflexion movement (89–91).

In a case series, Knutson et al. (92) recently evaluated the application of CCFES to the lower extremity as a therapy intended to improve poststroke motor recovery. CCNMES dorsiflexes the paretic ankle by stimulating the peroneal nerve in direct proportion to the degree of voluntary dorsiflexion of the (nonparetic) contralateral ankle. In two of the three subjects evaluated, improvements were noted in maximum voluntary ankle dorsiflexion, ankle tracking error,

and lower-limb FMA score at end of treatment and were sustained at three months posttreatment.

Lieberson et al. (93) described the first single-channel surface peroneal nerve stimulator (PNS) to provide ankle dorsiflexion during the swing phase of gait for stroke survivors. He commented, "On several occasions we observed, after training with the electrophysiologic brace [PNS] . . . patients acquire the ability of dorsiflexing the foot by themselves." A PNS device stimulates the common peroneal nerve near the head of the femur to activate both the tibialis anterior and the peroneus longus and brevis muscles. Multiple subsequent case series evaluating PNS neuroprosthetic systems described similar observations of improved ambulation function, more normal EMG muscle activation patterns, emergence of EMG signals in previously silent muscles, increased strength of EMG activity, and/or decreased co-contraction of antagonist muscles (94–103). Studies that have demonstrated a therapeutic effect of PNS have hypothesized that central mechanisms may be responsible (104–106). Everaert et al. (105) studied the effect of long-term use of a PNS device on residual corticospinal connections in people with central nervous system disorders. Following 3 to 12 months of use of the PNS device, both motor-evoked potentials (MEP) elicited by transcranial magnetic stimulation applied over the motor cortex and maximum voluntary contraction (MVC) of the anterior tibialis muscle were significantly improved in the subgroup of their subjects with stroke. The authors hypothesized that the increases in MEP and MVC were evidence that regular use of a PNS device strengthened activation of motor cortical areas and their residual descending connections, which may explain any therapeutic effect.

Presently, the standard of care intervention for moderate to severe poststroke dorsiflexion weakness associated with gait dysfunction is an ankle–foot orthosis (AFO). To challenge standard of care practice, definitive evidence would be necessary to show that an alternative intervention (PNS device) provided either an equivalent orthotic (neuroprosthetic) effect on walking or a superior effect on motor relearning in stroke. Importantly, two recent RCTs (107,108) did not demonstrate a motor relearning (therapeutic) effect associated with the use of a lower-extremity PNS device in chronic stroke survivors. In a single-blinded RCT, Sheffler et al. (107) compared the effect of 12 weeks of ambulation training with a surface PNS device to ambulation training with usual care treatment (*ankle–foot orthosis* or no device). One hundred and five stroke participants were evaluated at baseline, end of treatment, and 3 months and 6 months posttreatment. Primary outcome measures were the lower-extremity FMA (motor impairment), modified Emory Functional Ambulation Profile (activity limitation), and the Stroke Specific Quality of Life score (quality of life). At end of treatment, there was no evidence of a motor relearning effect on motor impairment (FMA score) in either group. However, both the PNS and usual care groups demonstrated improvements in functional ambulation and quality of life outcome measures that were sustained at 6 months after treatment. Similarly, a randomized trial by Kottink et al. (108) found no therapeutic effect of an implantable two-channel PNS system on walking speed in chronic stroke participants followed over a 26-week period of intervention. However, the authors did note a significant increase in voluntary muscle output of the tibialis anterior and gastrocsoleus muscles after the use of FES, which they hypothesized was indicative of some degree of neuroplasticity in the study participants. The implantable PNS device has not yet received FDA approval for clinical use in the United States, although the device is available for clinical use in Europe. The neuroprosthetic efficacy of both a surface and implantable PNS device is described later in this chapter.

Multichannel surface stimulation systems have been evaluated as neuroprostheses for stroke survivors with functionally significant proximal as well as distal lower-extremity weakness. Two case series demonstrated improvements in qualitative and quantitative measures of gait after training with a six-channel surface neuroprosthesis system (109,110) that provided ankle dorsiflexion, knee flexion and extension, and hip extension. A follow-up controlled trial demonstrated significantly greater improvement in gait performance and motor function in the treatment group (111). In general, as the number of electrodes increases, surface systems become increasingly difficult to implement and maintain clinically. The practicality of multichannel surface lower-limb systems is limited further by reduced muscle selectivity, poor reliability of stimulation, and pain of sensory stimulation. Accordingly, Daly et al. developed a multichannel percutaneous system to facilitate lower-limb motor relearning and mobility (112). A single-blinded randomized clinical trial demonstrated that percutaneous NMES-mediated ambulation training improved gait components and knee flexion coordination relative to controls (113).

As with upper-limb applications, many of the controlled studies of NMES for lower-limb motor relearning exhibit methodological limitations, including inadequate blinding, small sample sizes, limited follow-up data, and outcomes limited only to motor impairment measures. Evidence suggests that NMES in the form of cyclic stimulation or in combination with biofeedback may be effective in facilitating lower-limb motor relearning. Studies with multichannel lower-extremity surface and percutaneous systems suggest therapeutic benefit. However, these devices have not translated into clinical practice. Two recent controlled clinical trials of surface (107) and implanted (108) PNS systems did not demonstrate a therapeutic motor relearning effect of a PNS neuroprosthesis using standard clinical outcome measures. The use of a surface PNS device as an alternative to an AFO in select stroke survivors is a reasonable clinical decision. However, clinical decision making for use of a surface PNS device should be based on neuroprosthetic efficacy, as clinically relevant therapeutic effect has not been established at this time. Future research should focus on NMES delivery systems, including lower-extremity CCFES applications, NMES dosage, and lower-extremity FES paradigms.

Summary, Clinical Considerations, and Future Directions

Despite the methodological limitations of some controlled trials to date, there is evidence to suggest that NMES-mediated repetitive movement therapy reduces motor impairment in upper- and lower-limb hemiparesis. However, it remains uncertain whether any measured effect can translate into clinically relevant improvement in ADLs and mobility. A number of surface NMES devices are presently commercially available for clinical implementation for upper- and lower-limb paralysis. Because risks associated with NMES are low, a select group of stroke survivors should be considered for and may benefit from NMES therapy.

In the upper extremity, sensory, cyclic, or EMG-triggered NMES systems may reasonably be offered, and mode of delivery should be primarily a clinical decision based on residual motor function, ease of application and patient compliance, and clinician preference. For the paretic lower extremity, stroke survivors may benefit from cyclic peroneal nerve stimulation (85,114) and EMG-triggered NMES may be applied to those with evidence of volitional activation (90). Despite the high functional content and active, repetitive nature of ambulation, a surface PNS device was not shown to facilitate motor relearning in the largest controlled trial of chronic stroke survivors to date (107). However, gait training with a neuroprosthesis may be considered as an alternative to usual care gait training (AFO or no device), as functional ambulation and quality of life improvements were equivalent at end of treatment. Presently, multichannel lower-limb surface systems remain under evaluation, and percutaneous upper- and lower-limb NMES systems remain limited to research applications and are not as clinically accessible. The CCFES system is limited presently to research applications, but may be commercially available as a therapeutic option for both the upper and lower extremity in the near future.

Optimal timing of NMES treatment has not been determined. Nevertheless, because therapeutic benefit may be related to acuity, onset of treatment in the acute rehabilitation service should be considered if possible. Patients and family may be trained by an experienced therapist, and treatment may be continued in the home environment following acute rehabilitation discharge. Optimal dosing and duration for most NMES applications have not been determined. However, the consensus of studies reporting positive results suggests that patients should be treated for at least one hour a day for a minimum of three weeks.

Care must be taken to implement NMES in the context of the stroke survivor's clinical status. Many stroke survivors have concomitant cardiac conditions, so monitoring of blood pressure, heart rate, and clinical signs of cardiac distress should be done during ambulation training with NMES. NMES should not be used with patients who have demand-type pacemakers. NMES should be used with caution in stroke survivors with poorly controlled seizures, though there is no definitive evidence that NMES causes seizures. In stroke survivors with sensory and/or cognitive impairments, vigilance should be used to protect from skin irritation associated with both the electrode and the electrical current. Limb edema is a general contraindication for NMES. Lastly, the application of NMES during pregnancy should be avoided, as the effects of NMES on fetal development and health are not well known.

Future investigations on NMES for motor relearning should address issues on two fronts. First, the effect of NMES on motor relearning and impact on clinical outcomes should be confirmed by addressing the methodological limitations of prior studies. Randomized clinical trials, which carefully define the subject populations, identify potential confounds, and evaluate long-term outcomes using valid and reliable measures of motor impairment, energy consumption, activity limitations, and quality of life, should be completed. These trials should compare the various types of NMES, stroke patient populations and intervals after stroke to identify the most effective paradigm and the subgroup of patients that most likely will benefit from each approach. Second, future investigations should refine the stimulation technique to maximize patient compliance and clinical outcomes, as well as determine optimal dose and prescriptive parameters. Systems that increase cognitive investment by requiring initiation, maintenance, and termination of NMES, should preferentially be considered. Future studies should also investigate more natural proxies such as cortical control for cognitive intent (115). Neuroprostheses, which provide clear functional benefit to a broad range of stroke survivors, should continue to be developed and refined to provide goal-oriented, repetitive movement therapy in the context of functional and meaningful tasks. Finally, basic studies should investigate mechanisms further to optimize the treatment paradigm.

NEUROPROSTHESES

Introduction

A neuroprosthesis utilizes NMES to contract specific muscles in a specific sequence to move the upper limb to perform ADL or the lower limb to carry out functional mobility tasks. The objective of a neuroprosthesis is the safe and efficient completion of functional tasks while using the device.

Upper-Limb Applications

Several studies have evaluated the upper-limb function of limited sample sizes of stroke survivors with and without a hand neuroprosthesis (63,64,116,117). In 1973, Rebersek et al. (64) published the first paper on the use of a hand neuroprosthesis in which surface NMES opened the hand, and closing was mediated by termination of the stimulation and the subject's own volitional ability. The intensity of stimulation was controlled proportionally with a position transducer mounted on the contralateral nonparalyzed shoulder. With training, subjects demonstrated progressive improvements in the number of hand positions they were able to maintain and the extent of hand opening using the device. A subset

of subjects demonstrated progressive improvements in their ability to use the device, although upper-extremity ADL performance was not assessed.

In 1975, Merletti et al. (63) evaluated a similar surface hand neuroprosthesis system. The device provided hand opening such that subjects were trained to pick up and move a small plastic basket or bottle from one defined area to another and back again using a shoulder-mounted position transducer controlled stimulation. All subjects were able to perform the tasks with triceps and hand stimulation, although with varying degrees of success. None of the subjects could perform the assigned tasks without stimulation or with hand stimulation only. The authors noted that the functional tasks required a considerable amount of mental concentration. In several cases, voluntary effort to control the paretic limb produced tremors, spasticity, and erratic shoulder movement that compromised functional performance.

Alon et al. (116) evaluated the previously described hybrid NMES-orthosis neuroprosthesis (Figure 21.2). The orthosis positions the wrist in a functional position and five surface electrodes built into the orthosis stimulate specific muscles to provide coordinated hand opening and closing. Twenty-nine chronic stroke survivors participated in a home-based, three-week case series. Three ADL tasks were evaluated with and without the neuroprosthesis at baseline and at three weeks: (a) lifting a two-handled pot, (b) holding a bag while standing with a cane, and (c) performing a subject-selected ADL task. The authors reported significant improvements in the percent of successful trials to complete the ADL tasks. Leeb et al. (118) recently described an adaptable passive hand orthosis that, when coupled with FES, is proposed to synchronize grasping movements to produce a more functional hand grasp.

FIGURE 21.2 A hybrid brace-transcutaneous neuroprosthesis system that is worn on the hand and forearm. The orthosis positions the wrist in a functional position and the five surface electrodes built into the orthosis stimulate specific muscles to provide coordinated hand opening and closing.

NESS H200, courtesy, Bioness, Inc., Valencia, CA.

Due to the limitations of surface NMES, Merletti et al. (63) originally suggested that an implanted system might best meet the clinical needs of persons with hemiplegia. Chae et al. (117) evaluated four chronic stroke survivors implanted with percutaneous intramuscular electrodes to demonstrate the adequacy of intramuscular NMES for hand opening and closing, identify control strategies that reliably open and close the hand under subject control, and demonstrate functional utility. The percutaneous hand neuroprosthesis was able to open a spastic hemiparetic hand as long as the limb was in a resting position, the wrist and proximal forearm were supported, subjects did not try to assist the stimulation, and an individual other than the participant modulated the NMES. However, when subjects attempted to assist the stimulation or complete a functional task, hand opening was significantly reduced as a result of increased finger flexor hypertonia, even with increased stimulation intensity. Similarly, electrically stimulated hand opening was significantly reduced following voluntary hand closure, which precluded formal testing of ADL function. Makowski et al. (119) have focused on identifying the clinical ramifications of variable upper-extremity co-contraction patterns (synergies) on upper-extremity neuroprosthesis use noted when combining voluntary effort and FES.

Recently, Knutson et al. (74) described their experience with the first stroke survivor to be implanted with an upper-extremity neuroprosthesis to assist arm and hand function. The neuroprosthesis consisted of an implantable stimulator-telemeter (IST), 12 intramuscular stimulating electrodes, two epimysial EMG-recording electrodes, and an external control unit (Figure 21.3). The IST produced 12 independent channels of electrical stimulation and recorded, processed, and transmitted 2 independent channels of EMG signal to the external control unit. The external

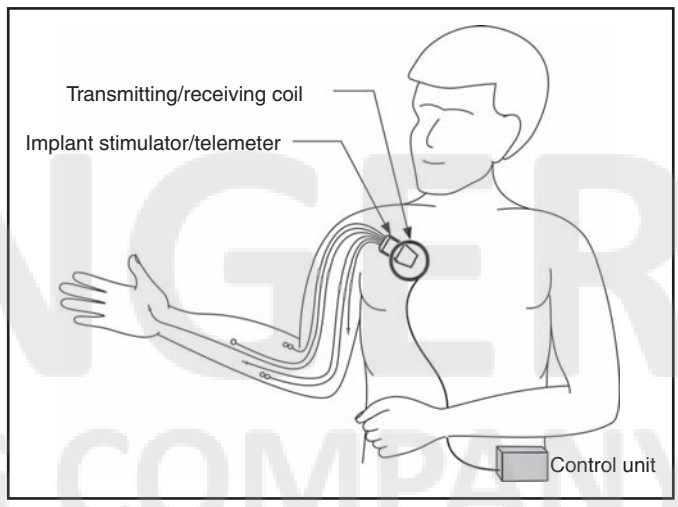

FIGURE 21.3 Implantable stimulator-telemeter (IST).

Courtesy, Cleveland Functional Electrical Stimulation Center, Cleveland, Ohio.

control unit transmitted power and stimulus commands for each electrode back to the IST. Following implantation and training, the subject was able to perform some bimanual tasks and use the neuroprosthesis for several ADLs and functional tasks, including meal preparation, eating, gardening, and exercising. The primary issues, which hindered consistent daily functional use of the neuroprosthesis, included inability to consistently achieve full extension of all digits, variable hand and wrist flexor tone associated with fatigue and/or extensor stimulation, inadequate EMG control signals necessitating an alternative push-button control system, and cumbersome size of the external control unit. Translation of an implantable neuroprosthesis into clinical care will require additional research focusing on mitigating hand and wrist flexor spasticity, optimizing EMG-recording electrode and EMG control strategies, adding implantable limb position sensors, increasing the number of stimulating channels to improve stimulation patterns and muscle recruitment, and miniaturizing the external control unit for ease of use.

FIGURE 21.5 The WalkAide® System.

Courtesy, Innovative Neurotronics, Austin, TX.

Lower-Limb Applications

The initial application of a lower-extremity neuroprosthesis in hemiplegia focused on a surface PNS device that dorsiflexed the ankle during the swing phase of gait (93). In an early randomized study of surface peroneal stimulation, Burridge et al. demonstrated that stroke survivors treated with the device exhibited significantly greater increases in walking speed with the device relative to baseline performance without the device, whereas the control group did not (120). More recent studies have demonstrated the neuroprosthetic efficacy of these devices (102), including studies that suggest comparable orthotic effects of an ankle–foot orthosis and a PNS device in hemiparetic gait (121–124).

Presently, there are three FDA-approved surface PNS devices prescribed in the United States for dorsiflexion weakness in hemiplegia. These devices are the Ness L300® Footdrop System (Bioness, Inc., Valencia, CA; Figure 21.4), the WalkAide® System (Innovative Neurotronics, Austin, TX; Figure 21.5), and the Odstock Dropped Foot Stimulator® (ODFS) (Odstock Medical Limited, Salisbury, UK; Figure 21.6). These devices utilize either a heel switch or a tilt sensor as a control to time stimulation to the swing phase of gait. From a clinical standpoint, use of a lower-extremity neuroprosthesis may not obviate the need for a custom-molded ankle–foot orthosis. Muscle fatigue, specificity of electrode placement, discomfort and inconsistent reliability of stimulation, insufficient medial–lateral control during stance phase, and limited technical support may all interfere with consistent extended-day use of the device. Prescription guidelines include dorsiflexion weakness with gait instability with the absence of lower-extremity edema, significant sensory deficit, skin breakdown, intolerance to stimulation, significant loss of passive range of motion at the ankle, or genu recurvatum.

FIGURE 21.4 The Ness L300® Footdrop System.

Courtesy, Bioness Inc., Valencia, CA.

FIGURE 21.6 The Odstock Dropped Foot Stimulator® (ODFS).

Courtesy, Odstock Medical Limited, Salisbury, UK.

These criteria should be considered in the context of general medical contraindications to NMES described in the motor relearning section.

Lower-extremity neuroprosthetic systems using surface electrodes have clear inherent limitations that might be remedied by implantable systems. An early study by Waters et al. (99) reported a significant increase in walking speed, stride length, and cadence with a single-channel implantable device relative to preimplantation performance. However, technical limitations included difficulty in balancing inversion and eversion, lack of an in-line connector that necessitated the removal of the entire implant in the event of component failure, and poor reliability of the heel switch and foot–floor contact transmitter. Kljajic et al. (100) also reported significant neuroprosthetic benefits from a single-channel implantable stimulator. However, nearly half of all subjects required reimplantation as a result of electrode displacement or failure. Two multichannel implantable peroneal nerve stimulators have been evaluated in Europe. A dual-channel device developed by the University of Twente and Roessingh Research and Development (the Netherlands) stimulates the deep and superficial peroneal nerves for better control of ankle dorsiflexion, eversion, and inversion (Figure 21.7) (125). A four-channel device, developed at Aalborg University (Denmark), utilizes a nerve cuff with four tri-polar electrodes, oriented to activate different nerve fibers within the common peroneal nerve (126). Both devices have the Conformité Européene (CE) mark in Europe. Kottink et al. (127) reported specifically on the neuroprosthetic effect of an implantable PNS on walking speed in a RCT.

To address gait deviations due to deficits proximal to the ankle, several studies evaluated multichannel surface NMES systems (109–111). However, although these systems were clinically implemented as neuroprostheses, neuroprosthetic outcomes were not assessed. Instead, these studies focused on therapeutic or motor relearning effects and, therefore, were discussed in the earlier section on motor relearning.

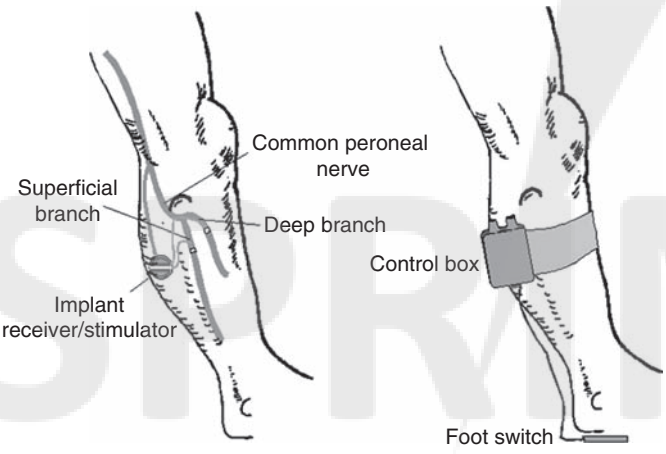

FIGURE 21.7 A two-channel implantable peroneal nerve stimulator (STIMuSTEP) allows individual stimulation of the deep and superficial branches of the common peroneal nerve for ankle dorsiflexion and eversion–inversion balance.

Courtesy, Department of Medical Physics and Biomedical Engineering, Salisbury District Hospital, Salisbury, UK.

Summary, Clinical Considerations, and Future Directions

At present, a hand neuroprosthesis using surface electrodes may allow stroke survivors to complete a limited number of selected functional tasks. However, a clinically viable hand neuroprosthesis system that provides broad functional benefit is not yet available. The requirements for a clinically viable hand neuroprosthesis using either surface or implanted technology are significant. Because stroke survivors can perform most basic ADLs with the unaffected upper limb, an upper-extremity neuroprosthesis will provide clear value only if it can facilitate performance of bilateral upper tasks or more complex ADLs such that the need for assistance from a caregiver is decreased. An upper-extremity neuroprosthetic system must address both proximal and distal motor control (128) and have sufficient miniaturization to allow the user to perform functional tasks without impeding the function of the unaffected limb or interfering with mobility. Control paradigms are necessary to produce effortless movement of the impaired upper limb (129). Finally, the system must "turn off" overactive muscles to address the problems of spasticity, associated reactions, coactivations, co-contractions and delay in termination of muscle contractions (117).

Lower-limb neuroprostheses that use surface peroneal nerve stimulation are increasingly being prescribed as alternatives to ankle–foot orthoses in stroke survivors. However, clinical adoption likely will depend on whether there is any significant added value relative to an AFO. Implanted PNS devices are available in Europe and may be appropriate for stroke survivors who experience significant improvement in mobility with the surface system, but have difficulty with electrode placement, skin irritation, painful sensation of stimulation, or donning and doffing of the device. However, in view of limited data, more definitive recommendations must await additional studies and the emergence of additional clinical experience. At present, multichannel, multijoint systems are clinically less accessible and are limited to investigative purposes.

Although the clinical prevalence of a lower-limb neuroprosthesis for hemiplegia is greater than upper-limb neuroprosthetic systems, several issues remain to be elucidated. First, surface systems can be limited by discomfort and difficulty with electrode placement for reliable muscle contraction. Implanted systems may address these issues, but at present, implanted technology is only available in Europe and potential benefits would clearly have to be weighed against the risks and costs associated with an invasive procedure. Second, optimal functioning will require control of multiple joints.

Although available devices focus primarily on the ankle, most stroke survivors also have difficulty with hip and knee flexion during swing and knee control during stance. Clinical implementation of a complex multichannel surface electrode system will be challenging. A multichannel implanted system may be needed. Lastly, clinical relevance must be established in a controlled trial by comparing the effects of the intervention with the standard of care on mobility and quality of life.

CONCLUSIONS

The principal goal of rehabilitation management of persons with hemiparesis is to maximize motor ability and thus enhance both functional performance and quality of life. NMES systems bypass the injured central circuitry to activate neural tissue and contract muscles with the intent to both facilitate motor relearning as a therapeutic intervention and improve functional movement as a neuroprosthesis. Recent technological advances in clinical medicine and biomedical engineering make the clinical implementation of NMES systems in stroke survivors with hemiparesis much more feasible. NMES for motor relearning in hemiplegia is a promising application of goal-oriented repetitive movement therapy. Whereas additional rigorous multicenter clinical trials to confirm effectiveness and fundamental studies to elucidate mechanisms are still needed, the clinical implementation of these devices is appropriate. Presently, upper- and lower-extremity cyclic NMES, EMG-triggered NMES, and neuroprosthetic devices should be included reasonably in the broader clinical armamentarium of stroke rehabilitation professionals and considered judiciously for select stroke survivors.

After decades of development, the clinical utility of NMES systems is becoming realized. By necessity, scientists and clinicians must continue to explore new ideas and improve upon the present systems. Components will be smaller, more durable, and more reliable. The issues of cosmesis and ease of donning and doffing will be a factor in the evolution of devices. Control issues will remain central, and the implementation of cortical control will dictate the nature of future generations of neuroprosthesis systems. Future developments will be directed by consumers. In the present health care environment, in which cost is an overwhelming factor in the development and implementation of new technology, the consumer will become one of technology's greatest advocates. Finally, the usual drive toward greater complexity will be tempered by the practical issues of clinical implementation in which patient and clinician acceptances are often a function of a tenuous balance between the "burden and cost" associated with using a system and the perceived impact of that system on quality of life.

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22

Robots in Stroke Rehabilitation

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Hermano Igo Krebs, and Neville Hogan

In contemporary society, the adoption of new technologies often is viewed as an inevitable component of progress. Stroke rehabilitation has been slower to adopt new technologically based therapeutic tools than many other areas of medicine and has largely remained a "hands-on" field. There are, however, several arguments supporting broader incorporation of robots and other technologies into stroke rehabilitation. An economic case can be made that the field of stroke rehabilitation ought to take advantage of the potential labor-saving nature of these technologies. In an environment in which labor costs continue to rise and the costs of technology are falling, using robots to reduce the reliance on skilled human labor for stroke rehabilitation will undoubtedly be cost-effective in the long run. The need for more efficient delivery of exercise therapy is amplified by the growing evidence that more intensive exercise training is an important factor in enhancing motor recovery after stroke.

A second consideration in favor of increasing the adoption of robots in stroke rehabilitation is that these devices are able to provide treatments repetitively without risking therapist fatigue. This can easily be illustrated by analogy with the low-tech example of continuous passive motion (CPM) machines after total knee arthroplasty. These devices can provide many hours of slow, steady, passive range-of-motion exercises after surgery. Although a human therapist is capable of performing similar exercises, he or she would not be able to sustain this effort for many hours.

Certain therapies and treatments can be provided only through the use of technology. For example, the incorporation of computerized games into robotic exercise therapy allows patients to become more engaged in the required task, converting what might otherwise be a tedious and repetitive set of exercises into a form of entertainment. Robots in particular are well suited to assisting with movements in individuals too weak to complete these movements unassisted, thus allowing individuals to complete a prescribed exercise that would otherwise require the assistance of another individual.

Similarly, robotic devices appear particularly well suited to facilitating motor learning. Evidence continues to accumulate that motor-learning principles, such as task repetition and progression, are critical elements of exercise programs to stimulate brain plasticity and recovery of motor function. Advances in robotic technology are increasingly capable of providing a flexible, programmable platform to engage stroke survivors in a growing array of interactive motor-learning activities.

Lastly, many stroke rehabilitation centers are seeking ways to distinguish themselves in a competitive marketplace. Although this is not a strong argument for the adoption of new technologies, it is nonetheless likely a driving factor among some early adopters of new treatment technologies.

Robotic devices may have particular application to stroke rehabilitation. This chapter describes the potential applications of robots as aids for rehabilitation and recovery in stroke survivors and discusses several of the specific systems currently in use and the evidence supporting their clinical efficacy.

WHAT ARE ROBOTS AND WHY USE THEM IN STROKE REHABILITATION?

The boundaries of robot technology overlap other emerging therapeutic technologies such as electromechanical exercise devices and virtual reality therapy. Rehabilitation clinicians have employed electromechanical devices for decades. CPM devices, treadmills, and isokinetic exercise machines perform automatic functions and can be programmed in advance. These relatively simple machines have primarily been used for orthopedic and sports medicine applications. Although some might consider these simple robots, we have used a somewhat stricter definition in this chapter.

The American Heritage Dictionary defines a *robot* as "(a) A mechanical device that sometimes resembles a human and is capable of performing a variety of often complex human tasks on command or by being programmed in advance. (b) A machine or device that operates automatically or by remote control" (1). In practice, general-purpose, anthropomorphic (human-appearing) robots have found little practical application in medicine, although they continue to captivate the popular imagination. The robots developed for rehabilitation have been specialized devices that bear little or no resemblance to humans and are of varying sizes,

FIGURE 22.1 InMotion Shoulder-Elbow robot (Interactive Motion Technologies, Inc.), based on the MIT-Manus design, provides planar exercises for the upper limb involving shoulder and elbow movements. Shown here with the InMotion Hand robot module in use, instead of the wrist-hand splint used in the basic configuration.

shapes, and complexity (see Figure 22.1). They share an increasing level of sophistication, with increasing capabilities and programmability.

USES OF ROBOTS IN STROKE REHABILITATION

Although the potential uses of robots in stroke rehabilitation are broad, we divide potential applications into three major categories: exercise training, wearable functional orthoses, and as aids for activities of daily living (ADLs). The vast majority of the research in the use of robots for stroke rehabilitation has focused on their use as exercise training devices, and this will form the majority of the focus in this chapter. Some of these devices are wearable exoskeletons in design and are the devices most easily adapted to potential applications as wearable functional orthoses. This chapter provides an overview of the arguments for and against the incorporation of these technologies into stroke rehabilitation in these different roles and the various clinical circumstances in which they might prove useful. Clinical research results are reviewed, where applicable.

Robot-Aided Exercise

Exercise is one of the key therapeutic modalities in stroke rehabilitation. Exercise treatments are most commonly provided under the direct personal supervision of physical therapists, occupational therapists, exercise physiologists, athletic trainers, or other practitioners. In many cases, this direct supervision is gradually withdrawn in favor of intermittent supervision as the patient progresses, and the patient is encouraged to engage in an independent exercise program at home or in a gym. This model of care requires extensive personnel time and yet is often unsuccessful in its ultimate goal of having patients perform exercises independently without direct supervision. Achieving long-term compliance with exercise programs remains a challenge in this traditional model of care, with many patients discontinuing exercises because of limited functional gains or insufficient motivation.

The use of robots to assist in stroke rehabilitation has been proposed as a labor-saving approach for the provision of exercise therapy. Robot-guided exercise can, in principle, be substituted for exercise provided under the direct guidance of a therapist, or perhaps more importantly, to supplement this therapy to achieve a greater total amount of exercise. Models for incorporating these devices into an exercise program include (a) having a single therapist provide supervision to several patients working with training systems simultaneously, (b) having a patient work at home with a robot or virtual reality system with remote supervision from a therapist, or (c) having a patient work independently with a technology-based training system with periodic review and adjustment of the exercise program by a therapist. With the available technology, most robotic therapy is currently delivered with one-on-one supervision of a therapist or rehabilitation aide in an institutional setting. We expect this to shift gradually to models that allow greater patient autonomy and efficient staff utilization to achieve the ultimate labor-saving benefits that robots must produce to justify their use.

Ultimately, the use of robots might provide improved therapeutic outcomes compared with traditional exercise therapies. Whereas these benefits have not yet been demonstrated in a clinical trial comparing robotic therapy to dose-matched human-delivered therapy, we believe there are reasons to anticipate that improvements in robotic design will ultimately achieve this goal. Specifically, the programmable nature of computer-based training devices allows the health care provider to design and institute an exercise program that is specific to the patient's impairments, predictable, and well controlled. These devices can also be interactive and alter the therapy provided based on the patient's immediate reaction or response to treatment over time. The parameters of exercise that can be controlled through the use of robots include the nature of the exercise activity, the movement pattern, the number of repetitions, the forces exerted by the robot on the patient, and others. Thus, there is the potential to deliver exercise in a more consistent and evidence-based fashion with robot aids and perhaps to improve the ultimate results of treatment.

For individuals with weakness, robots can provide physical assistance for task completion. Thus, for a stroke patient with some active movement at the shoulder and elbow, but unable to achieve antigravity strength, a robot might assist with a reaching movement. This capability is

similar to that provided by a human therapist who provides individual treatment by facilitating/supporting movements in a weak patient, but can be sustained for longer duration and more repetitions. Potentially, robotic algorithms could be developed to optimize the amount and type of assistance provided to maximize motor outcomes, although we do not yet possess sufficient understanding of the ideal motor retraining parameters after stroke to create these algorithms at present.

Resistance training has been studied as a therapy for poststroke weakness (2,3) and can be incorporated into robotic exercise (4,5). Whereas the possible therapeutic advantages of resistance training for hemiparetic stroke survivors continue to be studied, the availability of this mode of training in robotic exercise devices is an important capability and might be expected to be beneficial in certain clinical circumstances. Robots also can be programmed to exert force on the patient's limb that induces adaptation on the patient's part to counter the force exerted by the robot. Thus, a patient working with a robot that applies a consistent force field in a particular direction may develop a compensatory adaptation, increasing the effort to move the limb in the opposite direction. When the robotic training session ends, this adaptation may persist, although any long-term functional impact of this adaptive response remains to be established.

Robots can be designed and programmed to make repetitive exercise more interesting and enjoyable for a patient. Computer-based video games can be integrated with the robot training to provide a more stimulating therapy environment for the patient. Even relatively simple computer games, such as a "Pong"-type game, can relieve the boredom many patients associate with repetitive exercises. This ability to provide an interesting and structured environment for the performance of an exercise program holds promise as a means of improving compliance with exercise prescriptions in the future. More elaborate virtual reality visual displays are also being developed, and continued convergence between the two approaches is likely.

Robots can collect data on exercise compliance and performance and allow the supervising practitioner to provide appropriate feedback to the patient regarding his or her exercise activities even when the practitioner is not physically present during the exercise session. This data can be stored electronically and reviewed at the convenience of the supervising therapist rather than at the time of the actual exercise. Compliance with prescribed exercise training can be directly measured rather than estimated from patient self-reports. From a research perspective, data obtained through robotic devices have provided insights into the mechanisms of recovery of motor control after stroke (6–8).

The number of robotic devices developed has burgeoned over the past 20 years since their introduction, and more than 60 clinical studies using these devices have been published (see summary in Lo (9)). Corporations, ranging from small start-ups to large multinational companies have become involved in rehabilitation robotics (10). As with any emerging technology, devices that have not yet been tested in clinical populations are under development. This chapter focuses primarily on devices for which there are published reports in patient populations or which are commercially available in the United States.

Workstation Exercise Robots

Upper-Limb Robotic Exercise Training

Robotic devices for therapeutic exercise have been tested clinically for patients with neurologic diagnoses, including stroke, traumatic brain injury (TBI), multiple sclerosis, and spinal cord injury (SCI). Neurologic rehabilitation has been a particularly fertile field for robotic applications. For persons with stroke, it has been demonstrated that highly repetitive, task-specific exercise training can facilitate neuroplastic changes in the brain, with concomitant improved motor abilities and enhanced functional activity performance (11,12). Robotic devices can provide such augmented exercise therapies in accurate and reproducible dosage. Furthermore, they hold promise to become an economical complement to traditional, labor- and time-intensive neurologic rehabilitation.

Several research groups have tested the treatment effects of robotic therapy for poststroke upper-limb motor recovery. The robots reported in these clinical studies range in complexity from unimanual, single-joint devices to bimanual devices with multiple degrees of freedom.

The MIT-Manus robot (InMotion2 robot, Interactive Motion Technologies, Inc., Watertown, MA; see Figure 22.1) has two *degrees of freedom* that provide shoulder and elbow exercises in the horizontal plane. The patient's forearm and hand are supported and attached to the robot manipulandum with a splint. The MIT-Manus robot can administer active–assistive or resistive exercises or be programmed into a "passive" mode that provides neither resistance nor assistance. The design of the robot allows patients with a broad range of motor impairment to use this device. Even patients with severe weakness who are incapable of completing constraint-induced movement therapy can successfully undergo exercise training with this robot. Training algorithms continue to be refined, and an adaptive active–assistive exercise mode that alters the amount of guidance or assistance provided to the patient based on his or her performance has been developed (13). An electromyographic (EMG) triggered mode in which the user's surface EMG activity is used to trigger the robotic assistance has been piloted (14). In all exercise modes, subjects attempt to move the robotic arm while guided by target images on a computer monitor. Several different screen displays and accompanying motor tasks have been developed, although the best-studied "game" involves radial movements of a cursor in each of eight evenly spaced directions.

The MIT-Manus robot has been studied in a randomized controlled trial (15–18) of 96 patients within 1 month of stroke. Subjects in the treatment group received one hour of active–assistive exercises with the robot for the paretic arm 5 times per week for 4 weeks, and control subjects received sham exercise (i.e., with the robot in "passive" mode) with the robot once

each week. The robotic therapy consisted of active–assistive reaching practice in the horizontal plane toward eight targets. All subjects received conventional rehabilitation therapy, per standard clinical practice, in addition to robotic therapy. At the end of treatment, the robot therapy subjects experienced significantly greater improvement in motor impairment measured on the Motor Status Scale (MSS) and the Medical Research Council Motor Power Scale (MRC) for shoulder and elbow motor function. These improvements were maintained at the time of a three-year follow-up study (19).

The MIT-Manus robot has also been tested in several trials for stroke survivors with chronic hemiparesis. In one study (20), 42 subjects received either active–assistive or progressive-resistive reaching training for 1-hour sessions, 3 times per week for 6 weeks. Subjects performed up to 18,000 point-to-point movements over the course of the trial. Subjects in the resistive and active–assistive treatment groups demonstrated significant impairment-level gains using several scales (Fugl-Meyer, MSS, MRC) that remained improved over baseline scores when measured at four-month follow-up evaluations. No differences in outcomes were detected between the resistance training and active–assistive training groups (4). The other studies of patients with chronic hemiparesis found similar improvements in motor function (21–24). Seventy-two subjects received active–assistive training using an adaptive training algorithm to adjust the amount of assistance to the person's movement ability using the MIT-Manus robot.

The benefits of robot-assisted upper-limb exercise therapy in these studies of MIT-Manus were seen primarily in shoulder and elbow movements, rather than in the wrist or hand. This is consistent with a specificity of training effect, because the robot provides exercise only to these portions of the upper limb and keeps the wrist and hand immobilized in a splint. The magnitude of the changes in motor impairment has been clinically significant but modest, but would be expected given the limited nature of the robotic exercise. The training effects appear to persist over time (25).

A series of related robot modules have been developed, including a wrist device that provides wrist flexion and extension, radial and ulnar deviation exercises; a linear reaching robot that can be positioned to provide upward reaching movements at the shoulder and elbow; and a hand module that addresses grasp and release. A clinical trial combining the use of these four devices (shoulder–elbow, wrist, reaching, and hand robots) compared robot-assisted therapy with therapist-provided exercises and a usual care group (26). Whereas clinically significant benefits of this combined robotic therapy were seen when compared with usual care, the magnitude of these improvements were in the same general range as those seen on studies of the more limited shoulder–elbow robot in prior studies. Other studies are underway to clarify if utilizing robotic modules serially for different limb segments (e.g., performing wrist exercises followed by shoulder/elbow exercises) is more or less efficient than combining modules in multisegment configurations (e.g., wrist and shoulder/elbow exercises simultaneously) in achieving improved motor control. In spite of the results of the study by Lo et al., the hypothesis that the combined effects of training with multiple devices for different upper-limb segments will provide a larger benefit of overall motor function in the upper limb remains attractive (27).

Reinkensmeyer and colleagues have developed a robot, the Assisted Rehabilitation and Measurement (ARM) guide, designed to administer active–assistive reaching practice in three dimensions (28). Although this robot provides only a single active degree of freedom, the linear track can be repositioned manually into different spatial orientations during the course of an exercise therapy session to allow a variety of movements. The patient's forearm and hand rest in a splint that attaches to a motorized, linear track, and the robot supports the arm against gravity and assists the patient to reach along the track. Visual feedback is provided through a computer monitor. Kahn and colleagues (29) tested the effects of the ARM guide on reaching performance for patients with chronic hemiparetic stroke. Seven subjects received 24 one-hour robotic therapy sessions over the course of 8 weeks, whereas another 7 subjects received an equivalent dose of unassisted, goal-oriented reaching exercise. All subjects practiced repetitive reaching in multiple directions and vertical levels. After the trial, results of impairment-level measures were mixed. Neither group demonstrated improvements in free-reaching distance, all subjects showed improved straightness of reaching paths, and only the robotic therapy group showed improved movement smoothness. A timed measure of functional activities, the functional test for the hemiparetic upper extremity, demonstrated significantly decreased performance times for the free-reach group and a trend toward improved performance for subjects who received robotic therapy. An important limitation of this study is the small number of movement repetitions per session (65 movement attempts per sessions)—substantially below the number provided in many other trials of robotic exercise, and perhaps insufficient to provide a therapeutic benefit. A robot with one degree of freedom and an adjustable track is available (30) (InMotion1 Linear Robot, Interactive Motion Technologies, Inc., Watertown, MA, www.interactive-motion.com).

One limitation of many of the earlier generation of rehabilitation robots is that they generally omitted or had limited hand robotic retraining capabilities. The InMotion Hand (Interactive Motion Technologies, Watertown, MA) provides a single degree of freedom robotic training system focusing on grasp-and-release. The Amadeo (Tyromotion, Graz, Austria; see Figure 22.2) has the ability to provide individualized training for each finger. A small uncontrolled pilot study of this device demonstrated good tolerability and suggested benefit, and larger controlled studies are in progress (31).

In contrast to this modular approach to upper-limb robotics, some groups have focused on incorporating multiple limb segment training into a single device. The ReoGo (Motorika, Caesarea, Israel) focuses on shoulder–elbow movements but adds an additional degree of freedom by incorporating a telescoping support from a pedestal base.

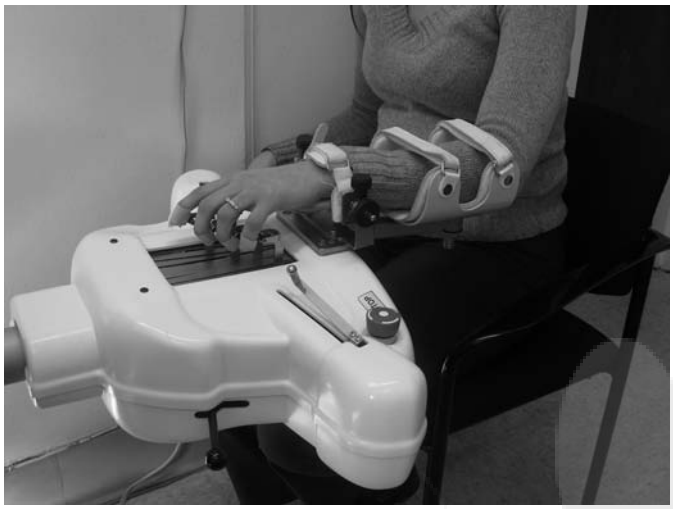


FIGURE 22.2 The Amadeo robot (Tyromotion, Inc., Graz, Austria) provides finger flexion and extension exercises.

Studies of this device have found reduced motor impairment, but large well-controlled trials have not been conducted thus far (32–34). The ARMin robot provides robotic assistance for movements at the shoulder, elbow, and wrist using an exoskeletal workstation design. Although only limited data on the clinical use of this device have been published (35,36), a commercial version, the ArmeoPower (Hocoma, Zurich) has recently been released (see Figure 22.3).

Bimanual robotic therapy using the nonparetic upper limb to help guide the movements of the paretic upper limb is another approach implanted in the mirror image movement enabler (MIME) robot and in the Bi-Manu-Track (Reha-Stim, Berlin). The MIME robot (see Figure 22.4) is a six degrees of freedom robot that can administer four distinct modes of upper-limb reaching exercise in three dimensions (5). Similar to the MIT-Manus robot, the patient's forearm and hand are supported and attached to the robot with a splint. Unimanual exercises include passive, active–assistive, and active–constrained movements. During active–constrained exercise, the MIME robot resists reaching movements toward a target with a viscous field and provides a spring-like assist to movements in all other directions. Bimanual exercise is performed while subjects attempt to move both arms in simultaneous reaching movements; the robot assists the paretic limb's movements, as necessary, to mirror the less-impaired limb.

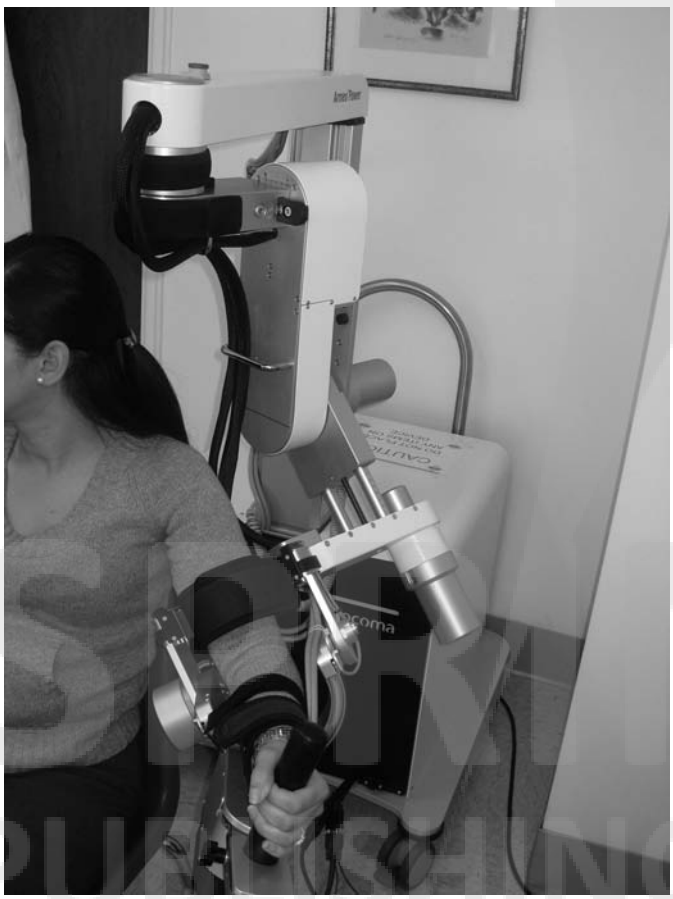


FIGURE 22.3 Armeo Power robot (Hocoma, Inc.), based on ARMin robot, includes multiple degrees of freedom at the shoulder, elbow, and wrist.

FIGURE 22.4 MIME robot, an upper-limb robot with six *degrees of freedom*, designed to assist with reaching movements.

MIME robotic therapy has been compared to conventional neurodevelopmental technique-based therapy (NDT) in a study of 27 subjects with chronic hemiparesis after stroke in a randomized controlled trial (5). All subjects received 24 one-hour sessions over the course of 2 months. Subjects in the robotic treatment group repeatedly practiced 12 reaching movements in 4 directions and at 3 vertical levels. They received identical proportions of robot-guided passive and bimanual exercise and variable amounts of active–assistive and active–constrained exercise graded by individual motor ability. The NDT control group received exercises designed to facilitate a progression from mass upper-limb movement patterns to more isolated control, in the context of functional task performance. Immediate posttreatment results revealed that subjects in the robotic therapy group improved more than the control subjects for Fugl-Meyer Assessment scores (proximal section only), upper-limb strength measures, and free-reach distance. At the six-month follow-up evaluations, the Fugl-Meyer scores of the treatment group no longer were significantly different from those of the control group.

Hesse and colleagues tested a bimanual robotic therapy for its effects on distal motor impairment and function in a single-group exploratory study (37). This robotic arm trainer administered bimanual practice of wrist flexion/extension and forearm pronation/supination using active, passive, and resistive exercise. The robotic therapy was administered as an adjunct to a daily 45-minute comprehensive motor rehabilitation program. Twelve persons with chronic, hemiparetic stroke trained with the robot for fifteen 15-minute sessions over the course of 3 weeks. At the end of the robotic intervention, subjects showed reductions in wrist and finger spasticity as measured by the modified Ashworth test, but there was no significant improvement in performance of functional motor activities according to Rivermead Motor Assessment scores. Participants reported favorable impressions of the robotic therapy.

A second study by Hesse and colleagues (38) compared this bimanual robotic training device to EMG-initiated electrical stimulation of the paretic upper limb in hemiparetic individuals four to eight weeks after stroke. Individuals receiving robot-aided exercise showed significantly larger improvements in Fugl-Meyer motor scores. The authors speculate that the reason for the different outcomes in the two groups was that the robotic training group received a ten-fold increase in the number of repetitions compared to the EMG-triggered electrical stimulation group.

As robotic arm exoskeletons evolve, the devices face several challenges: (a) they are heavy compared to the weight of the human arm, thus significantly altering the moving inertia of the natural arm; (b) they require precise alignment between the exoskeleton and human joints—often impossible to achieve because human joint axes are formed by relative motion of complex bony segments; and (c) they require exoskeleton link lengths to be the same as human segments, requiring adjustable segments to accommodate users of varying limb lengths. A novel lightweight Cable-driven Arm Exoskeleton (CAREX) recently was developed as an alternative approach (see Figure 22.5). Instead of the rigid links and joints typically used in conventional exoskeletons, CAREX uses lightweight cuffs and tensioned cables (39). The weight of CAREX is approximately one-tenth that of conventional robotic exoskeletons and does not require joint alignment or link length adjustment. In addition, the weight of CAREX is supported by motors to minimize additional weight on the arm. Preliminary studies show that the "assist-as-needed" force field applied by CAREX helps healthy subjects and those with stroke to follow a desired path more accurately, with increased arm extension for the stroke subject. The data also demonstrate that the desired movements are accomplished with similar patterns of muscle activation at a reduced magnitude, suggesting that CAREX can facilitate physiological movement patterns with the arm in a relaxed state.

FIGURE 22.5 Prototype of CAREX, a cable-driven arm exoskeleton for training of stroke patients.

Lower-Extremity Robotic Exercise Training

Robots for lower-limb use in neurologic rehabilitation have been developed primarily as devices for administering partial

body-weight-supported treadmill gait training (BWST). BWST consists of partially unloading the weight of a neurologically impaired person suspended above a treadmill, while therapists manually assist the patient to step, shift weight, and maintain appropriate kinematic gait patterns during gait training. Several studies have reported improved gait performance after intensive BWST for persons with stroke (40), Parkinson's disease (41), and cerebral palsy (42), with inconclusive results after SCI (43,44). A large clinical trial recently found no benefit to BWST for stroke survivors (45), however. Thus, the rationale for developing robotic versions of this therapy has been seriously undermined.

Hesse and colleagues have developed a robotic device for gait training, including BWST, called the electromechanical gait trainer (EGT) (46). Resembling an elliptical exercise trainer, the EGT uses footplates that move alternately to simulate stance and swing phases of a physiological gait pattern. A harness suspends the patient above the footplates to provide for variable unweighting during gait training and reportedly serves to maintain the center of mass in a phase-dependent manner. Werner and colleagues (47) tested the EGT against conventional BWST in a randomized control trial involving 30 hemiparetic subjects who were 4 to 12 weeks poststroke. All subjects required at least some physical assistance (functional ambulation category [FAC] ≤2) for overground ambulation at baseline. Subjects were assigned to either an A-B-A or B-A-B crossover group. "A" consisted of two weeks of EGT therapy, and "B" consisted of two weeks of BWST therapy. They received experimental gait training 15 to 20 minutes daily in addition to conventional therapies for 6 weeks. At the end of treatment, both treatment groups demonstrated gains in FAC, gait velocity, and Rivermead Motor Assessment scores. The authors report that EMG measures of muscle activation patterns were similar for patients on both devices. The treatment group that received two-thirds epochs of EGT therapy had comparatively higher FAC scores, with more subjects able to ambulate independently, but this advantage was no longer evident six months after treatment. Differences were reported in the amount of therapist assistance required for each treatment. At baseline, most patients using the EGT required one therapist, but they required two therapists for assistance using BWST. By the end of treatment, most patients could use the EGT without therapist assistance, whereas most subjects needed assistance from one therapist while receiving BWST. The majority of subjects (23/30) reported that they preferred gait training with the EGT over the BWST.

A larger, multicenter study recently compared gait training with a combination of EGT plus conventional physical therapy with a group receiving conventional physical therapy alone in 155 subacute (average 4 to 5 weeks poststroke) subjects (48). The EGT group showed a greater improvement in gait and ADL measures, both clinically and statistically, than the control group over the course of the four-week treatment protocol. Improved gait ability was maintained at six-month follow-up, though the difference in ADL ability was no longer evident. Commercial versions of the EGT, the GT-1 (Reha-Stim, Berlin, Germany), and the G-EO (Figure 22.6; Reha Technologies, Olten, Switzerland) have been developed.

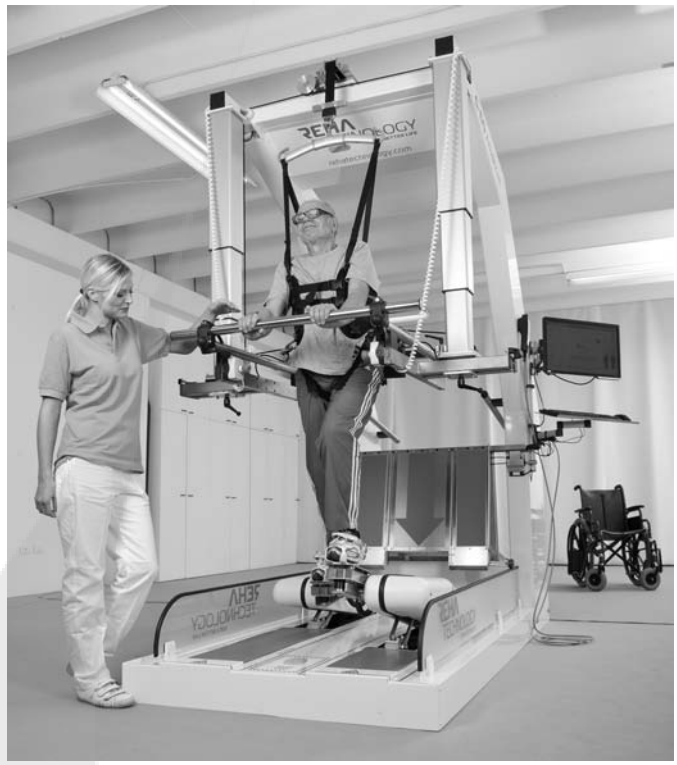


FIGURE 22.6 G-EO robot, an elliptical trainer-like gait robot that uses actuated footplates to guide and assist the user's gait.

Colombo and colleagues (49) have developed a lower-limb robot (driven gait orthosis [DGO]) for automated, intensive gait training. The DGO automates BWST by suspending two exoskeletal leg braces from a frame over a treadmill. Hip and knee motors in the exoskeletal braces are controlled by a computer to generate physiologically correct gait patterns for the patients who wear them. Ankle dorsiflexion is passively provided by elastic straps. The DGO requires a therapist operator but no direct human physical assistance while persons use the device for gait training. Studies examining the muscle activation patterns of subjects using the DGO compared with treadmill walking (50) and with manually assisted BWST (49,51,52) have reported conflicting results, and there is some evidence that users may reduce their effort during DGO assisted ambulation (52). A case series employing a DGO robot (Lokomat) (Hocoma AG, Volkestwil, Switzerland; see Figure 22.7) found gait improvement in patients with chronic incomplete SCI (43). Several studies comparing the Lokomat with conventional physical therapy have been published, with mixed and inconclusive results overall (53–55).

A *two active* degrees of freedom back-drivable robot for the ankle, the Anklebot, has been developed at MIT (Interactive Motion Technologies, Watertown, MA; see Figure 22.8). This tethered wearable device functions as a powered ankle–foot orthosis, with the ability to control and assist ankle dorsiflexion and plantarflexion as well as inversion and eversion.

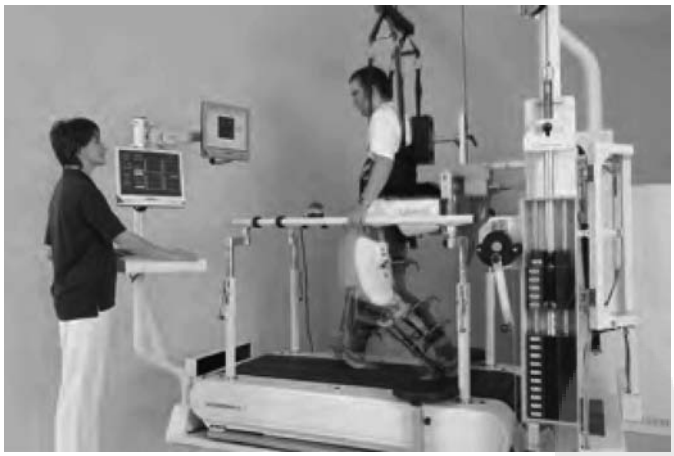
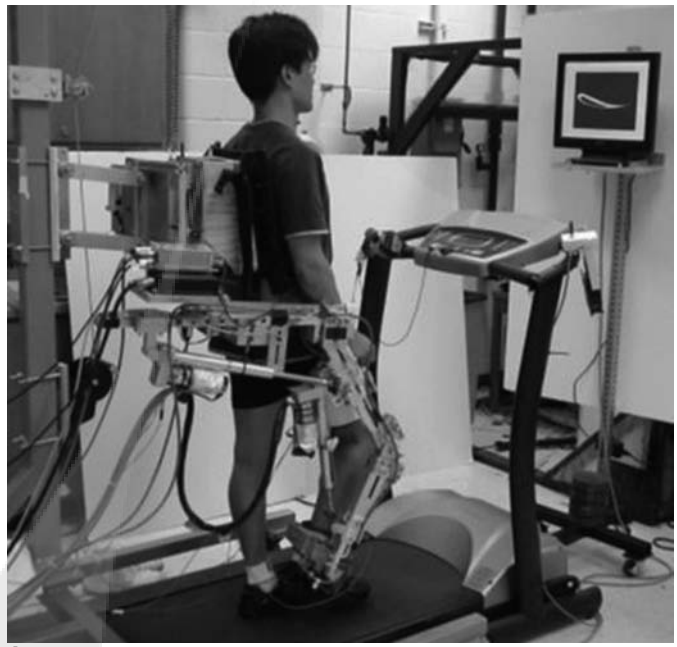


FIGURE 22.7 Lokomat robot (Hocoma, Inc.) provides partial body-weight support during assisted treadmill training.

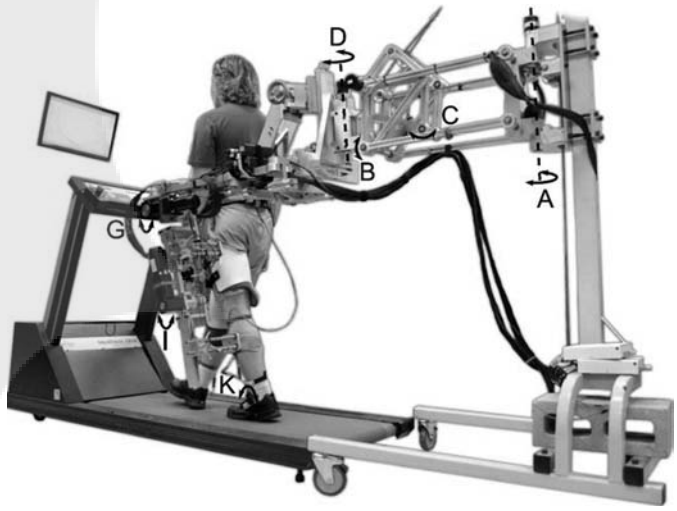
One study with chronic and another with subacute stroke found that training ankle movements in seated position with this device resulted in gait improvements (56).

A number of studies have been performed with Active Leg Exoskeletons (ALEX and ALEX II), shown in Figure 22.9, focused on the issues of design, human training, and optimal

FIGURE 22.8 Anklebot (Interactive Motion Technologies, Inc.) is designed to assist and train ankle movements during gait.



A



B

FIGURE 22.9 Gait training of healthy and stroke subjects using Active Leg Exoskeletons ALEX (A) and ALEX II (B).

haptic/feedback interface. ALEX has been used to study gait adaptation with "assist as needed" paradigm using healthy subjects and in a group of stroke patients (57–59). ALEX has also been used to study "error enhancement" paradigm in gait adaptation with healthy subjects and the role of feedback in human training and learning. ALEX is attached to a walker and strapped to a human subject on the trunk, upper- and lower-limb segments of the leg (see Figure 22.9). The attachment between the user's trunk and the device allows flexibility during walking. The hip segment of ALEX allows abduction and adduction with respect to the pelvis. The thigh and shank segments of the machine are telescopic to accommodate variability in leg geometry of users. The foot segment of the exoskeleton is a shoe insert. The orthosis has joint encoders

that record the movement of the trunk, hip, the sagittal plane motion of the leg, and the motion of the ankle. In addition, the exoskeleton has two 6-axis force-torque sensors that record the interaction force and torque between the machine segments and the corresponding segments on the human. The hip and the knee joints of ALEX are actuated by servo motors.

One of the significant aspects of ALEX is that its controller is designed to provide flexibility and maximize human learning. A virtual tunnel is created around a desired foot trajectory that is a function of subject size, age, and walking speed. Depending on the current position of the foot with respect to the tunnel, the controller can prescribe force on the foot—both normal and tangential to the desired foot trajectory (57–59). In the assist-as-needed paradigm, if the foot is within the tunnel, the normal force is close to zero while a tangential force guides the foot along the tunnel. As the foot goes outside the tunnel, the normal force brings the foot closer to the center line of the tunnel while the tangential force is kept small.

Wearable Robots/Robotic Orthoses

In contrast to the stationary exercise robots discussed so far, robots are also being developed that are "wearable," known as wearable exoskeletal robots or powered orthoses. Such robots may be useful to provide therapeutic exercise (similar to stationary exercise robots) and/or potentially as devices to help compensate for chronic weakness. Wearable exoskeletal robots are in an earlier phase of development than stationary robots, and the relative merits of wearable versus workstation robots remain largely unexplored. Potential advantages include the ability to move the location of therapy into a more "real-world" environment, including the patient's home, rather than confining treatment to a designated location in a health care facility.

FIGURE 22.10 Myopro (Myomo, Inc., Cambridge, MA) uses a custom-molded orthosis to provide actuated elbow flexion and extension movements using surface EMG control from the biceps and triceps muscles.

A small pilot study of a powered wearable elbow brace (see Figure 22.10; Myomo, Inc., Boston, MA, www.myomo.com) that uses surface EMG signals to control the level of torque provided found hemiparetic stroke survivors capable of using this device for exercise training (60). A small randomized controlled pilot study compared this device to conventional upper-limb exercise therapy and found that both were equally efficacious (61).

A wearable powered knee brace, called the AlterG Bionic Leg, is commercially available (see Figure 22.11; AlterG, Fremont, CA). This device uses a combination of sensors, including accelerometers and force transducers to determine the user's intended action and can infer whether the user is walking, ascending/descending stairs, or transferring from sit to stand. It then provides assistance to the user to achieve an idealized template pattern of movement. One small controlled study comparing this device with an exercise control intervention in chronic stable stroke survivors has been completed and found modest improvements in gait that were no different from the control intervention (62).

Several groups have developed bilateral wearable powered long-leg braces, including the ReWalk (Argo Medical Technologies, Ltd, Yokneam Ilit, Israel), Ekso (Ekso Bionics, Richmond, CA), and the Indego (Parker Hannifin,

FIGURE 22.11 AlterG Bionic Leg (AlterG, Fremont, CA) is a wearable powered knee brace.

Cleveland, OH). These devices seem useful most specifically for individuals with paraplegia due to SCI or other conditions, rather than stroke. Nonetheless, it is likely that selected stroke survivors may benefit from these devices. Further development and refinement may provide specific training options for the hemiparetic stroke survivor.

The use of wearable exoskeletal robots as compensatory aids has been proposed as a means of providing a "power assist" to chronically weak muscles. Such a robot might allow individuals to perform ADLs or ambulate independently despite severe weakness. Control and feedback mechanisms for this type of robot require further study and may vary with the nature and severity of weakness.

Potential Disadvantages and Limitations of Wearable Exoskeletal Robots

Wearable exoskeletal robots may be capable of providing a substantial number of clinically relevant degrees of freedom, although practical considerations, including the bulk and weight of the exoskeletal robot, may limit the actual number of degrees of freedom achievable. The ability to apply forces at multiple limb segments, rather than at a single point of contact, adds both complexity and sophistication.

Wearable exoskeletal robots must function in a much more varied and less controlled environment than workstation robots. Accordingly, they may expose the user to unanticipated risks because situations arise that are beyond the intended activities of the robot. For ambulatory patients, issues such as falls while using a wearable exoskeletal robot must be considered as a potential risk to both the user and the robotic device. The possibilities of striking oneself or being forced into an anatomically dangerous position are less easily prevented in a wearable exoskeletal robot design than in a workstation design. Another design concern is that a mismatch between the machine kinematics and those of the limb(s) to which it is attached could potentially generate forces large enough to cause injury. For certain movements, the bulkiness of the robot may reduce the usable range of motion. Issues of fit for individuals of varying size and shape also have to be considered. Slippage of the device on the limb so that the axis of rotation is no longer aligned with the target joint potentially could lead to injury with activation of the device. Donning and doffing a wearable exoskeletal brace also may pose challenges and require the supervision of a skilled therapist.

Technical issues, such as a lightweight, portable power supply and actuators for wearable exoskeletal robots, remain a work in progress. Some of these devices presently rely on external battery packs to provide enough power. Ideally, such robots would be lightweight, wearable devices that are as unobtrusive as possible. In reality, this goal has not yet been achieved. Actuators for wearable exoskeletal robots that are small, lightweight, durable, and generate sufficient force remain under development. Equally challenging is the need to develop effective and safe control systems for these devices. The use of surface or implantable EMG signals (63) or neural prostheses capable of capturing brain activity (64) all are under exploration and potentially could be applied to control powered orthoses.

Potential Disadvantages and Limitations of Robot-Aided Exercise

Both workstation and wearable robots are used predominantly for providing therapeutic exercise at present. There are many characteristics of the present technology and robot design that might limit the overall application of this type of therapeutic exercise. Generally speaking, existing robots are designed for very specific types of training and are limited in their degrees of freedom of motion. It is unclear whether this also is a clinical limitation, but there are different groups aiming at answering this research question (65,66). For example, the Bionic Leg is limited to actuation of flexion and extension at the knee joint, and does not provide actuators at the hip or ankle. The MIT-Manus robot provides only two degrees of freedom and is designed to provide reaching-type exercises for the shoulder and elbow (15). The MIME robot (5), although providing a larger number of degrees of freedom at the shoulder and elbow, does not include any robotic training for the wrist or hand. The ArmeoPower provides six degrees of freedom in the upper limb using an exoskeletal design, permitting actuated movements for the upper limb in a three-dimensional workspace, although it too lacks actuated hand movements. An alternative strategy is to combine the use of multiple mechanically simpler robotic modules sequentially, analogous to "circuit training" in a gym. This approach also has the advantage of allowing multiple patients to utilize the various devices simultaneously. As stated earlier, the clinical impact of this approach is still being evaluated (67).

Many existing upper-limb robots transmit force to the limb through a single point of contact in the distal limb, rather than exerting force at multiple more proximal limb segments (often termed "end-effector" robots). Examples of this include the MIT-Manus robot with a manipulandum centered at the user's hand, and the G-EO lower-limb robot with moving footplates as the point of contact. These are in contrast to exoskeletal robots that provide control of multiple limb segments, such as the ArmeoPower or Lokomat. Insufficient data exist to determine the relative utility of exoskeletal versus end-effector designs.

Several approaches have been used to assure the safety of robots for use in human exercise training, and a highly favorable safety record has been achieved. The InMotion shoulder–elbow robot uses an impedance-controlled, "back-drivable" system for generating force that provides a highly compliant machine–user interface that allows the user's limb to deviate from the intended movement path while providing a progressive amount of corrective force to help the user achieve the desired position. This approach limits the corrective force and may reduce the risk of injury. Other robots, such as the MIME robot, have used more conventional machine–user interfaces with padding and safety cut-offs. These devices generally are not back-drivable and have a less compliant interaction with the user. Although

not yet broadly used clinically, the robots being used to provide therapeutic exercise appear to have an excellent safety record. Whether such a record can be maintained outside of a carefully controlled research setting remains to be confirmed.

The development of training algorithms for robot-aided exercise remains in its early stages. Because of their programmable nature, there is no limit to the number of ways in which robot-assisted exercise can be designed. Questions remain regarding breaking down exercise tasks into simpler components versus performing more complex exercises, the importance of incorporating virtual environments, the most effective duration and frequency of training, the benefits of resistance training, and many other issues (68,69). Fortunately, the availability of robotic exercise devices provides the scientific tools to answer these questions in the coming years.

Overall, published research on the use of robot-aided exercise after stroke is encouraging but not yet definitive. Differences in robot design and training algorithms make it difficult to compare studies and likely account for the variable results. Training-specific effects on motor function are evident and may be dependent upon dose, device, and training algorithm. Further research should focus on expanding the scope of robot-aided exercise training to incorporate the entire upper limb, and on continuing the exploration of the best training regimens and algorithms based on the individual's movement abilities and goals.

FIGURE 22.12 JACO robot arm (Kinova, Inc.) is a wheelchair-mountable ADL robot arm that assists with reaching and grasping activities.

Robots for ADL Assistance

Computer-based technologic aids have become an important component of assistive technology for individuals with severe disabilities. These devices have been used to aid in communication, to assist with powered mobility, and to assist in ADLs. Appropriately designed robotic devices may be useful to help with manipulating objects in the environment that the user is incapable of manipulating independently.

The iARM robot (Exact Dynamics, Didam, the Netherlands, www.exactdynamics.nl) and the JACO (Kinova, Inc, Montreal, Canada; see Figure 22.12) are robotic arms that mount on a power wheelchair. These robots are controlled by a joystick, keypad, or sip-and-puff interface and can be used to pick up objects from the floor, open a refrigerator door and remove an item, and so on. This type of robotic device potentially is useful for individuals with large brainstem strokes with bilateral weakness, as well as nonstroke conditions such as spinal cord injuries, limb deficiencies, and neuromuscular conditions.

This type of robot arm has a substantial number of degrees of freedom, but accomplishing functional tasks may be slow and complex to master. The absence of proprioceptive feedback is compensated for by the use of visual monitoring of the robot's trajectory and target acquisition. The optimal terminal device (gripper) and force applied during robot grasp remain under study. Existing designs are capable of assisting in feeding, turning light switches on and off, and even opening doorknobs. The psychological benefits of improved ability to manipulate one's own environment appear considerable and are supported by case reports (70,71) and small case series (72). A study of one device found that users could rapidly learn to complete tasks, and an economic analysis suggested potential savings achieved through reduced caregiver hours (73). Novel control mechanisms, including brain–computer interfaces, are being studied in an effort to integrate these devices more closely with the central nervous system (74).

Potential Disadvantages and Limitations of ADL Robots

Technical issues include the absence of sensory feedback when using these devices, thus posing the risk of grasping an object too hard or not hard enough. These robot arm devices are slow and laborious to use and require patience, good perceptual abilities, and well-preserved cognitive abilities to master and use them appropriately. The risk of injury caused by misuse or errors appears small but has not been quantified.

The devices are designed for an intermediate degree of fine motor control. Tasks requiring very fine control, such as writing, or those that are bimanual in nature, are not feasible with the current generation of devices.

Cost is a major consideration for ADL robots, as discussed later (see "Economic Considerations" section). For example, the JACO robot arm costs more than $35,000—a price that places this device outside the affordable range for most patients unless a third-party funding source is available. In contrast to exercise robots, which are typically used for a limited period of time in a therapeutic environment, ADL robots are intended for long-term use in a home setting.

Robotic Walkers

Robotic walkers have been proposed both as therapy aids during gait training and as functional aids during independent ambulation. The Veterans Affairs Personal Adaptive Mobility Aid (VA-PAMAID) is under development as a navigation aid for elderly individuals (75). Successful implementation of this type of robot will have to address issues of cost, weight, complexity, and stability.

Another type of robotic walker has been developed to assist during gait training, the KineAssist (Kinea Design, Evanston, IL; see Figure 22.13). This robot is designed to assist a physical therapist during gait training by providing external stabilization for the patient. The robot does not provide therapy per se, but rather facilitates conventional physical therapy training and reduces the need for additional staff members to provide physical assistance to the patient for safety. The robot is designed for a therapeutic environment rather than for use in the community, although it can be used outdoors on smooth surfaces. Limitations include a large footprint, limiting use to relatively open areas, and cost. Clinical trials have not yet been conducted using this device. Tethered systems that support a user from a track above, such as the Zero-G (Aretech LLC, Ashburn, VA) are another approach to accomplish similar goals that may prove logistically easier.

FIGURE 22.13 KineAssist (Kinea, Inc.) is a mobile robot to assist with gait training. The ability of the device to support a patient when losing balance is shown.

Photo credit: Tom Probst, Movco Media Productions.

ECONOMIC CONSIDERATIONS

In more developed countries, such as the United States, Japan, and Western Europe, there has been a steady downward trend in the cost of technology-based devices, while at the same time labor costs continue to rise. As a result, there has been an ongoing substitution of computer- and robotic-based devices for workers, whenever feasible. Examples of this substitution abound and include the ubiquitous use of automated teller machines instead of bank tellers, the growing use of check-in kiosks in airports rather than airline representatives, and the continued growth of industrial robots in manufacturing to reduce the number of assembly line workers. Medicine is not immune to these trends, although it has been slower to adopt this approach than many other fields. One example of automation is the use of pharmacy dispensing systems that are now widespread in hospitals and help reduce the manual labor involved in managing medication inventories.

This trend of reducing the number of skilled workers required in favor of technological substitutes shows no sign of abating, and the economic forces that drive it are likely to persist or even accelerate. The aging of the population is now a major challenge in Japan, and the shortage of workers to assist older individuals is stimulating Japanese companies to explore devices to help bathe and care for the elderly. The U.S. population is also aging, and shortages of nurses and personal care attendants already plague health care systems in many areas of the United States.

The incorporation of newer technologies in rehabilitation depends on the clinical evidence, their cost, and health insurance coverage for these devices. In particular, assistive technology often is not adequately or not at all reimbursed by third-party payers because of annual caps on payment for "durable medical equipment" or definitions of "medically necessary devices." Although an ADL robot may provide substantial improvements in independence, it is not intended to directly treat the patient's medical condition, and thus may not be considered "medically necessary."

Establishing proof of efficacy for robotic devices remains challenging. Large randomized clinical trials comparing robotic with present rehabilitation techniques and demonstrating clinically meaningful improvement will have to be completed before third-party payers will reimburse their costs. Unfortunately, companies bringing robotic devices to market in the United States and Europe face incentives that discourage the conduct of definitive clinical trials. In the United States, robotic devices have generally achieved FDA clearance using the 510(k) mechanism that permits the sale of these devices without demonstrating safety and efficacy in large controlled clinical trials. The availability of this mechanism, coupled with the limited financial rewards currently achievable in the marketplace from the sale of robotic devices, has prevented most companies from supporting these clinical trials. In the United States, the NIH and foundations typically do not fund these types of studies, leaving a vacuum for the support of definitive clinical trials. Comparative costs for these systems also must

fall substantially or else the economics of incorporating these technologies into rehabilitation will remain unfavorable, unless research demonstrates added value in using these systems over present rehabilitation techniques.

Because of the novelty of therapeutic robots and virtual reality systems, these still are commonly used with direct supervision by a skilled caregiver (typically a physical or occupational therapist). Thus, little of the opportunity for these devices to be truly labor-saving has yet been realized. Over time, it is reasonable to expect that greater familiarity with these devices and simplified user interfaces will allow more autonomous use of technology-aided exercise therapy. Therapy might be provided in a group setting in a "high-tech" gym with a therapy aide providing intermittent supervision or even in a home-based treatment program without the presence of a health care worker during treatment sessions.

The specialized design and limited range of activities that the current generation of devices provides, however, preclude using these devices as substitutes for human-provided therapy, even if they can be operated autonomously. As an example, an upper-limb exercise training robot cannot teach a stroke patient to dress herself or manage her hygiene as an occupational therapist would. Thus, in the intermediate term, the likely role of robots and virtual reality systems is as adjuncts to skilled therapists—perhaps more of a rehabilitation "aide" than "therapist." Genuine cost savings appear to be at least several years in the future, but seem inevitable as the efficiency of delivering these types of therapy improves. Although a preliminary study examining the cost of robotic therapy is encouraging (76), additional studies that are specifically designed to examine cost-effectiveness are needed to determine the appropriate utilization of these technologies.

RESEARCH FRONTIERS

Engineering advances in computer technology and in the implementation of clinical applications is proceeding at a rapid pace. Successful commercialization of one or more robotic and/or virtual reality devices is likely to enhance investment in industrial research and development and further accelerate the rate of change.

As Yogi Berra is alleged to have said, "It's tough to make predictions, especially about the future." Many technological advances in stroke rehabilitation are impossible to foresee at this time.

One key question is the role of complexity in further technology development. Many new consumer technologies have become increasingly complex as new capabilities are added. Stroke survivors often are coping with perceptual and cognitive impairments, and concerns exist regarding their ability to effectively use highly complex systems. Cost concerns also are important, as more complex systems are generally more expensive than simpler systems. Ultimately, clinical trials will be needed to compare different approaches to determine the most effective strategy.

Larger randomized controlled trials of the efficacy of these treatment approaches are needed to validate the preliminary evidence of efficacy seen in smaller studies. Research in the application of technologically based therapies will also have to clarify the relative efficacy and efficiency of strategies that seek to combine complex multiple-limb segment training in a single activity versus training systems that use a more modular approach for training individual limb segments and movements. For example, it is not yet clear if it is better to perform upper-limb exercises incorporating the shoulder, elbow, wrist, and hand in a single movement versus individual exercises for each of these joints. In addition, the relevance and generalizability of robot-trained movements to functional, daily life tasks has not been well addressed in previous studies. It is possible that "hybrid" therapies systematically combining robot-assisted therapies with therapist-generated intervention will prove more effective. Randomized clinical trials will have to demonstrate "clinically meaningful improvement" if robotic therapies are to be accepted and reimbursed as effective therapies.

CONCLUSION

Stroke rehabilitation robots are undergoing a phase of rapid development and testing and are likely to begin to appear in clinical settings on a regular basis within the next few years. Special-purpose devices are likely to remain the mainstay of stroke rehabilitation technology for years to come, given the extraordinary complexity of attempting to create general-purpose rehabilitation devices. Cost considerations and reimbursement issues are likely to grow in importance as the cost/benefit ratio of incorporating these technologies into stroke rehabilitation is debated.

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23

Virtual Reality and Video Games for Stroke Rehabilitation

Judith E. Deutsch

The interest in and application of virtual reality (VR), using virtual environments (VE) and video games, for the examination and rehabilitation of individuals after stroke have grown steadily since the earliest papers published in 1997. A PubMed search (conducted in late 2013) using the terms *VR* and *stroke rehabilitation* yielded 227 references, with fewer than 5 publications per year until 2002, followed by triple that amount in 2006 (see Figure 23.1). This number is likely a slight underestimation, as not all papers on VR can be found in PubMed.

The appeal of VR augmented sensorimotor rehabilitation has been the promise of ecologically valid, intensive task-specific training (1), concurrent with multisensory training that would transfer from the virtual world to the real world (2). Additionally, some have suggested that VR could deliver training intensity (repetitions and duration) associated with neuroplasticity and positive behavioral adaptations (3) because it is particularly well suited to very high training doses (4,5). Relatively recent reviews of the field have shown that promise to have been partially met for recovery of upper-limb function in people after stroke (6,7), as did a more recent review (8) and meta-analysis that identified moderate improvements across the ICF domains for upper-limb function, walking, and balance for people after stroke (9).

VR augmented rehabilitation for people after stroke has been delivered using different technologies and for a range of purposes. Video games that are designed for entertainment, labeled either *commercial-off-the-shelf* (COTs) or *active video games* (AVGs), when applied to rehabilitation are often called VR. In this chapter, we describe VR systems (both customized and commercially available) and video games, and evaluate their application for sensorimotor rehabilitation of the upper-limb function and walking. We begin with relevant definitions of VR and an explanation of the VR delivery systems and conclude with the evidence to support their application.

IMPORTANT DEFINITIONS

Virtual Reality

VR has been defined as a computer-synthesized three-dimensional graphical environment created from numerical data (10) that is enhanced by visual, aural, and haptic devices, so that the human operator can experience the environment as real (11). From a rehabilitation perspective, it is the interactivity of the VR system that is important. A VR system consists of hardware and software. The hardware serves as an input, recording and transmitting movement into the VE that is animated by the software.

Simulation or VE or Game

Simulation or *VE* or *game* consists of task(s) performed by the user in the environment(s) with specific feedback. This could be knowledge of results or knowledge of performance (12). It occurs in the form of summary feedback at the end of the simulation, VE, or game. Research comparing the effects of training with a robot alone to those yielded by coupling the robot with VR demonstrated the latter to be far superior in transfer of training to over-ground walking (13). These findings underline the importance of the VE and its content as key elements in successful VR systems.

Avatar

An *avatar* is the graphical representation (often in three dimensions) of the person interacting with the VE, also called the user's *character* (14). The avatar can be customized to look like the user, creating a greater sense of agency or connection to the game. An avatar may be represented in a first- or third-person perspective. In the third-person perspective, one appears to be looking at oneself from the outside (either the front, back, or side). In the first-person perspective, one appears to be looking from the inside of the character; for example, users might see their feet stepping on a walkway, or their arms as they interact with objects in the VE.

Presence and Immersion

VEs are created to afford the user the sensation of being present and/or immersed in the environment. The term *(tele)-presence* was first used in this context by Minsky (15), who defined it as a sense of "being there." Minsky wondered

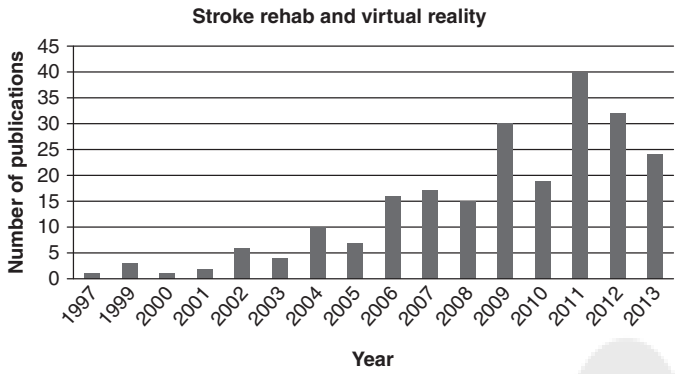

FIGURE 23.1 Number of publications on virutal reality and stroke organized by year.

whether tele-presence could be a true substitute for the real thing and if one could couple artificial devices naturally and comfortably to work together with the sensory mechanisms of human organisms (15). A more recent discussion by Lee (16) posited that presence is a psychological construct dealing with the perceptual process of technology-generated stimuli. He categorizes presence, based on the way humans experience the world in three domains, as physical, social, and self. It follows that users interact within virtual worlds through one or more of these domains. As a result, their experiences extend from their sense of presence as they relate to each of these domains. In the context of rehabilitation, Gaggoli and Riva describe presence as having two roles: locating the self in an external physical and/or cultural space and providing feedback to the self about the status of its activity (11, p. 8). This definition suggests that presence allows for interactivity and that action is more important than perception. Therefore, the well-designed VE makes a trade-off between perceptual realism and naturalness of interaction (11, p. 17).

From a practical standpoint, presence is a construct that can be measured. The experience and intensity of presence in a VE is a function of both individual differences and the characteristics of the VE. Thus, Witmer and Singer developed a Presence Questionnaire (PQ) and an Immersive Tendencies Questionnaire (ITQ) to address both the VE and user factors associated with presence (17). The PQ defines presence as a combination of immersion, a "psychological state in which you can interact with an environment that provides a constant stream of stimuli and experiences" (17, p. 227), and involvement, a "psychological state that is experienced as a consequence of focusing one's energy and attention on a coherent set of stimuli or meaningfully related activities and events" (17, p. 227). In other words, salience and interactivity are measures associated with presence.

Immersion

Immersion, defined as a state in which one can interact with an environment (17), is linearly related to presence. VR systems are described on a continuum of nonimmersive to highly immersive. Immersion is, in part, achieved by blocking out stimuli in the real world that may distract the user from interacting with the VE. Thus, hardware used to visualize the environment, such as a head-mounted display (HMD), would block the viewer's external view and be highly immersive, in contrast to a desktop computer display, where the viewer is looking into the environment, making the experience less immersive. Furthermore, the more natural the interface is with the VE, the more likely the user is to be immersed. Thus, one might hypothesize that a system that reads one's movement into a VE with great fidelity would be more immersive than one that distorts the movement.

The relevance of the VE, the specific hardware used to deliver the VE, and the user's personal qualities all interact to create a sense of presence and immersion. Rand and colleagues demonstrated that presence, for a group of healthy people ranging in age from 16 to 75 years, was an interaction between the simulation, the hardware used to deliver the VE, and the user's personal characteristics (18). Therefore, the degree of immersion based on the delivery method is only one important variable. Importantly, Rand's group also demonstrated that after stroke, individuals could be present in a VE, even when these environments would be defined as semi-immersive (19). From a rehabilitation perspective, we seek to have the user immersed and present in the environment.

VR TECHNOLOGY SYSTEMS

VR systems typically consist of hardware interfaced into the VE, equipment used to display the VE, and software that controls the system and creates the VE. The hardware interface collects movement data (the input into the system) using cameras, sensorized gloves, and/or robotic exoskeletons. The equipment used to present the visual information from the VE (outputs) can be (from less to more immersive) a desktop computer, television screen, a rear-projected single or multiple screens, or a HMD. The sensation of touch (haptic) that augments the visual and auditory stimuli is delivered using an exoskeleton, or a robotic interface, or (in the case of a mixed reality system), a real-world object. The sense of touch facilitates the addition of physical task parameters, such as rendering of environmental obstacles as well as provision of global forces such as gravity. Haptics also provide forces that produce biomechanical and neuromuscular interactions in the VE that approximate real-world movements better than the visual information alone (4). Finally, the simulation or VE is typically a three-dimensional animation that requires user interaction. For sensorimotor rehabilitation, the interaction requires the user's head, limb, or total body movements; for cognitive tasks, the interaction may be achieved with a keyboard or a joystick interface. For additional information on VR augmented sensorimotor systems, the reader is referred to references (5) and (20).

Systems are often categorized by their sensing elements. These may be grouped into two large categories: camera-based and sensor-based (with or without haptics) systems.

FIGURE 23.2 IREX motion capture system: on the left, participant is detected by the camera and placed into the VE. On the right, the participant's view of herself in the VE interacting with virtual objects.

Source: Reproduced with permission from GestureTek. http://www.gesturetekhealth.com/products-rehab-irex.php

Camera-Based Systems

Camera-based systems are referred to as *motion* or *video capture systems*. They capture motion using a single camera or multiple cameras. They detect motion by color, markers, or the outline of the human body and then reconstruct the images and represent them with an avatar, or capture the user's image and place the person in the environment. The system first developed for rehabilitation was GestureTek's IREX (see Figure 23.2). It uses a chroma key background, and the user's image is placed into a VE facing out. The user then watches his or her own image as he or she interacts with the VE. Weiss and colleagues reviewed the history of this system and the PS2™ (described in the following text) and their application in rehabilitation (21). The CAREN is an eight-camera system that tracks motion and displays the VE on a large rear-projected screen using the first-person perspective (see Figure 23.3). This system integrates motion capability by using a treadmill. Both of these systems are commercially available.

In addition to commercially available systems like the IREX and the CAREN, researchers have designed other systems for rehabilitation of people after stroke. Jaffee and Brown, for example, used a camera to track lower-extremity movements and display them to the user in a sagittal view on a HMD (see Figure 23.4) (22). There are also several variations of the treadmill systems to promote ambulation, which have environments rear-projected on three screens (23) or tracked by a head marker and displayed on a television screen (24).

FIGURE 23.3 CAREN system with a rear-projected environment on a curved screen. Participants ambulate on the treadmill and are detected by the cameras. In this simulation the participants have a first-person perspective.

Source: Reprinted with permission from MotekMedical. http://www.motekmedical.com/products/caren

Sensor-Based (Haptic) Systems

Sensor-based (haptic) systems use an exoskeleton or an instrumented robotic interface to sense motion and represent it in the VE. These systems can incorporate the sense of touch (haptics), further augmenting visual and auditory feedback. Commercially available systems that use endpoint control such as the Haptic Master have been incorporated into VE systems targeting the upper limb (see Figure 23.5). Other systems use robotic exoskeletons, one for locomotion (Lokomat) and the other for upper-limb movement (Armeo), and have interfaced their systems with VE (see Chapter 22 on robotics). A glove with sensing capabilities can be used to reproduce hand motions, such as illustrated in Figure 23.6 with a piano-playing simulation. An instrumented steward platform has been used to sense ankle and foot motion in the Rutgers Ankle Rehabilitation System (see Figure 23.7).

FIGURE 23.4 Participant using a head-mounted display (HMD) (left) to see a sagittal view of the leg as it is clearing an obstacle. The moving image of the leg is being captured by a single camera (right).

Source: Reprinted with permission from David L. Jaffe.

COMMERCIAL OFF-THE-SHELF VIDEO GAMES (COTS)

Motion-sensing video game consoles transformed video game play and have provided a low-cost option for introducing VR into the clinical environment. Using technology identical to the IREX system but at a much lower cost, the earliest COT video capture system was the Sony PlayStation 2™ with its camera the EyeToy™ (see Figure 23.8). Similar to the IREX, the user sees his or her image in the VE and can interact with virtual objects. The first studies that evaluated the feasibility of using video games for stroke rehabilitation were performed with the PlayStation 2™ and the EyeToy™ camera (19,25–27). Participants' engagement was measured and found to be positive (25); a single patient was able to use it for upper-limb and balance rehab in her home (26). Additionally, individuals in the chronic phase after stroke who were at a higher functional level had more meaningful game play than those in the subacute phase (19); however, subacute patients benefited from the addition of the games for their upper-limb movement and self-care, compared to a group of patients who just watched the EyeToy™ games (27). These early papers were met with

FIGURE 23.5 Participant using shutter glasses to view a three-dimensional simulation on a desktop computer. The haptic master with a dongle is the interface into the VE. The haptic master can render the haptic.

Source: Reproduced with permission of Sergei Adamovich, with photo credit to Larry Levanti.

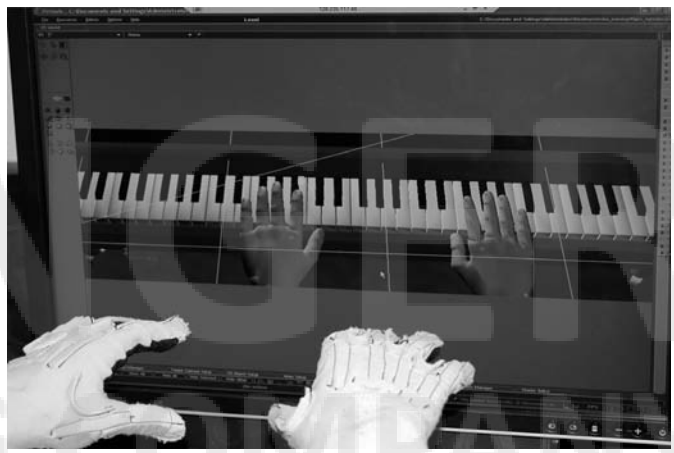

FIGURE 23.6 This sensorized glove system is reading hand motions into a virtual piano simulation.

Source: Reproduced with permission of Sergei Adamovich, with photo credit to Larry Levanti.

FIGURE 23.7 Rutgers ankle rehabilitation system: an instrumented robotic interface maps the movements of the lower extremity into a virtual seascape. The platform is programmed to provide haptic feedback.

Source: Reprinted with permission of Rivers Lab and Rutgers University.

mixed reviews. The main complaint was the lack of control over the game play, which differs from that afforded by systems designed for rehabilitation (21).

The introduction of the Nintendo Wii™ console and Wii Sports™ games in 2007 provided motion-sensing capabilities similar to haptic-based interfaces (Figure 23.9). The controller or Wiimote™ is instrumented with an accelerometer that reads the upper-limb gross movements. A vibratory element in the Wiimote™ provides a haptic sensation when an object is contacted. The Wii-Fit™, introduced in 2009, added a force platform as a user interface. Validation of that platform's (28,29) measurement capabilities and software to track improvements made it an appealing tool for rehabilitation of balance.

The Microsoft Xbox™ with its Kinect™ motion-tracking sensor, released in 2010, is the most recent motion-sensing console used for rehabilitation (30). The system uses an infrared projector, camera, and a special chip to track the movement of objects and individuals in three dimensions (31). It has been reported to have greater precision than the PS2™ and offers a variety of games such as Kinect Adventures!™ and Kinect Sports™ that may be applied to rehabilitation.

FIGURE 23.8 Sony PlayStation 2™ Slim Console with the Sony EyeToy™ camera.

Source: Reproduced with permission from Wikimedia Commons.

FIGURE 23.9 Poststroke participant playing the Nintendo Wii™ boxing game while having his oxygen consumption measured.

Source: Reprinted with permission of Rivers Lab.

UPPER-LIMB SENSORIMOTOR REHABILITATION

Customized VR Systems

Both upper-limb specific (4,7,32) and field overview reviews (8,9) have summarized the state of the field. The early reviews primarily included pre- and posttest single group studies that documented both motor impairment and motor function improvements with both camera-based and haptic-sensor-based systems (7). More recent work on comparative efficacy studies (6,8,9) finds a consistent but modest benefit of VR over standard of care.

Camera-based motion studies of the upper limb used commercial systems like the IREX and CAREN (33,34). Sensor-based motion capture systems of the upper limb used commercially available hardware like the phantom (35), Amadeo (36), and the Armeo (37,38), as well as many customized systems that used magnetic trackers (39–43); and pneumatic gloves as inputs into the VE (44). Haptics have been incorporated into several of the sensor-based motion capture systems (35,36,38,43,44). Mixed reality systems incorporated use of real-world objects (39–41).

The types of tasks used by the investigators studying upper-limb movements involved reaching, transport, and, in some cases, selective finger movement (36,45). Simulations consist of real-world tasks and game-based activities. Examples of real-world tasks included putting envelopes in a mailbox, or breaking eggs (40), or reaching for objects in a virtual supermarket (34). Examples of game-based tasks included intercepting flying spheres (43).

The findings across all of these studies is that VR augmented systems have a modestly positive outcome when compared to standard of care (6,9). The participants are predominantly in the chronic phase after stroke (more than six months), with a few exceptions for work with acute and subacute (less than three months) participants (43) (33,36). The predominance of positive outcomes is at the body function and activity level, with little or nothing reported on participation (9).

Fluet and Deutsch (8) synthesized the controlled trials on upper-limb studies that were published after the VR Cochrane review (6) and made several interesting observations. In the eight studies the authors analyzed, they found that reaching simulations consistently improved reaching, and game-based simulations produced less specific outcomes. This suggests that specificity of training is relevant in VEs. For studies that compared training with and without haptics (38,44), there was only a small additive effect of having the haptics. Thus, the value of adding haptics, with all the technical challenges it involves, remains an unanswered question in the field (8). Widespread adoption of these systems is also currently not possible because many of them are not commercially available.

Commercial Off-the-Shelf (COTs)

The low cost of the COTs makes them appealing as alternatives to the custom VR systems. All three consoles, the PS2™ with the EyeToy™ camera, the Nintendo Wii Sports™, and the Xbox Kinect™, have been used in upper-limb rehabilitation. The early work with PS2™ included a randomized controlled trial by Yavuzer (27) in which playing PS2™ games was compared to watching PS2™ games for people with motor recovery of Brunnstrom Stage II. The PS2™ was played for 30 minutes, 5 times a week, in addition to the

standard of care which ranged between 2 to 5 hours, 5 days a week. Outcomes measured by the self-care items of the FIM showed significantly better scores both at pretest and at follow-up for the group that played the games.

Several investigators have used the Wii for upper-limb poststroke rehabilitation, both with acute (46,47) and chronic (48) participants with moderate motor control. The study with the highest level of evidence (2b on the Oxford Center for Evidence Based Medicine; CEBM) compared playing table-top games that involved upper-limb use such as playing cards to Wii-based games. Both groups were seen in recreational therapy for 60 minutes, once a day, over 2 weeks. Both groups improved on the Wolf-Motor Function (WMFT) test at posttest and follow up. There were, however, no significant differences between the groups (47). The other two studies measured improvements in upper-limb function on the Fugl-Meyer (FM) scores and WMFT, but they had a lower level of evidence (CEBM 4) (46,48).

Two recently published trials by the same group of investigators (49,50) examined the Kinect™ games applied to upper-limb rehabilitation and ADLs. They showed that the addition of the Sports and Adventures! games to standard of care, during a six-week intervention, for individuals on an average seven months after stroke, was superior to standard of care alone in improving upper-extremity FM score, performance on the Box and Blocks, and active range of motion of proximal joints (50). Regrettably, both studies compared the addition of the Kinect games to standard of care, resulting in greater treatment time for the experimental group. However, their findings do suggest a specificity of training, with results seen primarily for the gross movements of the upper limb and not more selective distal movements or ADL.

In addition to the feasibility studies, two validation studies on the use of the video games have shed some light on the promise of exercise intensity relative to standard of care. First, the amount of upper-limb use by people after stroke was compared while they played with the Wii™ and the PS2™, with significantly greater movement reported for the PS2™. The PlayStation 2™ EyeToy™ group produced an average of 302.5 (228.1) upper-extremity active movements and 189.3 (98.3) weight shifts, significantly higher than the Nintendo Wii™ group, which produced an average of 61.9 (65.7) upper-extremity active movements and 109.7 (78.5) weight shifts. No significant differences were found in steps and other lower-extremity active movements between the two systems (51). In the second, Rand and colleagues (52) reported that the number of repetitions of purposeful movement with the Kinect group (median 271) compared to a standard-of-care group (48 repetitions) was more than five times greater. Further, these movements were tracked with a three-dimensional accelerometer and the game was played at a higher velocity, which the researchers interpreted as being of greater intensity (52). Motion capture systems, like the PS2™ and the Kinect™, appear to promote greater activity than the Nintendo Wii™ sensor-based haptics games that use a handheld controller.

To summarize: There is modest evidence (2b-4) that COTs are effective in improving limb function for people after stroke, but they are not superior to standard of care. The most robust findings were for people with acute (47) and subacute (27) strokes. Most participants presented with low levels of motor control. The addition of playing video games targeted at joint motion on the PS2™, Wii™, and Kinect™ between 8 to 10 hours, in addition to rehabilitation, improved upper-limb activity. Given their high levels of activity, individuals with mild impairment appear to generate sufficient movement with high acceleration that may be beneficial for upper-limb recovery (52).

WALKING AND BALANCE REHABILITATION

VR Systems

Use of customized VEs for walking recovery and balance has been reported in several topic-specific reviews (53–55) as well as in overview reviews (6,8,9). The volume of work is more modest compared to the upper-limb VR work. This may in part be explained by the physical and safety challenges of building walking systems, as well as the fact that most people after stroke recover walking to a greater extent than their upper-limb control. Most of the studies have involved the use of a treadmill augmented with the VE, or a real-world video recording (56), typically displayed on one (57) or several rear-projected screens (23) or on a television screen (24). Two groups used a HMD for their display (22,58). The remaining studies trained gait-related activities using either the IREX motion capture system (59–61), a standing frame both in the clinic and at home (62), or a lower-extremity robot interfaced with a VE displayed on a computer screen (13,63).

What the research has in common is that the simulations have rich feedback, and generally positive outcomes are being reported. In a motor learning review by Imam and Juras (55), the authors reported that lower-extremity studies provided external focus of attention, with variable and unpredictable practice. The outcomes are typically gait speed, balance, and balance confidence measures. The positive walking and balance outcomes represent a transfer of training in VR to walking. For the studies that are not task-specific, the investigators did not train gait directly (13,59), and the doses (repetitions) are much higher than for the task-specific training. Four of the studies (57,59–61) used commercially available technology, though the remaining research groups developed their own systems. One group demonstrated the feasibility of training both in the clinics and at home using tele-rehabiliation (62). Cost and system availability are barriers to the positive transfer of training from VR to walking and, consequently, translation of real-world findings into clinical practice. This has prompted the exploration of COTs as an alternative to VR systems.

COTs for Balance and Mobility

Very few studies have employed COTs for balance and mobility training of people after stroke. Several case reports of people with chronic symptoms after stroke report

positive outcomes of balance and mobility training (26,64). Four pilot trials have been reported in this area, three for people in the chronic phase (65–67) and the other for people in the acute phase (68). Studies were executed primarily with the Nintendo Wii™, using the Fit™ games, although one study used both the Wii™ and the PS2™ (66).

Two of the trials had active control groups (65,68). Bower and colleagues (68) reported trends toward improved balance in the Wii Fit Plus balance group while no changes were observed in the control group, who played Wii-Resort games in sitting. In contrast, Deutsch and colleagues (65) reported no between-group differences, but a greater number of within-group improvements for balance and mobility measures for people in the standard-of-care group.

The importance of these two trials is the care taken in designing the control groups. Bower and colleagues had a game control group, so it was easier to isolate the specific effects of the type of game. Deutsch and colleagues ensured that comparable categories of exercise—warm-up, sitting, and standing balance and choice of games or tasks—organized the therapy in each group. They found, however, that the video game group had a limited selection of games that might have addressed their primary therapeutic goals. Customization of the plan of care was easier in the standard-of-care group. Although it is likely that video games will not be found superior to standard of care, the question of how best to incorporate them remains.

FIGURE 23.10 The Virtual Reality Augmented Cycling Kit (VRACK) converts a regular bicycle into a VR augmented cycle. It uses heart rate and pedal forces as inputs into the VE to promote both fitness and motor control.

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ACTIVITY PROMOTION

Implementation of movement-based VR systems has focused on sensorimotor rehabilitation, but there is an emerging application to fitness promotion in persons with disability secondary to stroke. Given the importance of physical activity (69) and the barriers to exercise encountered by people after stroke (70), VR is proposed as a facilitator of activity. There is a customized VR augmented cycling system that uses heart as an input to the VE. The Virtual Reality Augmented Cycling Kit (VRACK) is designed to convert any bicycle into a VR augmented system (71) (see Figure 23.10). Preliminary findings indicate that people after stroke (n = 4), who used the system for one hour, two times a week for eight weeks, demonstrated significant improvements in VO_2 max and mobility outcomes (72). Although the treadmill-based VR systems used to improve walking did not assess cardiorespiratory improvements, this is a possible future application.

In addition to their use as movement re-education tools, the games' activity-promoting capabilities have been explored for people after stroke. COTs that are designed to promote activity are called AVGs. Hurkmans characterized two predominantly upper-limb Wii games (tennis and boxing) and reported that they produced moderate exercise intensity (73). Kafri and colleagues, in a case-control series, compared the energy expenditure and exercise intensity between individuals after stroke with moderate deficits to semi-active healthy matched controls, while playing both Kinect and Wii games in sitting and standing positions (74). The games were selected hierarchically from least effort required from a standing balance task to upper-limb predominant (boxing) and lower-limb predominant (running). Generally, individuals after stroke had lower energy expenditure (at the low end of moderate) compared to the healthy controls (moderate to low end of vigorous), at similar exercise intensity. It appears that individuals after stroke are unable to expend as much energy, possibly due to lower muscle mass and incoordination to sustain the movements. Interestingly, when compared by the matched activities typically performed in therapy (such as a standing reaching task with the standing balance Penguin game), the games had lower energy expenditure. However, the games may be a tool for activity promotion, given their potential to increase motivation for exercise and to promote adherence.

CONCLUSIONS

The use of VR systems for sensorimotor rehabilitation and fitness promotion has grown from a novelty to a partial reality. Generally positive outcomes are reported for the custom VR systems at the body-function and activity levels. The quantity of the evidence is smaller for COTs and the findings for efficacy less robust. However, their low-cost makes them appealing. All systems have the provision of feedback and multisensory stimuli. The participant profile, dose, addition of haptics, superiority of customized systems compared to video games, fidelity of movements in the VE compared to real-world

movements, and the degree of immersion needed to produce positive outcomes remain unresolved questions in the field. Recent events, such as the purchase of Oculus Rift, a HMD that projects VEs, by Facebook, may reduce the cost of technology and allow for quicker translation of the technology into practice. In addition, the efforts to build games for rehabilitation for the commercially available consoles may bring the application of VR technology into the forefront of stroke rehabilitation.

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24

Walking Recovery and Rehabilitation After Stroke

Sara J. Mulroy, Steven A. Kautz, and Katherine J. Sullivan

Motor control deficits are a common manifestation of and a major contributor to walking disability after stroke. As a result, limitations in mobility related to walking are evident in 75% of individuals who sustain a stroke (1). During the first 6 weeks after stroke, the majority of stroke survivors will regain some ability to walk; however, 40% will have severe motor impairment that restricts functional walking to household ambulation. For those with mild to moderate motor impairment, independent walking ability is likely, but of those who achieve physical independence in walking, 60% will be limited to community ambulation (2). Furthermore, motor impairments that limit walking ability contribute to balance deficits after stroke (see Chapter 25). Individuals who have mild to moderate motor impairment and are functional ambulators after stroke have a 73% incidence of falls within the first 6 months after stroke (3,4). This culminates in a fourfold increase in falls risk after stroke and among those who fall, a tenfold increase in hip fracture.

The greatest predictor of community ambulation and participation in home and community mobility is walking speed (5). Perry et al. conducted a cross-sectional study of individuals with gait impairments after chronic stroke and classified them into one of six functional walking categories based on the degree of community ambulation and social interaction (5). The most significant difference between groups was preferred walking speed, with mean speeds ranging from slower than 0.4 m/s for household walkers, 0.4 to 0.8 m/s for limited community walkers, and faster than 0.8 m/s for unlimited community walkers. As expected, the higher the amount of community ambulation ability, the more likely one was to participate in social activities such as family outings, grocery shopping, going to church, and so on. However, achieving the break point of faster than 0.8 m/s (1.8 mph) in walking speed only represents 60% of what is normal for most healthy adults (6). Thus, the functional impact of walking impairment after stroke is significant. Activity outcome measures of walking function such as the Barthel index (BI) (7) or the functional independence measure (FIM) (7) are poor indicators of community mobility and participation after stroke because the majority of stroke survivors can achieve high BI or FIM scores (i.e., independent walking 10 meters or less) without any consideration of walking speed (8).

The impact of motor control impairments and walking disability extends beyond the acute and subacute phases to the chronic phase after stroke. Poststroke, lower-extremity, motor control deficits contribute to specific lower-extremity primary and secondary motor impairments and activity restrictions that impact balance ability and walking skills and increase the risk of secondary complications related to impaired walking ability such as an increased risk of falls and hip fracture, and, ultimately, mobility limitations that restrict participation across the lifespan for an individual after stroke. Walking recovery and rehabilitation after stroke includes therapeutic strategies that are designed to address the complicated and multivariate predictors of walking function. The overall purpose of this chapter is to describe all of the following:

1. Biomechanical features of poststroke walking impairment
2. Primary and secondary motor impairments and recovery factors that contribute to activity restrictions in the acute and chronic phases after stroke
3. Effects of stroke severity (i.e., severe compared to mild–moderate sensorimotor impairment) and secondary impairments on walking outcomes
4. Rehabilitation interventions for poststroke walking recovery that are currently being used in practice to address the sensorimotor sequelae of stroke

BIOMECHANICS OF POSTSTROKE GAIT

Stroke results in a constellation of sensorimotor impairments such as weakness, impaired selective motor control, spasticity, and proprioceptive deficits that interfere with the typically invariant features of normal adult gait. There is a wide range of walking ability after stroke that depends on the severity of these sensorimotor impairments. After stroke, there are obvious gait deviations apparent during observational gait analysis. Biomechanical gait characteristics such as spatiotemporal features (i.e., interlimb symmetry), kinematics (i.e., joint motion relationships within and between limbs), and kinetics (i.e., forces required for stance and forward progression) can be quantified in an appropriately instrumented gait lab. This section describes the biomechanical features of

poststroke gait because biomechanical analysis is an essential element for understanding the mechanisms of walking recovery and responsiveness to specific walking rehabilitation interventions.

Changes in Temporal Gait Characteristics

Although asymmetry is a dominant characteristic of hemiparetic walking, the heterogeneity of the hemiparetic population has made it difficult to develop an integrative understanding of how spatiotemporal asymmetry is related to the underlying impairments. There are a multitude of variables that have been used to quantify spatiotemporal asymmetry, and inconsistent reporting of important variables has limited our understanding of the basis of asymmetry. For example, temporal asymmetry is often reported, whereas spatial asymmetry is not (or vice versa), with few studies reporting both variables in detail. Additionally, the general speed dependence of spatiotemporal characteristics must also be considered when interpreting hemiparetic spatiotemporal data (9) because most persons with hemiparesis walk slowly with an altered stride length and/or cadence. Despite all of the complications that have limited a more detailed understanding of hemiparetic spatiotemporal asymmetry, some general relationships are beginning to emerge.

For example, walking speed is determined by a combination of cadence and stride length (distance between consecutive foot placements of the same foot in the direction of progression). Although both are reduced in hemiparetic walking when compared to nonimpaired persons walking at their self-selected speed (10), neither appears to be consistently different when compared to nonimpaired persons walking at the same speed (9). This is likely explained by the mechanical constraints of walking and the required symmetry imposed by the definition of stride length and cadence. Hemiparetic subjects differ most dramatically from nonimpaired individuals walking at the same speed in the spatiotemporal measures that indicate interlimb asymmetry.

There are two main temporal asymmetries in hemiparetic walking. First, it has been consistently reported that persons with hemiparesis spend significantly more time in stance phase on the nonparetic leg (non-PP) than on the PP (10,11). Note that this also requires that they spend significantly more time in swing phase on the PP than on the non-PP. Second, it has been somewhat less consistently reported that the double support phase preceding PP foot-off (which we will define as paretic preswing) is longer in duration than is the initial PP double support phase (which we will define as paretic weight acceptance). Olney et al. found an average increase in duration for 32 persons (25% vs. 20% of the gait cycle) (12). Similarly, de Quervain et al. also found that the paretic pre-swing phase was prolonged for 18 persons (13). However, Goldie et al. reported no significant differences in the duration of the two double support phases in a group of 42 persons (9).

The main spatial asymmetry of hemiparetic walking is characterized by differences in the paretic and nonparetic step length (i.e., paretic step length is the distance in the direction of progression that the paretic foot is placed in front of the non-PP, and vice versa for nonparetic step length). Although many studies have reported that on average the paretic step length is longer than the nonparetic step length, these studies typically find substantial variability in that some persons with hemiparesis exhibit substantial asymmetry in the opposite direction. Until recently there has been no mechanistic explanation advanced to explain this variability.

In a recent study, Balasubramanian et al. found that step length asymmetry was related to propulsive force generation during hemiparetic walking (14). Propulsive force generation was quantified from the forward directed component of the horizontal ground reaction forces (GRFs) by the time integral of the propulsive GRF (positive area under the GRF versus time curve), because it is that impulse that acts to accelerate the body forward. Paretic propulsion in particular is defined as the proportion of the total propulsive impulse produced by the PP (i.e., impulse of PP divided by sum of the impulses of the paretic and non-PPs). Paretic step ratio is used to quantify step-length asymmetry and is similarly defined as step length of the PP divided by sum of the step lengths of the PPs and non-PPs. Specifically, these authors found that the subjects who generated the least paretic propulsion walked with relatively longer paretic steps, suggesting that increased propulsion by the non-PP may be one mechanism contributing to production of a longer paretic step (Figure 24.1). Further, those with more severe hemiparesis (those dependent on abnormal flexor and extensor synergies) walk with the longest paretic steps

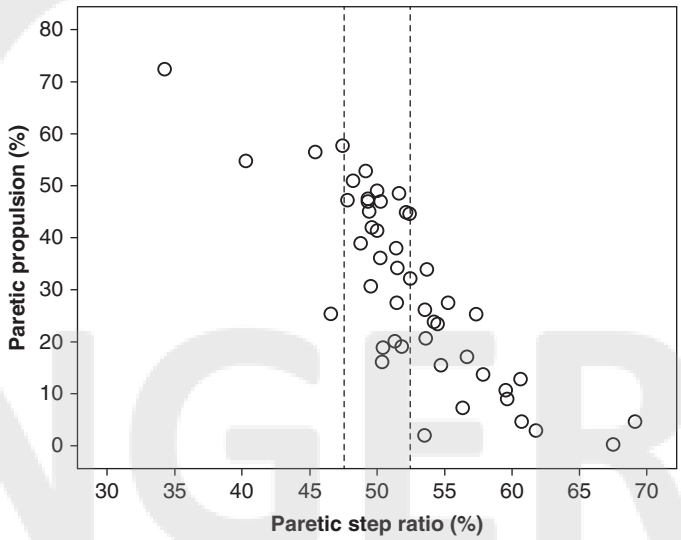

FIGURE 24.1 There is a strong relationship between step length asymmetry and paretic propulsion ($r = –0.83$, $P = .001$). Subjects with a longer paretic step generate less propulsion with their PP.

Source: Modified from Ref. (14). Balasubramanian CK, Bowden MG, Neptune RR, et al. Relationship between step length asymmetry and walking performance in subjects with chronic hemiparesis. *Arch Phys Med Rehabil*. 2007;88:43–49.

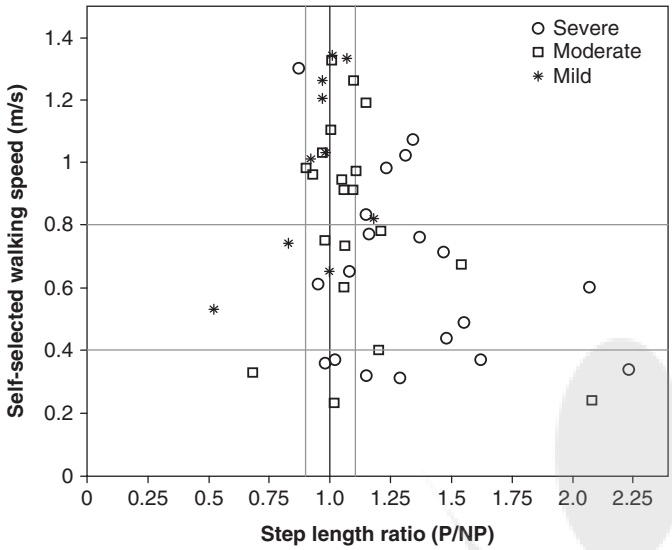

FIGURE 24.2 Relationship between step length asymmetry, walking speed, and hemiparetic severity. The solid black vertical line indicates symmetric steps (SLR), vertical gray lines indicate the SLR subdivisions at SLR = 0.9 and SLR = 1.1. Horizontal lines indicate subdivisions of walking speeds (< 0.4 m/s, house hold walkers; 0.4–0.8 m/s, limited community walkers; > 0.8 m/s, community walkers). Note that subjects with different SLR walk at all levels of walking speeds, yet the majority of those with severe hemiparesis walk asymmetrically at SLR greater than 1.1.

Source: From Ref. (14). Balasubramanian CK, Bowden MG, Neptune RR, et al. Relationship between step length asymmetry and walking performance in subjects with chronic hemiparesis. *Arch Phys Med Rehabil.* 2007;88:43–49.

relative to nonparetic (Figure 24.2). However, these results indicated that asymmetrical step lengths do not necessarily limit the self-selected walking speed (i.e., some subjects with longer paretic steps walk faster), likely because there is compensatory generation of propulsion by the non-PP.

Changes in Kinematic Parameters

The kinematics of hemiparetic walking are altered in both legs relative to healthy walking, with the changes being necessarily consistent with the slower speed, slower cadence, and greater asymmetry of hemiparetic walking. Paretic hip motion becomes more abnormal during preswing as self-selected walking speed declines (13). De Quervain et al. found that of 12 subjects studied after stroke, seven with severe hemiparesis did not begin hip flexion until toe-off, five more did not begin hip flexion until the last third of preswing, and in the subjects with moderate hemiparesis, beginning hip flexion occurred at the midpoint of preswing (13). In contrast, the timing of nonparetic hip flexion was normal in even the slowest walkers. Ankle kinematics may also be important for the performance of paretic preswing because peak plantarflexion is less than in normal walking, even when the ankle is in a more plantarflexed (i.e., equinus) position throughout much of stance (13). Nine of twelve subjects with severe hemiparesis were found to have little or no plantarflexion in preswing (13).

Two studies performed detailed analyses in persons very early in the recovery phase (13,15). Using the kinematic data, both studies classified subgroups of hemiparetic subjects with similar characteristics. Based on visual identification of common patterns of knee and ankle motion coupling, De Quervain et al. classified 18 subjects into four groups (13). Mulroy et al. used a nonhierarchical cluster analysis based on spatiotemporal characteristics and peak sagittal plane joint angles for each gait cycle phase and classified 47 subjects into four groups (15).

Subjects with slow walking speeds (i.e., severe hemiparesis) demonstrated more variable kinematics; however, similar kinematic patterns are described in the two studies. The "extension thrust" pattern described by De Quervain et al. was very similar to the "extended" pattern described by Mulroy et al. with increased ankle plantarflexion and knee hyperextension throughout stance, inadequate ankle dorsiflexion in preswing, and inadequate knee flexion in swing. Similarly, the "buckling-knee" pattern described by De Quervain et al. was similar to the "flexed" pattern described by Mulroy et al. with greatly increased ankle dorsiflexion and knee flexion throughout stance, decreased thigh extension in preswing, and decreased ankle dorsiflexion in swing. De Quervain et al. also described a "stiff-knee" pattern in which knee flexion remained constant throughout the stance at an angle of 20° to 30° of flexion in combination with decreased ankle dorsiflexion. Mulroy et al. did not identify any subjects who exhibited a similar "stiff-knee" pattern in the acute poststroke phase. Neither study identified a group of subjects with a fixed equinus deformity at this early stage of recovery, although others have reported it to be a major impairment during the later phases of recovery (16).

The kinematics of subjects who exhibit moderate to fast walking speeds (i.e., moderate to mild severity) tend to be more similar to those of nondisabled walkers, although some who are classified as the "extended" or "flexed" groups by Mulroy et al. are able to walk at these higher speeds. Mulroy et al. classified subjects into a "moderate" and "fast" group within this range, with the main difference being increased knee flexion in stance and decreased thigh extension and plantarflexion in preswing for the "moderate" group as compared to the "fast" group. De Quervain et al. appear to have combined these two groups into a single group, with intermediate characteristics.

The kinematics of the non-PP differ from the normal in a much more consistent fashion than did those of the PP. Hip angles seem generally consistent with nondisabled walking at slower speeds with a shorter stride (13,17). Those walking slowly tended to show the biggest differences at the ankle, where dorsiflexion in late stance is increased and the ankle plantarflexion in preswing is decreased or absent.

Changes in Kinetic Parameters

Generally, the GRFs and joint kinetics in hemiparetic walking are infrequently reported. This is beginning to change as

instrumented treadmills become more common and available for stroke research. An instrumented treadmill provides exceptional benefits for understanding of hemiparetic walking, such as the ability to measure bilateral kinesiological information for a large number of consecutive cycles in order to quantify both the step-to-step variability and the steady-state walking pattern. Supporting the use of instrumented treadmills to study hemiparetic walking, a large study (n = 56 persons with hemiparesis), compared overground and treadmill walking and concluded that treadmill walking was a valid method for determining poststroke motor control deficits and walking impairments (18). Kautz et al. (18) demonstrated that persons with hemiparesis do not demonstrate immediate improvements in symmetry (neither temporal nor spatial) when they walk on a treadmill without support (either a hand rail to hold or body weight support). Instead, treadmill walking increased step length asymmetry, which reflected a similar asymmetry seen when the same persons were asked to walk as fast as possible overground. This was interpreted as treadmill walking providing a challenge and exacerbating the hemiparetic participant's existing motor control deficit. The differences observed between treadmill and overground walking, primarily were manifest as differences in spatiotemporal measures (and the associated kinematics that accompany slower walking speed and shorter strides), and not changes in key kinematic and EMG measures that reflect motor control deficits.

Vertical forces have been investigated predominantly to determine symmetry of weight bearing. Three different patterns of vertical GRF are typically observed in the PP: double-peaked with early and late peaks (similar to normal), one single peak in midstance, and a plateau with no discernable peak (19). Kim and Eng investigated 28 hemiparetic subjects of varying ambulatory ability and found that all but three had reduced vertical GRFs in the PP and that symmetric weight distribution between the legs was related to increased temporal symmetry but not spatial symmetry during walking (20). Raja et al. (investigated PP loading in 44 subjects and found that the magnitude (average vertical force) was reduced and the duration (time to load the leg to 50% of body weight) was increased compared with the non-PP and nondisabled controls walking at matched speeds (21). Additionally, they found that both loading and unloading of the PP was significantly correlated with average leg angle, whereas the non-PP significantly correlated with average knee angle. Also, abnormalities in PP loading increased with increased lateral placement of the paretic foot and slower walking speed.

Bowden et al. used the propulsion force as a performance measure to quantify the contribution of the PP to hemiparetic walking (22). Lacking such a performance measure has been a significant barrier to understanding PP motor performance during walking. Measures have typically focused on bilateral gait-related outcomes such as walking speed, over-ground ambulatory capacity, endurance, and balance. The biomechanical and mechanistic contributions of the PP to such measures are not unique. For example, the same gait speed can be achieved with many levels of coordination of the PP if the non-PP provides different levels of compensatory output. Previously, estimates based on mechanical work calculations had suggested that the PP does 30% to 40% of the total mechanical work over the gait cycle, regardless of hemiparetic severity (17). However, these work estimates could be flawed because they may be dominated by the support of body weight and not a unique contribution of each leg to forward propulsion, this being a critical component of walking performance.

The purpose of the Bowden et al. study was to establish a quantifiable link between hemiparetic severity and PP contribution to propulsion during walking using a measure based on the anterior-posterior (A-P) GRF (22). In particular, the measure defined the proportion of the summed propulsion from both legs generated by the PP. Total body forward propulsion by a leg is calculated by integrating over time (e.g., stance) the forward propulsion produced by that leg. PP is the ratio (in percent) of the total body forward propulsion produced by the PP to the summed forward propulsion by both legs. Forty-seven participants with chronic hemiparesis walked at self-selected speeds. Spatiotemporal parameters and GRFs were collected. A-P GRF measures were correlated with both walking speed and hemiparetic severity (Figure 24.3). The percentage of propulsion generated by the PP was found to be 16%, 36%, and 49% for those with severe, moderate, and mild hemiparesis (as assessed by Brunnstrom stages (23), respectively (Figure 24.4). Thus, PP provided a quantitative measure of the coordinated output of the PP that indicates that the motor performance of the PP can be assessed independently and corresponds to the severity of hemiparesis.

Subsequently, additional studies successfully used propulsion based measures to explain step length asymmetry (14) and the consequences of abnormal electromyographic (EMG) timing (24) to assess the contribution of the PP to hemiparetic walking. Forward body propulsion by a leg at any instant is defined as the force that acts on the body to accelerate it forward (represented by the red vector at the hip in Figure 24.5A), which results from the anteriorly directed, forward GRF (red vector parallel to the ground in Figure 24.5A) acting on the leg at that instant.

PP is sensitive to differences in motor control not captured by multi-construct measures such as gait speed, and therefore it may be an effective tool for distinguishing functional compensation by the non-PP from physiological restitution of PP performance. Quantifying forward propulsion provides great insight into overall PP performance because it measures both the active generation of propulsive forces by muscles (e.g., plantarflexors) and the indirect contribution of other muscle activity (e.g., hip and knee flexors) through their influence on walking mechanics. For example, in terminal stance, or preswing, of normal walking, the heel rises and the forefoot acts as a "rocker" that allows body forward progression (Figure 24.5A). An inverted pendulum representation of walking illustrates this contribution to propulsion because the resultant GRF acts along the axis of the leg (blue vector), which results in an anteriorly directed component

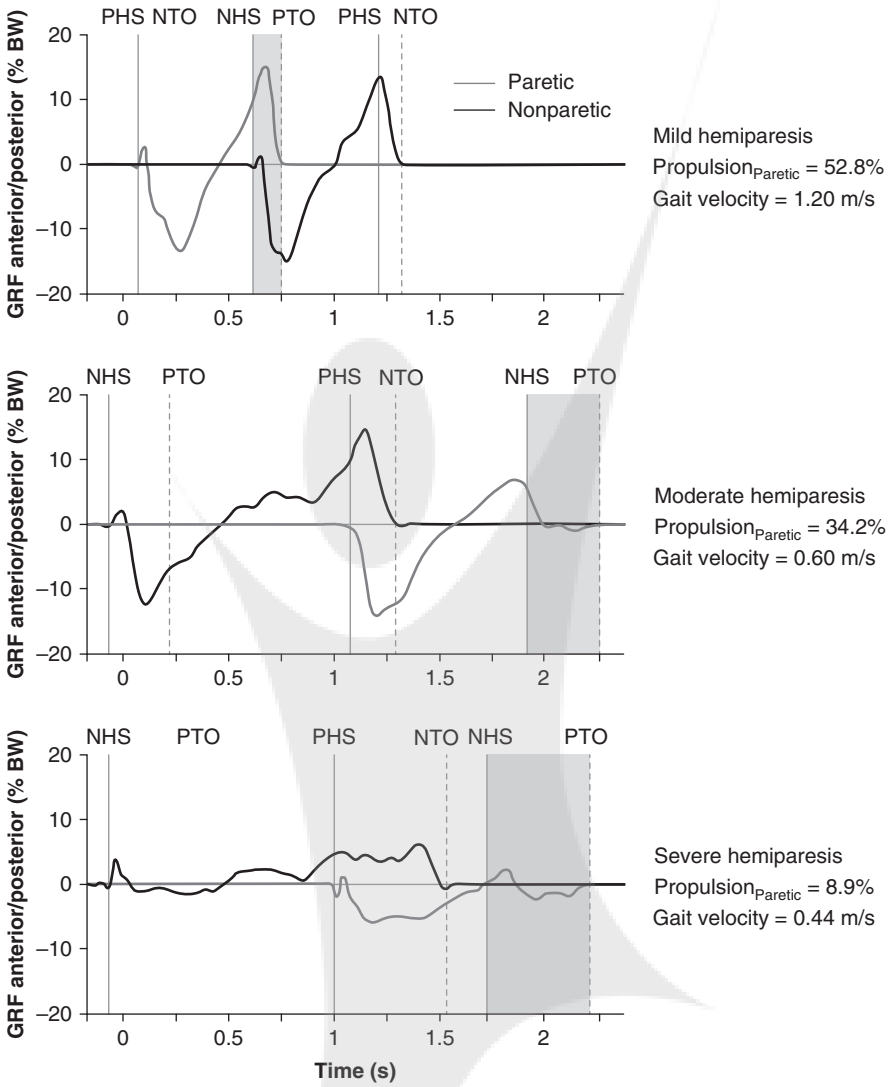

FIGURE 24.3 A-P GRFs for three subjects of differing hemiparetic severity. Positive values represent propulsion, and the positive area under the curve is the propulsive impulse. Increased hemiparetic severity was associated with decreased PP and decreases in self-selected walking speed.

Abbreviations: NHS, nonparetic heel strike; NTO, nonparetic toe off; PHS, paretic heel strike; PTO, paretic toe off.

Source: Modified from Ref. (20). Kim CM, Eng JJ. The relationship of lower-extremity muscle torque to locomotor performance in people with stroke. *Phys Ther*. 2003;83:49–57.

(red vector parallel to the ground) of a particular magnitude in direct relation to those walking mechanics. Thus, reduced propulsion will occur as a result of walking mechanics per se should early initiation of leg flexion prevent the foot from moving sufficiently posteriorly relative to the pelvis (i.e., should the hip not extend sufficiently; Figure 24.5B).

As would be expected during slow hemiparetic walking, joint moments and powers are greatly reduced when compared to nondisabled subjects walking at their self-selected speed. However, the differences are much reduced when compared with walking at a matched speed. In fact, it is remarkable the extent to which the PP moment and power profiles are similar in pattern but reduced in amplitude in comparison to the non-PPs, which are mostly similar to those of matched speed control subjects (17). Thus, the main power generation bursts in hemiparetic walking are the same as that in nondisabled walking. There are the power generation bursts associated with the ankle plantarflexor moment in preswing (commonly referred to as A2, as by Olney et al.) (17), the hip extension moment during initial double support (H1), and the hip flexion moment during preswing (H3). The A2 positive power burst associated with the ankle plantarflexor moment in preswing is usually greatly reduced on the paretic side. H3 has also been found to be reduced in some subjects, especially those who walk most slowly, although it has been hypothesized for

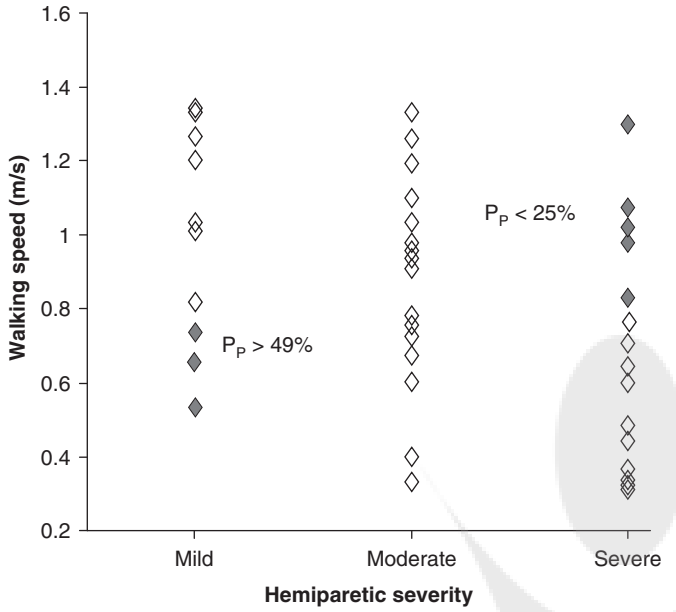

FIGURE 24.4 Individual walking speed data show that there is substantial variability in the weak relationship between walking speed and severity. Note, however, that PP helps explain much of this variation, as the five participants with severe hemiparesis who achieve faster walking speeds (> 0.8 m/s) all demonstrate substantial decreases in PP, whereas the three participants with mild hemiparesis who walked > 0.8 m/s have normal PP (> 49%).

Source: Modified from Ref. (20). Kim CM, Eng JJ. The relationship of lower-extremity muscle torque to locomotor performance in people with stroke. *Phys Ther.* 2003;83:49–57.

FIGURE 24.5 Illustration of the potential contribution of mechanics to the propulsive GRF for two leg configurations in preswing. Reduced hip extension would result in decreased contribution to forward propulsion from walking mechanics.

some subjects that H3 compensates for the absence of ankle plantarflexor power.

Ankle joint plantarflexor power (A2) was barely evident in the PP in a group of 10 household walkers (17). In addition, when ankle moments during gait were compared with maximum isometric moments, it was suggested that the walking speed of 10 of 17 hemiparetic subjects was limited by plantarflexor weakness (although the four fastest walkers in that group appeared to compensate by increasing hip flexor moment) (25). Ankle moments are also substantially reduced in hemiparetic persons in comparison to slow walking controls, with household walkers having reduced moments compared to limited community walkers (17). In contrast to the PP, the non-PP A2 power generation is equal to or greater than speed matched control subjects, as the A2 power bursts supply about half of the positive work generated by the joint moments (26).

Increased pre-swing hip flexor moments and powers would appear to be able to compensate for plantarflexor weakness and produce faster walking speeds in some faster walkers (27). Hip flexor moments and powers seem to be reduced for slow walkers and increased for fast walkers with respect to healthy controls (11,17). Because hip flexion abnormalities during preswing differentiated the functional walking groups, De Quervain et al. concluded that "insufficient power and inappropriate initiation of flexion of the hip must be assumed to be the cause, as no activity was noted in the extensor muscles" (13). Although the H3 burst may be greater in the non-PP in some subjects, this nonparetic burst does not seem to be used to produce substantial amounts of compensatory positive work as does the nonparetic A2 burst.

The other potential mechanism for increased positive power generation is the hip extensor burst in initial double support (H1). Although H1 has a positive relationship with speed across different subjects (17) and a positive relationship with change in speed after rehabilitation (26), it produces less overall work than the other two bursts. Interestingly, the non-PP H1 appears to produce some compensation as it is increased in slow walking subjects (17).

There is also an important nonsagittal plane power burst at the hip that is seen in persons with hemiparesis; a study found the hip abductor moment is prolonged in hemiparetic walking in more than half of the subjects (20). Because it is seen most often in the faster walking subjects, Kim and Eng suggest that it is a compensatory mechanism for poor dorsiflexion and knee flexion during swing (20). This finding challenges the notion that treatment approaches should be directed toward restoring "normal" kinematic and kinetic patterns of walking if the goal is to achieve optimal functional performance rather than an aesthetic one.

Thus, kinetic measures such as GRFs and joint moments can provide much insight into the impaired mechanics of walking after stroke. Propulsion is a crucial task during

walking, and new biomechanical measures based on the anteriorly directed GRF provide a measure to quantify the contribution of the PP to walking and offer great potential for distinguishing compensation from recovery in the PP performance. Furthermore, the ankle plantarflexors during push off, the hip flexors during pull off, and the hip extensors during weight acceptance have been identified as the primary sources of power generation during normal and hemiparetic walking, with ankle plantarflexor power generation being particularly impaired in hemiparetic walking.

EARLY POSTSTROKE PATTERNS OF RECOVERY

Immediately following stroke, the most common feature of motor impairment is either paresis or paralysis, partial reduction or complete loss of the ability to generate force in the muscles of the extremities contralateral to the stroke (28). At this time point after stroke, the primary contributors to contralateral paresis are disruption of the motor neural pathways leading to reduced motor recruitment (29) and disuse atrophy (30). Consequently, in the early poststroke phase the characteristic asymmetrical gait results primarily from inadequate muscle force generation (31).

Abnormal Motor Unit Recruitment and Muscle Weakness

Paresis in the lower extremity can impair both the ability to advance the limb for swing and to support body weight during stance (6,11,20). Support of body weight can be compromised by inadequate activation of the ankle plantar flexors, knee extensors, or hip extensors (32). Paresis of the ankle dorsiflexors may result in poor foot clearance in swing (31). If the hip flexors are also weak, inability to compensate by lifting the limb results in a toe drag and limited step length.

Alterations in EMG timing and intensity during walking result from both reduced activation and from compensations for loss of force (15,31). Few studies have described muscle activity patterns in the early poststroke phase (13,15,31,33). The impact of reduced muscle activation and resultant weakness on the characteristic patterns of walking after stroke was identified in 47 individuals at admission to acute rehabilitation and again at 6 months after stroke (15). Four distinct gait patterns were discerned. Those subjects in the two groups with greater walking impairment walked at just 10% to 11% of normal velocity, and lower-extremity muscle strength ranged from 17% to 36% of the normal with weakness most severe at the ankle. In both of the slower groups, marked paresis of the ankle plantar flexor muscles removed the normal restraint of the tibia in stance. The pattern of walking compensation adopted initially was reflected in the knee position in mid-stance. The relative strength of the proximal muscles in the PP was the factor that determined which compensatory pattern was adopted. In those individuals with greater extensor muscle strength at the knee than at the hip, the knee collapsed into flexion with the demand shifted to the quadriceps (flexed group). In contrast, subjects with stronger hip extensors and weaker quadriceps thrust into hyperextension at the knee (extended group) relying on passive stability at the knee and increased activation of the hip extensors for stance control and progression of body weight.

In the two faster groups (fast and moderate), walking velocity was 44% and 21% of normal, respectively (15). Ankle plantar flexion strength was less than normal (53% and 38% of normal), but not as markedly reduced as in the two slower groups (flexed and extended). This greater residual plantar flexion strength resulted in only mildly excessive knee flexion in stance for the moderate group and normal extension in the group with the least walking impairment (fast). Moreover, activation intensity was *greater than normal* at admission for the two faster groups in vastus intermedius and gluteus maximus, indicating increased proximal activity in stance as a substitution for reduced distal control (Table 24.1). The significant impact of reduced activation of the calf muscles on walking function in the acute poststroke phase was confirmed by Lamontagne and colleagues, who documented that gastrocnemius EMG intensity during gait explained a full 52% of the variance in walking speed in the early poststroke phase (31).

The swing-phase movement pattern in the acute phase was characterized by the amount of dorsiflexion achieved in mid-swing (15). The decreased activation of anterior tibialis in both of the two slower groups produced inadequate dorsiflexion in mid-swing (Table 24.1). Although volitional ankle dorsiflexion strength was also less than normal in the two faster groups, the muscle response was adequate to achieve at least a neutral ankle in swing.

In addition to reduced EMG intensity, alterations in the timing of muscle activity have been identified during walking (13,15,33). In our study of walking recovery (15), at the early poststroke assessment, onsets of muscle activity were delayed in the two groups with the slowest velocities for all hip and knee extensors that have a typical onset in mid- or terminal swing (gluteus maximus, gluteus medius, semimembranosus, biceps femoris, and vastus intermedius). This finding is indicative of a reduced need for limb deceleration in swing because of the subjects' very slow velocities. In contrast, EMG onsets for the faster subjects were premature in vastus intermedius and adductor longus, indicating that these subjects had the capacity to activate the muscles, but the decreased muscle force output required an early onset to achieve the desired swing-phase motions. Muscle activity was prolonged with cessations in mid-stance for the hamstrings and in terminal stance for gluteus maximus and vastus intermedius for subjects in all groups, indicating the need for increased proximal stability in stance to substitute for the reduced plantar flexor activity distally. Rectus femoris activity was prolonged through swing for both fast and slow velocity groups, which may indicate either spasticity or the increased need for hip flexor force in swing. Because of its insertion below the knee, however, prolonged rectus femoris activity results in inhibition of the necessary knee flexion required for foot clearance and limb advancement.

TABLE 24.1 Mean EMG Intensity During Walking at Admission to Rehabilitation and Six Months After Stroke

		EMG INTENSITY (% MAX MMT)			
		STROKE—ADMISSION		STROKE—SIX MONTHS	
	ABLE-BODIED	SLOW	FAST	SLOW	FAST
SMEMB	20	12 ± 11	18 ± 8	17 ± 10	21 ± 9
BF long	13	11 ± 9	13 ± 10	16 ± 14	17 ± 8
GMAX	18	17 ± 9	23 ± 9	21 ± 11	20 ± 8
VI	13	15 ± 9	29 ± 15	24 ± 16[a]	29 ± 17[a]
SOL	35	17 ± 13	30 ± 20	27 ± 19[a,b]	36 ± 15[a,b]
PB	20	5 ± 12	10 ± 8	7 ± 9[a,b]	18 ± 17[a,b]
ADL	14	9 ± 8	12 ± 7	15 ± 7[a,b]	26 ± 11[a,b]
RF	15	8 ± 7	12 ± 12	14 ± 10[b]	17 ± 11[b]
AT	25	10 ± 6	26 ± 18	20 ± 11[a]	28 ± 16[a]

[a]Significantly greater in fast than in slow.
[b]Significantly greater at six months than at admission.

Abbreviations: ADL, adductor longus; AT, anterior tibialis; BF long, long head of biceps femoris; GMAX, gluteus maximus; PB, peroneus brevis; RF, rectus femoris; SMEMB, semimembranosus; SOL, soleus; VI, vastus intermedius.

These results are consistent with those of den Otter and colleagues, who identified premature onset of gastrocnemius and prolonged activity through stance in biceps femoris and rectus femoris (33,34). As they utilized surface electrodes to record EMG activity, the rectus femoris recording likely also reflects activity from the underlying vasti.

CHRONIC POSTSTROKE PATTERNS OF RECOVERY

As time following stroke progresses, muscle strength, activation, and walking ability begin to improve (15,35,36). Incomplete recovery and development of additional impairments, however, can contribute to continued gait dysfunction (11,13,20,37). Spasticity or contracture of the ankle plantar flexors can cause excessive plantar flexion and toe drag in swing and impede forward progression during stance (31,37). Knee extensor or hamstring spasticity can inhibit limb advancement in swing (38). In the chronic poststroke phase, disuse muscular atrophy compounds the initial neurologic injury, and consequently, muscle weakness remains prevalent despite the functional recovery during the acute phase (39). The relative contributions of reduced activation and atrophy to poststroke muscle weakness vary between individuals and muscle groups. A recent study of contributors to ankle plantar flexion weakness after stroke determined that reduction in voluntary activation (measured by supramaximal interpolated twitch) was the primary factor related to maximal torque production whereas muscle atrophy and antagonist coactivation had less influence on muscle strength (40). In contrast, both activation and atrophy were identified as significant causes of reduced muscle force production for the quadriceps and hamstrings in the PP (41). Decreases in activity level contribute to reduced cardiovascular fitness and endurance across the chronic phase after stroke (42) (see Chapter 27 for more information).

Abnormal Motor Unit Recruitment

In the study of walking recovery at six months after stroke, consistent with improvement in walking speed, lower-extremity muscles, particularly distal ones, demonstrated increased activation intensity during walking compared to the early poststroke phase (15). Improved walking speed was associated most strongly with increased activation in soleus and adductor longus. Anterior tibialis intensity increased at the six-month assessment for subjects in the slow groups, whereas it remained unchanged for those in the faster groups at levels similar to those exhibited by able-bodied subjects. Subjects in the two faster groups exhibited a greater-than-normal intensity in both vastus intermedius and adductor longus in this later assessment. Those in the slow groups had greater than normal intensity only in vastus intermedius (Table 24.1). Thus, the increase in soleus activation intensity seen for all walking speed groups represents partial recovery of initially impaired plantar flexor function, whereas increase in adductor longus activation, primarily in the faster walkers, represents compensation to increase hip flexor power generation to substitute for the remaining residual reduction in ankle plantar flexor power generation.

Timing of muscle activity also improves with recovery but remains altered compared to normal phasing for most individuals (15,33,34,43). The hip and knee extensors, which initially displayed a delayed onset late in terminal swing, began earlier in swing as recovery progressed at six months. Onsets were premature compared to normal timing for semimembranosus, vastus intermedius, and soleus. These premature onsets can interfere with the flexion necessary

for limb advancement in swing. The swing-phase muscles—adductor longus, rectus femoris, and anterior tibialis—also displayed earlier onsets at six months after stroke, resulting in premature activation.

The swing-phase movement pattern at six months was more influenced by the magnitude of knee flexion than ankle dorsiflexion, consistent with the improved anterior tibialis activity exhibited by subjects with slower initial walking speed (15). Those subjects who retained the extended pattern developed a stiff-knee gait with severely decreased knee flexion in swing. All four subject groups (e.g., fast, moderate; flexed, extended) demonstrated excessively prolonged activity of rectus femoris throughout swing, which would inhibit knee flexion. Only the intensity of adductor longus activity (a hip flexor in gait) differentiated those who displayed markedly reduced knee flexion in swing. It appears that individuals with sufficient activity in adductor longus were able to overcome the knee extension force from excessive activity of rectus femoris by generating a strong hip flexion force from adductor longus, resulting in thigh flexion and secondary knee flexion. Thus, restoration of the walking function in the sub-acute poststroke phase is accomplished both by restitution of distal muscle activation and greater than normal proximal muscle activity (see Chapter 19 for a similar discussion).

Muscle Weakness

Although muscle strength improves from the acute to the chronic poststroke phase (after six months), for most individuals, strength remains less than normal in the muscles of the lower extremity contralateral to the side of the stroke (15,35,44). Ankle plantar flexion and dorsiflexion weakness still dominate in the slowest individuals. Neckel et al. documented greater than normal knee extension strength in a group of individuals at least one year after stroke (44). They postulated that knee extensor muscles may have been strengthened from increased activity during walking as part of a compensatory strategy. This is consistent with the finding of a greater-than-normal intensity of vastus intermedius activity (15).

Musculoskeletal models of walking have identified the function of muscle activity in normal walking and predicted the impact of paresis in individual muscles for subjects with pathology (45,46). The results of these studies can increase our understanding of the consequences of poststroke muscle weakness. In walking at self-selected speed by able-bodied adults, a model of walking demonstrated that force production by plantar flexors in terminal stance and preswing is critical to forward progression of the trunk, swing initiation, and power generation (46). This is consistent with the robust finding of reduced ankle joint power that is strongly related to walking velocity after stroke (12,25,47).

Compensatory strategies to substitute for distal muscle weakness have been identified in the proximal musculature of the PP as well as in muscles of the nonparetic limb (32,45,48,49). Increased distal muscle coactivation in the non-PP during the double-limb support phases was documented as a compensatory mechanism in subjects with more severe motor impairments (31,49). Musculoskeletal modeling demonstrated that an individual with severe plantar flexion weakness and the flexed-knee poststroke walking pattern would exhibit increased contributions from the paretic hip and knee extensor muscles in single-limb stance as an alternate source of stability confirming the experimental EMG evidence (32,45). Later in the stance phase, the model also identified that increased hip flexor activity can compensate for plantarflexor weakness and produce faster walking speeds (32) (see Chapter 19 for more information on the relationship between proximal and distal power strategies during walking).

Abnormal Muscle Synergies

Clinical observations of volitional movement patterns in both the upper and lower extremities following stroke have been described as abnormal muscle synergies that are stereotypical combinations of secondary, unwanted motions that accompany the primary desired motion (23,28,31). During attempts of isolated, volitional joint movement, lower-extremity abnormal synergistic movement combinations have been described as massed extension of the entire limb with adduction and internal rotation and massed flexion with abduction and external rotation. Measurement of secondary torques during isolated, isometric contractions in subjects with stroke, however, did not confirm the patterns observed during the attempted dynamic movements (44). Individuals who have impaired selective movement control can utilize these mass extension and flexion patterns of the lower extremity for stance and limb advancement during walking. The extent of dependence on the abnormal synergy patterns and the strength of the patterns during walking vary greatly among individuals such that the subjects that depend on abnormal movement patterns for walking have greater functional impairment (50). The mass extension pattern utilized in the stance phase does not have the normal graduated increases in muscle activation necessary for controlled knee flexion in initial double-limb support or ankle dorsiflexion in single-limb stance. The flexion pattern for swing limb advancement can limit stride length when knee extension in terminal swing is incomplete with continued hip and knee flexion. Excessive, premature ankle plantar flexion and hip extension in late swing often accompany attempted knee extension, which also impedes limb advancement and reduces stride length. Abnormally increased heteronymous facilitation has been implicated in the extensor synergy in persons after stroke with early activation of soleus identified during periods of typical quadriceps activity (51). This premature facilitation of soleus during quadriceps activation is consistent with the high intensity plantar flexor activity seen in loading response and premature plantar flexion in terminal swing in persons who exhibit an extensor synergy during walking. Abnormal activation of soleus during knee extension efforts was inversely related to walking speed.

TABLE 24.2 Duration of EMG Activity Following Rapid Stretching at Admission to Rehabilitation and Six Months After Stroke

	ADMISSION					SIX MONTHS				
	% < 1 SEC	% 1–3 SEC	% > 3 SEC	MEAN SEC	MEDIAN SEC	% < 1 SEC	% 1–3 SEC	% > 3 SEC	MEAN SEC	MEDIAN SEC
Gluteus maximus	90	6	4	0.44	0.12	90	8	2	0.33	0.10
Semimemb	45	15	40	2.03	1.14	32	19	49	2.49	2.96
Biceps femoris	63	10	27	1.5	0.32	59	8	33	1.65	0.26
Adductor longus	11	6	83	3.77	4.24	8	6	86	3.80	4.20
Rectus femoris	65	14	21	1.25	0.36	53	10	37	1.94	0.84
Vastus intermedius	76	10	14	0.98	0.24	74	13	13	0.97	0.38
Soleus	60	13	27	1.42	0.16	79	3	18	1.01	0.10
Anterior tibialis	94	2	4	0.28	0.06	89	8	3	0.35	0.04

Reliance on muscle synergies during walking can be quantified by analyzing EMG activity to determine the number of independent patterns of muscle coexcitation. Using factor analysis techniques to analyze the EMGs recorded from healthy individuals, Clark et al. (52) found that four independently timed patterns of muscle coexcitation accounted for muscle activity in eight muscles over a wide range of walking speeds. They hypothesized that the health of the poststroke locomotor control system depends on the number of coexcitation patterns needed to account for the EMG signals and found that lower-extremity muscle activity in most persons with poststroke paresis could be accounted for with only two or three independent patterns compared to that in nondisabled individuals where four independent patterns were needed. This reduced independence of muscle excitation was associated with poorer walking performance, including decreases in speed, step length symmetry, propulsive force symmetry and speed adaptability (fastest minus self-selected speed). Thus, factor analysis techniques provide compelling evidence for locomotor control after stroke ranging from massed flexion and extension patterns to more selective control of individual muscle groups. The number of independent patterns of muscle coexcitation that exists was also found to be a superior predictor of walking performance than the lower-extremity Fugl-Meyer (LEFM) assessment (53).

Spasticity

In his classic descriptive study of recovery after stroke, Twitchell described the timing and pattern of the onset of spasticity (28). He noted that spasticity began between 2 and 20 days after stroke and was most common for the lower extremity in the ankle plantar flexors. Clinical measures of spasticity are related to both the intensity and duration of EMG activity elicited during passive stretching of the muscle (54).

In a study of walking recovery after stroke, the duration of EMG responses to a manual quick stretch was recorded as an indicator of spasticity at an average of 21 days after stroke and again at 6 months after stroke (Table 24.2) (15). A normal EMG response to quick stretch lasts for less than 0.10 seconds. At both time periods adductor longus was the muscle that most frequently exhibited a prolonged response to quick stretch (greater than 3.0 seconds in over 80% of subjects). This excessive stretch sensitivity, however, was not related to increased functional deficits in walking. In fact, greater adductor longus activity during gait was associated with greater (more normal) swing-phase knee flexion despite prolonged activation in rectus femoris. One-third to one-half of subjects exhibited prolonged responses to quick stretch in the hamstrings (semimembranosus and biceps femoris long head), rectus femoris, and soleus. Though less frequent, the impact of severe spasticity in these muscles on walking was greater than that of the adductor longus.

Spasticity of the hamstrings can limit knee extension in terminal swing and inhibit thigh flexion in initial swing with secondary decrease in peak swing knee flexion (38). Rectus femoris spasticity is a common contributor to reduced knee flexion in swing (38), and soleus spasticity can contribute to equinovarus, which can impair forward progression of body weight over the ankle in stance and impact foot clearance in swing (37). Both semimembranosus and rectus femoris demonstrated increased spasticity at the six-month test compared to the earlier evaluation, which corresponded with greater impairment in swing phase knee flexion.

Although anterior tibialis does not often demonstrate increased response to passive stretch, excessive or continuous activity during walking is a common contributor to excessive subtalar joint varus (55). Although spasticity is not a strong determinant of walking function for the majority of individuals following stroke (56,57), for those who do exhibit obstructive spasticity, both surgical interventions and anti-spasticity medication can produce increases in walking speed and reduce gait deviations at both the ankle and knee joints (37,38,58) (see Chapter 29 for more information).

Joint Contractures

After stroke, longstanding weakness in a muscle group or spasticity in the antagonist group can result in increased passive stiffness and joint contractures (31,54,59). In the lower

extremity the ankle plantar flexion contractures are the most common site for restrictions of joint motion, although inversion contractures are also common, and flexion contractures at the knee and hip joints develop occasionally, particularly in individuals with limited standing and walking function (37,55,60). Adequate passive joint mobility is necessary to obtain a stable passive alignment during the stance phase of gait.

Using a mechanical modeling simulation, Kagaya and colleagues (61) confirmed the clinical impression of the lower-extremity postures that produce maximal passive stability during stance, which comprised 5° of dorsiflexion at the ankle, 0° flexion at the knee, and 15° of extension at the hip (61,62). The model predicted significant increases in muscle demand for postures at or greater than 6° of plantar flexion and 20° of flexion at the knee or hip joints. In a subsequent mechanical modeling simulation, hip or knee flexion contractures of no greater than 15° or ankle plantar flexion contractures of less than 0° were required to maintain positive step length and forward movement of the center of gravity (61,63). These theoretical models indicate that, although moderate to severe contractures are destabilizing, mild contractures may be accommodated, and in fact, mild ankle plantar flexion tightness (0°–5° of dorsiflexion) can augment support for weak calf muscles in stance (6,49).

Proprioception

The influence of impaired joint position sense has proved to be more of a "yes/no" threshold rather than a scalar determinant of gait quality (4,5). No significant difference in proprioceptive ability was identified between poor and good hemiparetic walkers (5,20). Proprioception loss in the lower extremity tends to be more severe distally.

Absence or impaired proprioception in the ankle joint can be controlled with an ankle-foot orthosis that limits available motion at the ankle. If lack of proprioception extends to the knee joint, a knee-ankle-foot orthosis (KAFO) may be required to stabilize the knee in stance. If proprioception at the knee is impaired, but not absent, an unlocked KAFO may provide sufficient sensory input, but if joint position sense is absent at the knee, a locked KAFO is usually required for stability in stance. This is important for safety during walking because absent proprioception in the knee is related to the risk of frequent falls (64). The weight of the orthosis and increased energy cost of walking with an extended knee in swing typically result in KAFO use for household or exercise use only. If proprioception loss extends to the hip, potential for functional ambulation is typically limited (see Chapter 36 for more detailed description of indicators for orthotic prescription).

Non-PP Leg Motor Patterns

A recent study (65) analyzed non-PP EMG patterns in a large group of subjects after stroke (n = 60) to identify compensatory patterns. They defined two types of compensations: *expected compensations*—increased activity during regions typically active in walking in healthy persons, presumably to increase the contribution to a muscle's usual biomechanical function—and *novel compensations*—increased activity in regions in which a muscle is typically off or active at a low level that results in either a new biomechanical function being performed or the same function being performed at a different time. Expected compensations included increased activity in hamstrings in early stance and plantarflexors in late stance and novel compensations included plantarflexors in early stance, vastus medialis and rectus femoris in early single leg stance, and hamstrings and rectus femoris in preswing. Most of these compensations were considered likely to contribute to increased propulsion to make up for the decreased propulsion by the PP.

POSTSTROKE WALKING REHABILITATION

Customary walking speed has been identified as the primary indicator of overall functional locomotor ability after stroke (5,20). Moreover, improvements in walking speed categories following rehabilitation have been related to significant improvements in quality of life, confirming the impact that reduced walking speed has on functional mobility (66). Thus, the primary goals of walking rehabilitation programs are to develop walking ability at speeds and distances that are functionally significant for community ambulation (see Chapter 19 for further discussion of walking speed as a global indicator of locomotor ability after stroke).

In addition to gait training, walking rehabilitation programs address the various residual motor impairments identified as significant predictors of walking speed after stroke. Physical contributors to walking deficits after stroke include selective motor control (i.e., synergy stage), muscle strength, balance, and aerobic capacity (20,56,64,67–73). It is beyond the scope of this chapter to address all physical rehabilitation interventions that may contribute to walking recovery. We focus, rather, on the main predictors of walking recovery and best-practice strategies based on current evidence as guides for the clinician in developing effective walking rehabilitation programs for their patients with stroke.

Predictors of Walking Recovery and Responsiveness to Rehabilitation Interventions

Improvement in walking after stroke is accomplished by a combination of natural recovery and rehabilitation intervention (74). Premorbid factors as well as stroke-related variables can impact an individual's ability to respond to intervention. Both older age and greater initial severity of stroke have been found to be predictors of poor outcome following rehabilitation (75,76). This finding may give the erroneous impression that older individuals or those with severe stroke do not make significant or functionally useful gains in rehabilitation. In individuals with more severe involvement, functional improvement occurs more gradually and

the magnitude of improvement is not as large as that seen in subjects with moderate or mild stroke (77). Moreover, the mechanisms underlying functional improvement may differ depending on initial impairment level.

Degree of Neurologic Damage and Multiple Comorbidities

There are numerous covariates associated with motor recovery and responsiveness to therapy such as the pathophysiologic consequences and degree of neurologic damage directly related to the stroke as well as the personal and environmental factors associated with the individual. Cramer (78) discusses the impact that clinical variables such as stroke characteristics (e.g., location, volume, hemorrhagic, or ischemic injury), time after stroke, age, poststroke depression, and other comorbidities have on recovery potential. With advances in imaging techniques such as functional magnetic resonance imaging and diffusion tensor imaging, the relationship between damage to neurologic structures, motor severity, and functional recovery potential are being elucidated (79,80).

In particular, the degree of pyramidal tract damage has been associated with both stroke severity and recovery potential for the upper extremity (81,82). Jayaram and colleagues identified a similar relationship ***for the lower extremity*** and poststroke walking recovery using diffusion tensor imaging to assess the integrity of the corticospinal tract and transcranial magnetic stimulation motor evoked potentials to directly assess functional connectivity from the motor cortex to lower-extremity muscles bilaterally (79). They documented that both increased ipsilateral connectivity and reduced integrity of the tracts on the lesioned side were associated with reduced LEFM scores as well as slower walking speeds. Additionally, case-series evidence for relationships between lower-extremity motor involvement and walking recovery is emerging in adults and children with stroke at birth (62,83). For both upper and lower-extremity function, motor impairment severity measures such as the Fugl-Meyer motor assessment appear to be correlated with the degree of pyramidal tract damage. In other words, lower Fugl-Meyer motor scores indicate more synergistic movement patterns that are associated with a greater degree of pyramidal tract damage and less motor recovery potential. Thus, LEFM score may be a general indicator of both the potential for functional walking recovery and the extent of poststroke brain damage. More importantly, therapeutic strategies for walking recovery that may be most beneficial for individuals with mild to moderate stroke may differ compared to those with more severe stroke (see Chapter 19 for more information on physiological and clinical predictors of recovery after stroke).

Motor Severity

Recovery of walking speed is most strongly linked to the magnitude of initial motor impairment, with less recovery in those individuals with the greatest initial severity (70). The strength of this relationship increases up to the first month after stroke (23,84). Prediction of further recovery after the first two to six months is less clear. The total score from the LEFM has been identified as a moderate predictor of both walking speed and stride length in patients after a stroke (70,85). Walking speed was positively correlated with the Brunnstrom motor stage (measure of selective motor control) in the proximal limb, but not with the motor stages of the ankle or foot (71). The authors concluded that the ability to compensate for poor distal motor control determined the individual's walking speed. More recent literature delineated the limitations of the LEFM for more than just a general indicator of ***current walking speed*** after stroke (53). Complexity of muscle activity synergies during walking was more strongly associated with walking speed than the LEFM, which is based on voluntary isolated movements rather than integrated, multi-joint control of movements and postures involved in walking.

Lower-extremity muscle strength in the paretic limb is strongly correlated with maximum walking speed after stroke (20,56,64,67,68,86). Specific muscle groups that demonstrated the strongest relationship with walking velocity varied greatly between studies depending on the number of muscles investigated, the parameter used to quantify strength (hand dynamometer force, isometric or isokinetic torques), and the method of documenting gait velocity (comfortable or fast speeds, distance walked, with or without assistive devices and orthoses).

Studies that compared multiple muscle groups most frequently identified strength in the hip flexor (27,72,87) and ankle plantar flexor (20,25,68) muscle groups as the strongest predictor of walking speed after stroke, although strength in the knee extensor (72,73) hip extensor (67), and ankle dorsiflexors (64,87–89) muscle groups were also identified as significantly related to gait speed. The dominance of ankle plantar flexion strength in the studies of multiple muscle groups is consistent with the relationship of calf strength and initial severity of the stroke (90). Moreover, the contribution of the hip flexors and ankle plantar flexors to maximizing walking speed has been related to their large bursts of power generation late in the terminal stance and pre-swing phases of the gait cycle (12,17,20,25,27).

Kosak and Reding investigated the effectiveness of gait training using a treadmill with body weight support (TM-BWS) in stroke subjects who required moderate assistance to ambulate prior to training (91). In a posthoc analysis, they found locomotor outcomes varied based on the initial severity of neurologic impairments; training using the TM-BWS was more effective for individuals who required moderate assistance to ambulate initially and presented with combined motor, sensory, and visual impairments. However, it should be noted that this study only investigated stroke patients with severe locomotor impairments and was not a study that compared different locomotor impairment severity levels.

In contrast, Sullivan and colleagues specifically investigated the effect of locomotor severity in chronic stroke (92). Neurologic motor impairment, functional locomotor ability, and locomotor severity were analyzed as potential factors

that might contribute to treatment effectiveness. They demonstrated that initial walking speed was independently correlated to change in overground walking speed as a result of training with TM-BWS. Lower-extremity motor impairment severity as measured by the LEFM score was correlated highly with the magnitude of ***walking speed improvement***.

The mechanisms behind the functional recovery in walking stimulated by the gait training using a TM-BWS after stroke are likely dependent on the individual's initial motor severity (93). The increase in free walking velocity after 6 weeks of training with TM-BWS and strengthening exercises in 15 individuals 6 months to five years after stroke was related more strongly to initial LEFM score (r = 0.65) and isometric ankle plantar flexion torque (r = 0.57) than to initial walking velocity (r = 0.42) (93). This finding indicates that those subjects with more preserved motor function in the paretic limb, in particular distally, have a better capacity for restoration of walking function, and it is also consistent with the finding that relatively fast walking speeds can be achieved after stroke with abnormal kinematic patterns through compensatory strategies (22,94).

Subjects with higher initial LEFM scores (above 25) increased gait speed by improving the terminal stance mechanics of the paretic limb at both the ankle and hip (93). The increase in the plantar flexion power in terminal stance was associated with improved pre-swing hip flexion power, which contributes to increases in both cadence and stride length. In fact, soleus was the only muscle with a significant correlation between increased activation level and increased pre-swing *hip flexion power* (r = 0.54). Increased soleus activation likely augmented hip flexion power by increasing acceleration of the hip into extension in terminal stance (95). Increased hip extension in stance would increase the passive elastic contributions to hip flexor power generation by stretching the soft tissue structures of the anterior hip (96). Most of those individuals with higher LEFM scores also had stronger ankle plantar flexors (more preserved distal function) and responded to the intervention with increased activation intensity of the soleus to accomplish these improved mechanics (increased by 15% of maximum) (93). This represents restitution of the walking function (Figure 24.6).

In contrast, for those subjects with lower initial LEFM scores (and weaker plantar flexion strength), there was no correlation between change in ankle plantar flexion power and improved walking velocity (93,97). Those subjects with low LEFM scores and a few individuals with higher LEFM scores but poor distal function improved paretic limb mechanics by other mechanisms (not related to increased soleus) including improved activity of proximal muscles (gluteus maximus, semimembranosus, and gluteus medius) leading to better knee and hip extension in stance, but no change in ankle plantar flexion power (98). Hip extension power absorption in terminal stance and hip flexion power generation in preswing, however, were related to improved velocity for those with low LEFM scores, indicating that these subjects relied on proximal muscle control of the paretic limb and increased swing phase power of the nonparetic limb.

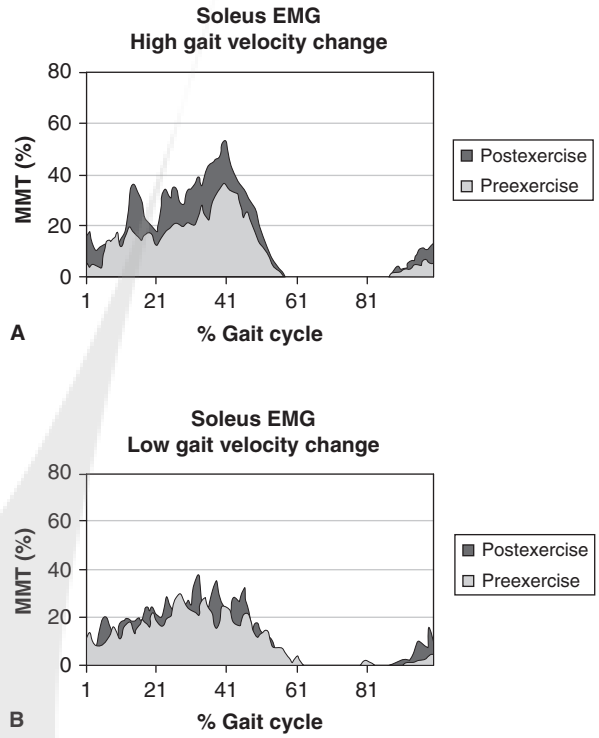

FIGURE 24.6 Change in soleus EMG during walking for subjects who demonstrated high gait velocity (top) and low walk gait velocity (bottom) increases with treadmill training with body-weight support.

This same proximal compensation pattern was documented in subjects without active ankle control from amputation at the ankle joint (Symes level) (99) and for those with reduced ankle power from high-heeled shoes (100).

The proximal muscles demonstrating increased activation in subjects with poor distal control are consistent with predictions of a simulation model developed by Jonkers and colleagues (48), who demonstrated that gluteus maximus, medial hamstrings, and gluteus medius would all contribute to hip extension and heel-off in single-limb stance. Thus, individuals with less severe initial motor involvement from the stroke demonstrated a greater capacity to restore distal control and walking function with intervention, and those with more severe distal motor impairment made more modest improvements by increased proximal and contralateral activity.

The predictive relationship between preserved motor function after stroke and responsiveness to locomotor intervention was confirmed in a study by Bowden and colleagues who found that baseline LEFM scores were significantly higher in participants with a strong response (greater than 0.16 m/s increase in self-selected walking speed) to a 12-week TM-BWS intervention compared to those who had more modest improvements (24.7 ± 4 vs. 19.0 ± 3, $P < .01$) (101). Interestingly, they also found evidence of distal recovery in the responder group with improvements in LEFM, Berg Balance test, and terminal stance propulsion, and evidence of compensatory mechanisms behind the small improvements

in the nonresponders. Bowden's 12-week/36 session study used a higher threshold of walking speed increase for responsiveness than that used with the 6-week/12 session intervention (0.16 vs. 0.08 m/s). Their graph of walking speed change over time indicates continuing improvement over the 12-week intervention without clear evidence of plateau in walking speed improvement in either group indicating a positive dose-response relationship.

Locomotor training interventions with TM-BWS used in the Mulroy (93) and Bowden (101) studies were conducted at faster than customary overground walking speeds. Examining the biomechanical mechanisms used to increase walking speed in the short-term after stroke provides a compelling picture of possible mechanisms underlying the long-term increases in walking speed in the high and low responders with intervention. In a single session study by Jonkers and colleagues, poststroke individuals with faster initial walking speeds went from free to fast walking by increasing both ankle and hip powers, although the increase in ankle power was less than in a speed-matched nondisabled control group (102). The slower walking participants with stroke, however, did not increase joint powers consistently at either the hip or ankle of the PP, but relied on increases in joint powers on the contralateral leg. In the TM-BWS locomotor intervention studies (93,101), those individuals who had the capacity to increase muscle activation particularly in soleus, also increased power generation in the PP engaging in repeated practice at activating muscles at a higher intensity and more rapidly than in their customary free walking which, over time, translated into an increase in free walking speed. Those individuals with lower residual motor function walked at increased speeds primarily by further driving the contralateral leg, which was sufficient for faster walking in the short-term during the intervention sessions, but didn't translate into clinically meaningful increases in free walking speed. A recent study by Routson and colleagues confirmed the critical role of improved soleus activation underlying increased walking speed after TM-BWS intervention particularly for those with less residual poststroke impairment (103). They documented improvements in both timing and intensity of soleus activity during walking after 12 weeks of TM-BWS. For those individuals with faster initial walking speeds and more selective control during walking initially (those who had 4 EMG modules or phasic muscle activity patterns in lower-extremity muscle groups with distinct and independent timing), improved timing of soleus activity was the only significant change in muscle activity after the intervention. These individuals had large increases in walking speed (0.32 m/s), and greater leg extension in preswing, and improved propulsion symmetry. These results closely parallel those of the high response group in our previous study (93).

Standing Balance

Standing balance also has shown strong correlation with walking speed after stroke, particularly for individuals with more severe impairments (56,97,104). Patterson et al. (56) identified that the strongest predictor of both short- (30 feet) and long-distance (6 minute) walking speed in a cross-sectional analysis was the Berg Balance Score for subjects who walked at or below the median speed (56). In contrast, peak VO_2 was the strongest predictor for the faster subjects. Standing balance and lower-extremity strength are strongly related after stroke, and this relationship is particularly strong for those with greater impairments (73).

Improvement in standing balance correlated with increased walking speed after basic rehabilitation and muscle strengthening interventions, particularly for individuals with more severe impairments (73,97). For subjects with less severe initial impairments, however, Pohl et al. documented that improvements in lower-extremity motor function and cardiovascular fitness were most strongly associated with increased walking speed (97). This suggests a hierarchy of functional substrates for walking with the ability to control balance during single-limb stance as a requisite skill for even slow walking and greater muscle strength, selective motor control, and fitness as determinants of faster walking speeds (56,73).

Walking Rehabilitation Interventions

Determining the appropriate and most effective interventions to use for walking recovery is one of the primary roles of the physical therapist during the acute, subacute, and chronic phases after stroke. Evidence is building that innovations in poststroke walking rehabilitation such as resisted lower-extremity strengthening, task specific training, and aerobic training are more effective than conventional neurophysiologic approaches used by physical therapists (69,105–107). Recent innovations in therapeutic approaches to walking rehabilitation derive from understanding the biomechanical and neurologic mechanisms that result in walking impairment after stroke.

As discussed earlier in this chapter, poststroke severity caused by primary motor impairments such as the extent of lower-extremity weakness and selective motor control are significant predictors that contribute to the biomechanics of poststroke gait and responsiveness to rehabilitation interventions. In addition, other secondary impairments such as balance dysfunction and deconditioning also contribute to poststroke walking disability. Current evidence from rehabilitation research suggests that lower-extremity strength training, task specific training such as body-weight supported treadmill training, and aerobic conditioning are interventions that contribute to gait recovery and increased community ambulation for individuals with walking disability after stroke (Figure 24.7).

Strength Training

Resisted strength training for the upper or lower limb after stroke has been questioned by therapists in the past because of the concern that resistance increases muscle spasticity and abnormal movement patterns. However, evidence is building that strength training leads to improvements in both lower-limb muscle strength and gait endurance after stroke (105) without increasing spasticity (108,109). The effectiveness

FIGURE 24.7 Rehabilitation interventions of treadmill training with body-weight support (B), resisted lower-extremity cycling (A), therapeutic progressive resistive exercise example (C), and upper-extremity ergometry (D).

of muscle strengthening to improve walking speed and endurance appears to relate to whether the strength training program is directed at single muscles or groups of muscles that are typically activated during the stance and swing phases of gait. For example, muscle strengthening for a single muscle group after stroke increases muscle strength but results in little or no improvement in walking speed or endurance (110). In contrast, strength training of multiple LE muscle groups is associated with modest functional changes in walking distance or improved balance and/or sit-to-stand ability but not increased walking speed (111–114). This finding is consistent with a recent study that used a resisted LE cycling task specifically designed to strengthen extensor and flexor groups with torque demands biased to emphasize the stance and swing phases of gait. The moderately high-intensity cycling program for 20 to 30 minutes of resisted cycling, 2 days a week for 6 weeks, resulted in significant increases in postintervention LE flexor torque production and walking endurance as measured by the distance walked in six minutes, but did not increase walking speed.

For individuals with moderate to mild walking impairment (i.e., baseline walking speeds approximately 0.30–0.80 m/s), strength programs that incorporate functional weight-bearing activities or dynamic high-intensity resistance training resulted in increases in strength of LE flexors and extensors that produced increases in walking speed, as well. Yang et al. used a program of progressive LE strengthening using functional weight bearing activities for exercise such as step climbing and single-limb heel raises to realize gains in LE strength and walking speed (115). Patten et al. found

that a dynamic resistance training program of eccentric muscle strengthening using isokinetic exercises (15 sessions over 5 weeks) followed by clinic-based gait training (nine sessions over 3 weeks) resulted in increases in both gait speed and LE torque production (116). Increases in speed were not evident for the group that received concentric strength training with gait training. Together these findings suggest that functional task strengthening or strength training programs that emphasize the dynamic muscle control needed to support the kinematics, kinetics, and muscle activation of more normal gait are more effective strength training programs for walking recovery after stroke.

Although it is evident that resisted LE strength training after stroke does not cause harm, there remains a relatively small body of literature that clearly elucidates the overall benefits or limitations of strength training. The recent Canadian Stroke Network (109) systematic review of LE strength training and mobility after stroke concludes that there is strong evidence that strength training improves distance walked after stroke but only moderate evidence that benefits extend to improved performance in other activities of daily living. Furthermore, there is little understanding of the appropriate dosing (i.e., intensity, frequency, duration) necessary to incur significant strength gains in patients with central as well as peripheral mechanisms of weakness. This knowledge gap is further compounded by few to no studies that have examined how principles of exercise for healthy young and older adults translate to individuals with stroke. For example, a recent study that investigated the combined benefits of a rehabilitation program that alternated therapy days of LE strength training with high-intensity treadmill training with body weight support found evidence of overtraining (i.e., impaired strengthening) in the group that received successive days of LE muscle exercise with the group that received a program in which UE and LE exercise were provided on alternate days (117). Clearly, more investigation into maximizing the effects of resisted exercise after stroke is needed.

Task-Specific Training

Task-specific training is the repetitive practice of a task that is specific to the intended outcome. Treadmill training is a therapeutic modality that allows the individual with stroke to actively engage in repetitive stepping. Walking on a treadmill is an example of task-specific gait training that can lead to the achievement of improved walking speed and endurance (111,118–120). TM-BWS is an adaptation of treadmill walking that involves fitting the patient in a harness and suspending him or her over a treadmill with a portion of the patient's body weight reduced so that a physical therapist, with help from another therapist or aide if needed, can assist the patient to step on the moving treadmill belt. Visintin et al. demonstrated that TM-BWS with 40% body weight support provided in early training that was progressively decreased over training sessions resulted in better walking outcomes for individuals in the acute and subacute phases after stroke than treadmill training without body weight support (121).

In a control-comparison RCT of 80 individuals with chronic stroke who had severe to moderate walking impairment (average gait velocity: severe, 0.25 ± 0.12 m/s; moderate, 0.71 ± 0.12 m/s), Sullivan et al. demonstrated a statistically significant, and clinically meaningful, increase in both walking speed and distance that was maintained at a six-month follow-up for *any* of the exercise groups that received TM-BWS compared to the group that received resisted cycling (117). In this study, there were four exercise groups that received exercise four days per week for six weeks. Three of the groups received TM-BWS combined with another exercise such that the program included two days per week of TM-BWS alternated with two days per week of upper-extremity ergometry, progressive resistance LE exercise, or resisted cycling. The fourth group received two days per week of resisted cycling alternated with two days per week of upper-extremity ergometry. Each group was controlled for time in the exercise session (one hour per session) and intensity (moderately high). Moderate- to high-intensity TM-BWS sessions included 20 minutes of cumulative walking time on the treadmill at speeds that ranged from 1.8 to 2.3 mph. In addition to providing specific dose parameters and intervention protocol specifications for the exercise programs, this study demonstrated the overarching benefit of an exercise program that included TM-BWS for making long-term changes (six-month follow-up) in both walking speed and distance in individuals after a chronic stroke.

The locomotor experience applied after stroke (LEAPS) study, a large multi-site randomized clinical trial comparing the effectiveness of TM-BWS in the early (2 months) and late (6 months) poststroke recovery phases with an early phase home exercise program in participants who had been discharged from inpatient rehabilitation, was a landmark study for poststroke rehabilitation of walking (122). All 3 interventions were in addition to "usual care" physical therapy (received by 82% of participants). Several important conclusions can be drawn from the results, and with over 400 participants, the results of the study can be generalized widely. There was no difference between the 3 treatment groups in the primary outcome, transition to a higher functional walking level from baseline to one year after stroke. At six months after stroke, the late TM-BWS group had ***only*** received "usual care" physical therapy and had a mean increase in walking speed from baseline of 0.13 m/s that was approximately 55% of the increase seen in the other 2 groups who had completed the TM-BWS or home exercise program. Addition of TM-BWS after the six months assessment in the late TM-BWS group further increased walking speed so that all groups had similar gait speeds at one year. This study demonstrated that "usual care" physical therapy intervention is not sufficient to optimize potential walking recovery after stroke. The addition of high-intensity intervention to "usual care" even at 6 months after stroke can produce functionally significant improvements in walking. A positive dose–response relationship between treatment week and gait speed increase was seen for all 3 groups. The slope of the improvement trajectory increased for the late training at

the onset of TM-BWS. The more task-specific TM-BWS intervention was not superior to the impairment-based home exercise program in increasing walking speed. The authors felt the critical ingredients in the two experimental interventions that were missing from "usual care" physical therapy were: higher dose (number and frequency of sessions), participant engagement in goal setting, challenging intensity within each session, a progressive increase in intensity over the duration of the program, and task-specific walking training or impairment-based exercise (123). Additionally, the authors felt that conducting the home exercise program in the individual's natural environment may have facilitated retention of the gains (123). In support of that hypothesis, those in the home exercise group did continue to show small gains in walking speed and daily stepping activity from the six-month to the one-year follow-up assessments whereas the early TM-BWS demonstrated slight reductions (122). So although intensive task-specific walking training can optimize walking speed after stroke, it is not the only type of intervention to produce similar results.

Several recent systematic reviews have suggested that the collective findings on treadmill training or TM-BWS effectiveness compared to other gait interventions remain inconclusive (105). However, there is strong evidence that task-specific functional training ***performed at high intensity*** may be a critical factor that modulates gait training effectiveness (106,124,125). With task-specific gait therapies such as treadmill training or TM-BWS, responsiveness to this particular intervention is related to the training parameters used. Recent evidence consistently demonstrates that treadmill training at higher speeds (i.e., higher intensity), with or without body-weight support, is more effective for improving gait speed after stroke than training at slower speeds (92,126,127). These reports of differences in therapeutic effectiveness related to the type and dosing of the exercise program illustrate the importance of exercise prescription. Exercise prescription is a major contributor to therapy outcomes and most likely contributes to the inconclusive findings of systematic reviews that have not included trials in which training intensity is controlled.

Why are higher intensity, task-specific gait interventions more likely to achieve functionally significant changes in walking outcomes after stroke? We propose that walking rehabilitation that combines *specificity* of training intrinsic to walking with the *intensity* of walking at challenging speeds requires that the individual after stroke respond to and develop the gait dynamics and muscle activation patterns associated with more normal gait parameters.

Given the results of the LEAPS trial, intensity and speed may be the most important factors in effective interventions for restoring walking function after stroke. In fact, even a single session of fast functional movements produced increased intensity of muscle activation in both flexor and extensor muscle groups as well as improved temporal coupling of the movements and postural control variables (128). No retention test was included, so it is not clear if the effects persisted over time. More than one session would likely be necessary for long-term change in muscle activation. A 12-week ***combined*** program of high intensity, fast velocity muscle strengthening with TM-BWS produced increased muscle activation during maximal contractions and large increases in walking speed (increase of 0.46 m/s) for participants with mild to moderate impairment in the sub-acute phase after stroke (129). Muscle activation ***during walking*** was not measured in either study, so we cannot be certain that increased muscle activation during maximal effort strength testing generalizes to locomotion. The studies by Mulroy et al. (93) and Routson et al. (103) did measure muscle activation during walking before and after TM-BWS. Based on their results, we can conclude that improved walking speed (in high responders) after this high intensity, task-specific intervention results in increased intensity of soleus activation and a greater number of distinct muscle synergies used in walking.

A study from Hornby's group provides further support for the importance of intervention dosage required to optimize walking recovery after stroke and the lack of intensity in usual care physical therapy (130). Participants were on average 13 months after stroke and had completed an outpatient usual care physical therapy program resulting in a modest increase in walking speed (0.05 ms/s). Number of steps/session in usual care averaged 1886. Participants did not change in daily stepping activity following the usual care program. Participants then underwent four weeks of high intensity TM-BWS with an average of 3900 steps/session. Walking speed increased a further 0.05 m/s and daily stepping activity increased by 850 steps/day. Moreover, they found a moderately strong correlation (r = 0.57) between number of steps in the intervention and increase in daily stepping activity after the intervention. Thus, usual care physical therapy is low in intensity and insufficient to optimize walking recovery in the chronic as well as subacute phases after stroke. Dosage in terms of both intensity within a session and program duration are important determinants of the extent of walking improvement. Neuro-biomechanical mechanisms underlying improved walking after TM-BWS vary depending on initial motor impairment.

In summary, changes in walking recovery and response to appropriately selected and dosed interventions are related to the residual damage to the nervous system after stroke and the response of the nervous system to interventions that provide an appropriate dynamic stimulus to drive recovery. Long-term changes in performance are consistently achieved when the intervention intensity is high and challenging for the individual. Conditions of task practice that are similar to the task and conditions in which long-term changes in performance are expected can facilitate long term improvement in walking function after stroke (131) (see Chapters 19 and 20 for similar discussions).

Aerobic Training

Deconditioning after stroke is a chronic health condition that is evident across the acute, subacute, and chronic phases after stroke (see Chapter 27 for more information). Aerobic training can be safely incorporated into rehabilitation exercise

programs after stroke. Physical activity and exercise after stroke are highly recommended to address deconditioning and to reduce secondary risks for the poststroke survivor (132). In addition, valuable evidence-based sources are now available for the rehabilitation specialist that provide heart rate and blood pressure guidelines to individually monitor the patient during moderately high exercise programs (e.g., see http://www.apta.org/AM/Template.cfm?Section=PFSP_Pocket_Guides&Template=/MembersOnly.cfm&ContentID=42129). Although cardiovascular fitness is essential for good health after stroke, there is building evidence that specific types of aerobic programs are also associated with improved walking outcomes for the stroke survivor.

Pooled data from systematic reviews and well-designed RCTs reveal that walking outcomes such as walking speed and distance, functional tasks such as stair climbing, and increased community mobility and participation are positively impacted by aerobic training for patients with subacute and chronic stroke (105,133,134). Across these studies large-muscle activities such as walking, treadmill, stationary cycle, combined arm-leg ergometry, arm ergometry, and seated steppers were used. Exercise intensity among studies in which walking outcomes were improved ranged from 3 to 19 weeks, 20 to 40 minutes, 3 to 5 days per week at 50% to 80% of heart rate reserve. Pooled data show that aerobic exercise had a small, statistically significant effect on walking speed 0.26 m/s (95% CI: 0.05–0.48, $P = .008$) and a moderate, statistically significant effect on walking distance 0.30 meters (95% CI: 0.06–0.55, $P = .008$).

Aerobic exercise training specifically designed to improve gait and gait-related activities is associated with greater clinically and statistically significant gains in walking outcomes (see systematic review by Van de port (135). Activities such as cycling, water-based exercise, and gait-oriented cardiovascular training resulted in greater postintervention changes in walking speed 0.45 m/s (95% CI: 0.27–0.63) and distance 0.62 meters (95% CI: 0.30–0.95). Across the studies reviewed the most common exercise prescription (i.e., frequency, intensity, duration) averaged three times per week for 60 minutes across 4 weeks (ranges: 8–90 minutes; three to five times per week; 4–19 weeks). Exercise intensity in terms of percentage of heart rate maximum, heart rate reserve, or rate of perceived exertion was not reported.

The wide confidence intervals are most likely associated with the wide variety of exercise methods and prescriptions that ranged across the various trials. Once again, well-designed aerobic exercise rehabilitation clinical trials are needed to better understand the exercise method and aerobic training parameters that result in clinically significant walking recovery in individuals after stroke. However, efficacy of physical activity and aerobic training to improve walking outcomes after stroke is evident.

Research Frontiers

Future directions in walking rehabilitation therapies will most likely include the use of technology to enhance current walking rehabilitation interventions. Currently, technological advances in walking neurorehabilitation that are in either experimental (pre-clinical) or early phase I clinical trials are in the areas of lower-limb assisted robotics, implantable electrodes for neuromuscular function, electrical stimulation, virtual reality enhanced training, and transcranial magnetic brain stimulation.

Lower-limb assisted robotics are in development that will provide machine-assisted stepping because the physical demands during treadmill training are high for the therapist. Examples include both motorized (136) and gravity-balanced (137) exoskeletons that serve as gait-assisted orthotics during walking on a treadmill with a supportive harness and body-weight support. A clinical trial conducted in 2008 that examined walking outcomes in patients with chronic stroke demonstrated that therapist-assisted stepping was more effective than robotic-assisted stepping with a motorized exoskeleton (138). "First-generation" devices, like the Lokomat (Hocoma AG, Switzerland) were developed based on the approach of enforcing gait upon a patient by moving the legs through a prescribed gait pattern diminishing the need for the patients to actively contribute to the required motion. To encourage active participation, more recent robotic devices (including a newer version Lokomat) (139) have been developed with assist-as-needed strategies to control the interaction forces by using impedance or admittance control algorithms (140). They guide the leg by applying a force rather than imposing a trajectory. Impedance control makes the robot's behavior more flexible and adaptive to the patient's capabilities, progress, and current participation. Depending on the impedance levels, small errors are still possible, promoting motor recovery. Catch trials can be utilized to detect and prevent reliance on the robotic support (141). The majority of robotic devices for locomotor training are designed to be fixed to a treadmill (140,142), but devices that can be worn during overground walking act like powered orthoses, such as the ReWalk (Argo Medical Technologies Ltd) are emerging technologies (143). However, more study is needed to determine the optimal training paradigms that integrate the expertise of the therapy clinician with the most effective mechanical assistance.

Advances in technology and reduced device size have allowed neuromuscular electrical stimulation (NMES) to be used functionally as a neuroprosthesis. There is strong evidence that NMES, particularly peroneal nerve stimulation, in conjunction with gait training is an effective walking rehabilitation strategy (105,144) with some evidence of carry-over after long term use (145). Electrical stimulation to ***both*** the ankle plantar flexor and dorsiflexor muscle groups during walking resulted in greater swing-phase knee flexion, greater ankle plantarflexion angle at toe-off, and greater forward propulsion than that produced by stimulation only to the ankle dorsiflexors for persons in the chronic poststroke phase (146). The combination of this stimulation paradigm paired with the fastest sustainable speed TM-BWS further increased the peak anterior GRF (propulsion) providing a more extended leg angle in late stance compared to fast

walking without stimulation and self-selected speed walking with stimulation (147). This research group also identified a dose-response relationship with 36 sessions (12 weeks) of TM-BWS combined with electrical stimulation required to elicit increases in walking speed that exceeded the minimally clinically important threshold (148).

Surface electrode stimulation devices are readily available for clinical use; however, future research endeavors will most likely include the development of implantable electrode devices that will increase the effectiveness of NMES and increase ease of use and comfort for the patient (149). Recent studies demonstrated initial evidence for the feasibility and effectiveness of NMES with implantable electrodes for peroneal stimulation as an adjunct to walking rehabilitation therapy (150–152). Moreover, Daly et al. conducted a randomized clinical trial testing the impact of the addition of 8 channels of electrical stimulation delivered by implantable electrodes to TM-BWS in a 12-week intervention (153). Walking speed and gait coordination outcomes were superior with the addition of the stimulation. The implanted electrodes (as compared to surface stimulation) allowed more specific targeting of individual muscles, particularly in deeper muscles, and permitted higher levels of stimulation without discomfort, because they bypassed the cutaneous pain fibers.

Virtual reality (VR) enhanced interventions provide an enriched training environment and multimodal feedback with the potential to produce superior walking outcomes for persons with poststroke impairment. VR integrated into a 4-week seated ankle motion control program resulted in a 0.16 m/s increase in walking speed with increases in preswing ankle plantar flexion power whereas those who performed the training program without VR and visual and auditory feedback did not improve (154). VR has also been integrated into TM-BWS (155). After three weeks of VR enhanced training walking speed increased by 0.17 m/sec and community walking activity was greater whereas those who received the TM-BWS without VR exhibited minimal improvements. VR enhanced interventions offer several benefits; they provide a variety of different environments, feedback that can be modified according to individual's specific characteristics, and the ability to manipulate and incrementally progress the difficulty of the task as well as obtain an objective assessment of changes in patient's performance. Training in a new environment enhances motivation and engagement (156). VR systems also can be combined with manipulation of physical environments and sensory feedback to create a mixed reality system. Fung and Perez developed a mixed reality advanced locomotor system incorporating VR, a treadmill with surface perturbations, and light touch with a haptic bar that was specially designed to provide somatosensory information through fingertip contact (157). The variety of virtual environments may be able to facilitate transfer of gains produced in walking in the artificial environment of a treadmill to the more complex real-world settings.

Several noninvasive brain stimulation protocols including repetitive transcranial magnetic stimulation (rTMS) can be used to modulate local neural excitability of selected brain areas. These techniques have shown promise in enhancing the effectiveness of locomotor training after stroke. For rTMS, the effect depends mostly on the stimulation frequency. High-frequency rTMS facilitates and low-frequency rTMS suppresses local neural activities (158). Low frequency (1 Hz) rTMS delivered to contralesional hemisphere prior to functional gait training activities every day for 10 consecutive weekdays produced decreased interhemispheric asymmetry of the amplitude of the motor evoked potentials and improved gait speed compared to those who received sham rTMS and gait training (159). Differences in stimulation protocols and gait training interventions have produced mixed results. Transcranial direct current stimulation (TDCS) is another noninvasive brain stimulation protocol that can be either inhibitory or facilitory depending on the stimulation parameters (158). Facilitatory TDCS to the ipsilesional hemisphere had no additional effect on robot-assisted gait training delivered in ten 50-minute treatment sessions, 5 days a week, for two consecutive weeks (160). In contrast, a single session of high-frequency facilitatory rTMS applied over the leg motor areas in ***bilateral*** hemispheres using a double cone coil produced a significant short-term increase in walking function (0.90 to 1.03 m/s) in poststroke hemiparetic patients when compared to sham stimulation (161). The authors used the bihemispheric facilitatory rTMS to enhance uncrossed motor pathways originating from the ipsilateral hemisphere as well as the crossed motor pathways. The stimulation protocol has not been tested with multiple sessions or in conjunction with locomotor training programs. Future studies will need to determine the optimal combination of stimulation protocol, locomotor training program, and patient characteristics for improving poststroke walking function with rTMS. For a review of the complexities involved with using noninvasive brain stimulation to improve walking function after stroke, see Rogers et al. (162)

CONCLUSION

This chapter summarizes the temporal gait characteristics and kinematic and kinetic features associated with poststroke gait dysfunction. Stroke severity affects the dynamic strategies used for walking after stroke. Stroke severity assessed by clinical measures of LE motor impairment (i.e., selective movement control, strength, spasticity) or functional walking ability (i.e., walking speed or distance) is associated with walking outcomes and disability. The capacity to recover movement control as indicated by changes in force production, increased movement selectivity, and appropriate motor unit activation and recruitment during walking appears to be related to the degree of corticospinal tract damage and the methods used during walking rehabilitation.

Walking recovery after stroke is facilitated with rehabilitation strategies that incorporate strengthening of functional muscle groups with power and activation patterns that are more similar to those used in gait. Task-specific interventions such as treadmill walking with or without

support of body weight are examples of effective rehabilitation strategies that incorporate the demands of gait into repetitive stepping and task-specific practice most similar to that of normal gait demands. Furthermore, aerobic training in gait-related activities or LE cycling tasks appears to be an effective intervention to increase cardiovascular fitness associated with reduced activity levels and deconditioning after stroke. Collectively, these types of rehabilitation interventions improve walking outcomes and lead to enhanced participation and quality of life for individuals with stroke.

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25

Recovery and Rehabilitation of Standing Balance After Stroke

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Difficulties with balance leading to disability are common occurrences after stroke. This chapter examines the problems of standing balance accompanying stroke and its rehabilitation. The review will synthesize mostly recent information about these themes by:

1. Discussing the scope of the balance problem from the standpoint of interactive motor control factors that may normally contribute to sustaining standing balance
2. Identifying the functional balance limitations and changes in motor control that have been consistently noticed and their relationship with falls
3. Examining the clinical outcome measures used in assessing balance and the intervention approaches directed at improving balance
4. Introducing a protective stepping model of balance control for linking dynamic balance capacity, functional performance, and falls
5. Providing a glimpse of emerging new research frontiers in balance recovery after stroke

SCOPE OF THE BALANCE PROBLEM

Balance: A Multifaceted Control System

In mechanical terms, standing balance involves the maintenance of the relative position and motion of the body center of mass (COM) with respect to the base of support (BOS), usually represented by the feet in contact with the ground (1). Virtually limitless variations of body surface contact with the environment that provides support may reconfigure the BOS conditions that influence balance. Hence, the interplay between the COM position and motion (velocity or momentum) in relation to a stationary (e.g., feet-in-place and/or grasping a fixed rigid object) or moving BOS (e.g., stepping and/or reaching to contact or grasp a secure surface) determines the moment-to-moment conditions of balance stability. The critical importance of the dynamic nature of these relationships is illustrated by observations showing that even healthy adults often naturally respond to balance challenges by rapidly changing their BOS by stepping or grabbing for support even when the COM is positioned well within the BOS boundaries (2). These responses have traditionally been considered to indicate falling in clinical assessments of balance, such as the Romberg test (3). The complexity and multifaceted nature of the interactive factors that normally comprise the standing balance control system are represented in Figure 25.1 and discussed in this section.

Neural Factors

Concerning the neural control mechanisms by which standing balance may normally be achieved, much attention has been given to the role of the spinal cord and brain stem-mediated postural reflexes involving visual, vestibular, and proprioceptive subsystems operating in a reactive mode of control (4–9). Anticipatory postural adjustments involving proactive control processes that may precede and accompany particularly voluntary goal-directed movements have been proposed to involve several higher-level brain centers, including motor cortical areas, basal ganglia, and the cerebellum (10). The interface between reactive and proactive neural control processes for standing balance is not well understood. This dichotomy appears to have somewhat limited current neuromotor approaches to balance rehabilitation after stroke by emphasizing volitional balance tasks with limited focus on reactive responses to balance perturbations (see Intervention Approaches).

Although a commonly held view is that, in mammalian systems, including humans, the balance regulatory system is phylogenetically old and operates relatively autonomously and automatically using polysynaptic reflex pathways involving the spinal cord and brainstem (6,10), emerging perspectives suggest that standing balance may operate like any other form of movement by requiring planning, anticipation, and adaptive internal models (11,12). For example, even during the quasistatic situation of stationary standing balance, sagittal plane sway regulation cannot be achieved by continuous muscle activation adjusted by reactive stretch reflexes at the ankles as generally believed (11). This is because

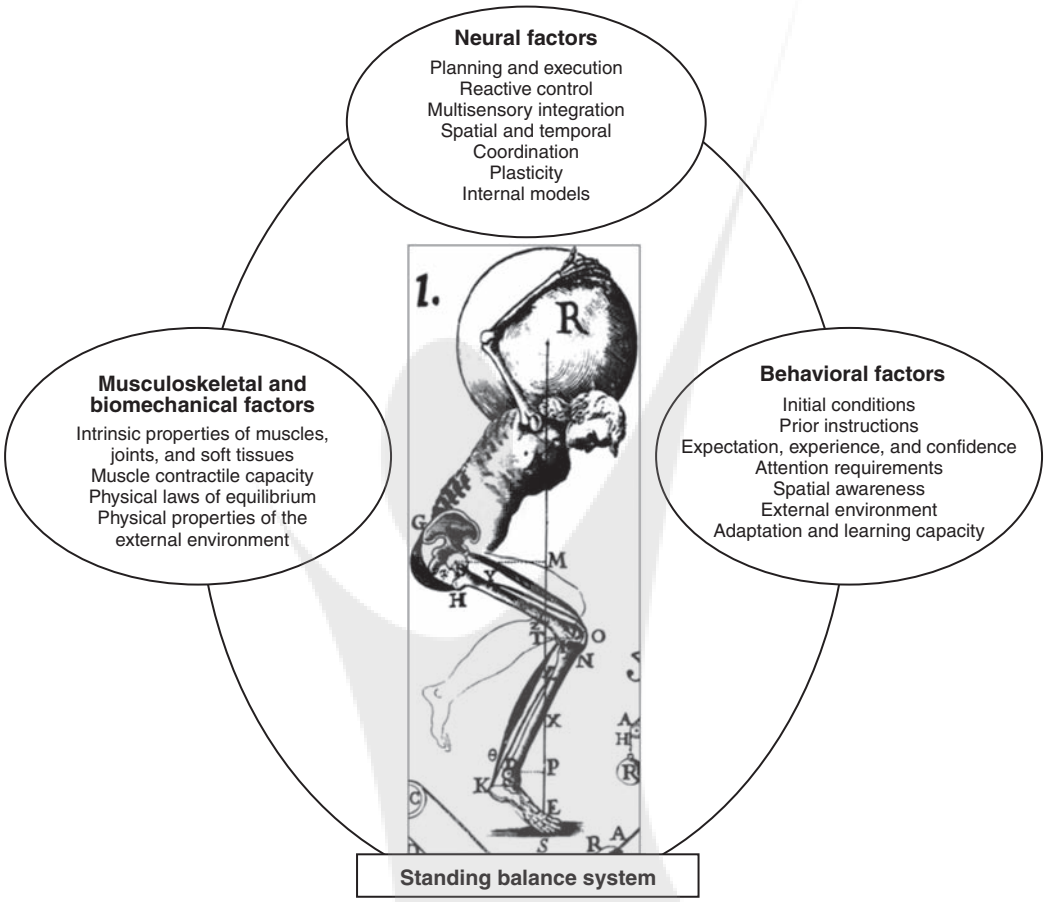

FIGURE 25.1 Conceptual scheme of the multifaceted interactive factors that normally comprise the human standing balance control system.

Source: Adapted from Borelli GA. De Motu Animalium (1680).

the net series elastic component of the calf muscles is less stiff than the body's load stiffness (11,13). Hence, proactive, cyclic calf-muscle activations produce catch-and-throw-like ballistic movements of the body that regulate the COM motion relative to the BOS and produce sway (11). Further details of this form of balance control suggest predictive planning mechanisms implicating the use of internal models relating COM motion and muscle activity linked with skilled, learned behavior (11,12,14,15). Moreover, global, integrated sources of contextually weighted multisensory information, rather than local, joint-specific proprioception information at the ankles are likely utilized to identify the motion of the COM relative to the BOS to maintain balance (16–21). Along these lines, other recent work has focused on cortical and subcortical activity during balance perturbation tasks related to central-set or the readiness to respond, motor preparation, and planning. Postperturbation events have begun to identify links between higher-level neural control processes and balance control (22–33). The influence of attention and other cognitive functions on balance regulation has also become an increasing area of study (see below). The developments illustrated by the foregoing and other studies have important implications for formulating conceptual and theoretical models for understanding and assessing problems with standing balance and for designing the most effective interventions to enhance balance function and prevent related disability after stroke.

Musculoskeletal and Biomechanical Factors

In addition to active muscle contractile capacity and fatigability that can directly impact standing balance stability at the effecter level (34–36), musculoskeletal and biomechanical factors also afford certain advantages and limitations that must be taken into account by neuronal controllers (37). For example, the intrinsic mechanical properties of muscles are designed so they produce greater forces if their rate of strain increases based on the force velocity relationship (38,39). Hence, this effect would rapidly oppose any abrupt stretching effect on muscle caused by disturbances of posture as a first line of defense against instability in advance of reinforcing reactive neuromuscular responses. Similarly, if a contracting muscle is abruptly unloaded, its speed of shortening and force generation decreases (40). Muscle-stabilizing effects on balance will also be influenced by the passive length-tension properties of muscle that are related to the positions of joints at the instant of disturbances to balance (37,41), which may also influence the motor unit recruitment patterns that activate muscles. Moreover, stabilizing joint

torques also depend on changes in the moment arm distances of muscles around a given joint as it is being rotated (42) and on the stiffness of collagenous tissues, like tendons (43).

- At the whole body level, several mechanical factors affecting the COM–BOS relationship at any point in time should be taken into account. Such factors include:
- The height of the COM above the ground
- The load-bearing patterns beneath the feet
- The positional orientation of the feet and any other body surface contacts with the environment that makes up the BOS
- The physical properties of the surfaces used for support (e.g., friction, compliance, and levelness)
- The inertial state of the system (at rest or in motion)
- The mass distribution if external loads are held or applied to the body

Behavioral Factors

The remarkable modifiability and flexibility of essentially all forms of balance-related neuromotor activity to meet the needs of a large variety of functional situations suggest that behaviorally driven factors are another important component of the balance system. Behavioral influences are reflected by:

1. Prior instruction to respond in a particular manner (44)
2. Changes in motor-set reflecting expectations (45)
3. The cognitive demands of attention sharing when performing concurrent tasks (46–50)
4. The experience with a given balance stabilizing situation and confidence (51–54)
5. Changes in initial conditions (55–57)
6. The prevailing environmental conditions (58)

Therefore, a growing body of information has supported the capacity for cognitive processes to influence the control of standing balance. Many of these modulating influences on standing balance have, at least in part, implicated cerebral cortical areas in contributing to shaping neuromotor activity for balance control (59,60).

RECOVERY OF STANDING BALANCE

Clinical Outcome Measures

Problems with balance function accompanying limitations in physical mobility are believed to be common after stroke. Following a total anterior circulation infarct, the median time to recover the ability to stand for 10 seconds is 44 days (61,62). The impact of difficulties with sustaining balance on function has been assessed by studies of balance disability, physical mobility, and performance of activities of daily living (ADLs). The World Health Organization International Classification of Function (ICF) provides a framework for examining both outcome assessments and interventions across a spectrum of functions including Body Structure and Function and Activities and Participation (61). Investigations of balance after stroke should include clinical measures across all three of these domains.

The category of Body Structure and Function includes features of body function that may contribute to balance control and should be part of a comprehensive assessment of persons with balance dysfunction. These measures may include lower extremity joint range of motion, strength and/or muscle recruitment, as well as lower extremity somatosensation. Status of cardiovascular functions may have an impact on the body's ability to adjust to changes in position or maintenance of an upright task and is frequently the underlying factor of the initial stroke. In addition, owing to the multifactorial nature of balance control, assessments of other sensory systems such as somatosensory, visual, and vestibular function that may be impacted by stroke and contribute to overall balance abilities should be included in a comprehensive evaluation (see Chapter 18).

In the Activities domain of balance function, a number of outcome measures have been used in the poststroke assessment of balance. These assessments can be categorized into the aspects of postural control they evaluate: static balance—the ability to hold an upright posture; volitional balance control—the ability to maintain upright postural control while moving; and reactive balance—the ability to respond to an external perturbation. Some of these tools are exclusively measures of balance control whereas others are general mobility assessment tools with balance subsections. Commonly used assessments used to evaluate postural control in a person after stroke include:

Static

One-legged stance test (63)
Clinical test of sensory integration of balance (CTSIB) (64,65)

Volitional Balance

Dynamic Gait Index (DGI) (66,67)
Functional Reach/Multidimensional Reach (68,69)
Timed Get Up and Go (70)
Berg Balance Scale (BBS) (71)
Performance Oriented Mobility Assessment (POMA) (72,73)
Postural Control and Balance for Stroke Test (74)
Balance Evaluation Systems Test (BEST)* (75)
Postural Assessment Scale for Stroke Subjects (76)

*Contains an item of reactive control

Reactive Balance

Equitest (77,78)

Mobility Assessments With Balance

Chedoke McMaster (79)
Brunel Balance Assessment (80)
Rivermead Mobility Index (81,82)
Fugl-Meyer (Balance subscale) (83,84)
Clinical Outcome Variables (85–87)
Community Balance and Mobility Scale (88)

Although each of these tests is a generally valid and reliable assessment of balance function, they vary in their psychometric properties such as their sensitivity to change, their floor or ceiling effects, or their applicability to a wide range of balance abilities (89).

A generally consistent finding in the literature is a positive relationship between balance function and other aspects of functional mobility and ADLs (90–95). It is somewhat difficult to extract a clear picture of the precise relationship between these aspects of recovery because of the variability in outcome measures and subject selection criteria between the studies (96). In one of the more comprehensive studies focused on balance disability in the acute phase of recovery after stroke (2–4 weeks), 75 subjects with a single-incident anterior circulation stroke were evaluated (96). A regression modeling approach was applied to assess the frequency of balance problems, characterize the different severity levels of balance function, and determine the factors associated with balance disability. Balance disability (Brunel Balance Assessment (80)) was present in 83% of the subjects, 40% were able to stand without assistance from another person though they could not step or walk, whereas 33% could step but with limited balance. Subjects in the stepping balance group were less impaired and disabled than those with more limited standing balance, and this reflected differences in the severity of stroke pathology. None of the demographic or stroke pathology factors, including age, gender, premorbid disability, side of stoke, or stroke type, were associated with balance disability. Multiple regression analysis of significant impairment factors indicated that clinical measures of sensation and weakness were independently associated with balance disability and accounted for 47% of the variance. These results were broadly comparable to the few earlier reports of balance disability (97–99) that used correlation designs. The exclusion of assessments of other potentially important balance factors, such as vision, psychomotor speed, musculoskeletal factors, and attention and other cognitive factors, likely accounted for the 53% of variance that was unaccounted for. The contribution of balance self-efficacy or perceived ability to these results and those of other investigations of balance function and disability should also be taken into account (100).

Another representative study (101) of early balance recovery of function in 29 mild and moderately involved individuals after stroke (1 month and 3 months) included functional (Berg Balance Scale [BBS] (71) and Clinical Outcomes Variables Scale [COVS] (85)) and physiological assessments (electromyography and center of pressure recordings). Functional balance and mobility improved over the two-month recovery period in both groups who received inpatient rehabilitation for either one month (moderate group) or four days (mild group). The moderate group showed a threefold greater improvement than the mild group on the COVS and improved performance on the BBS, whereas the mild group approached maximum scores on both outcomes at three months. Improvements in health-related quality of life (Medical Outcomes Study 36-Item Short-Form Health Survey—SF 36) (102) physical component occurred for both groups but remained lower than normative values. These profiles were accompanied by impairments in muscle activation patterns and postural sway that showed some improvements over time but remained significantly impaired relative to healthy controls even in the mild group, which achieved virtually maximum performance scores on functional balance and mobility. Change in physical component COVS scores and change in functional or physiological balance measures were uncorrelated. These results and those of other studies emphasizing balance impairments (see below) suggest that improvements in balance and mobility functions can be uncoupled from changes in many balance-related control factors assumed to be contributing to disability that may limit participation in occupation and leisure interests. These observations direct attention to the need to improve understanding of the relationship between the natural evolution of impaired balance-control factors following stroke, and the adaptive compensatory strategies adopted by individuals to sustain their standing balance.

Balance confidence and falls efficacy may very well be important factors in the third ICF domain of participation that contribute to willingness to engage in life's activities and have also been linked to reduced balance performance and falls (103). The scales used in poststroke research related to balance control and falls include the Falls Efficacy Scale (104), Activities Specific Balance Confidence Scale (ABC) (105,106), the Stroke Impact Scale (67,107) and the WHO—Quality of Life Brief (108).

In summary, a comprehensive clinical assessment of a patient with balance dysfunction after stroke should include assessments across all three domains of function to better understand all the contributing factors to a given individual's balance control that will aid in the development of a specifically targeted intervention to restore balance control, reduce fall risk, and facilitate return to independence in community functioning.

Instrumented Studies of Balance Impairments

Unperturbed Stationary Standing

Instrumented tests of stationary standing balance after stroke have frequently used force platforms to evaluate the patterns of loading forces between the limbs and the center of pressure (COP) excursions beneath the feet, reflecting postural sway. The tests also reflect active contributions from muscle contractions related to ankle joint torque (anterior-posterior [A-P] direction) and hip joint torque (mediolateral [M-L] direction) (109). These measurements generally represent impairment-level outcomes.

A common finding of such reports has been an overall reduced loading and relative overloading of the forefoot beneath the paretic limb side compared with the nonparetic side; increased postural sway (COP excursion area, amplitude, and velocity), especially in the frontal plane; and impaired spatial and temporal characteristics of leg muscle activation patterns (90,91,110–122). COP fluctuations correlated under

both feet indicate movement in the same direction and synchronization of balance control. The between limb synchronization is reduced among individuals with stroke and has been reported to be correlated to motor impairment and prospective fall risk (121).

Building upon earlier reports, de Haart et al. (91) conducted one of the more comprehensive longitudinal studies of standing balance recovery of 37 subjects who received inpatient rehabilitation beginning 10 weeks after first-time stroke (intracerebral infarct or hematoma). COP excursions under each foot were recorded separately when subjects could first stand unsupported for at least 30 seconds and were repeated 2, 4, 8, and 12 weeks later. At the start of training, postural sway (root mean square of the COP velocities) while attempting to stand as still and symmetrically as possible was four to five times greater in both the A-P and M-L directions than age-matched healthy controls. Across time, sway velocity decreased by 33% in the frontal plane and 18% in the sagittal plane. This improvement was mainly reflected in reduced amplitude of sway in both directions and a relatively larger improvement in the frontal plane when tested with eyes closed. Dual-task interference (concurrent arithmetic task) increased overall sagittal sway velocity by a small amount (14%). Static and dynamic parameters of kinetic asymmetry between the sides showed that, at baseline, 13.5% more weight was borne beneath the nonparetic side and was reduced to 10% at 4 weeks with no further change across the 12-week period. The ratio of paretic side COP velocity regulation to nonparetic side regulation was greater than two to one and remained unchanged. The level of paretic side forefoot loading was about 7% to 9% greater than the nonparetic side across standing conditions and did not vary with time of progression. Lack of vision did not affect weight-bearing asymmetry, but introduction of the dual task increased weight-bearing asymmetry by 32% overall compared with standing with the eyes open. This effect did not change with time. Clinical characteristics showed no effects of age, time after stroke, or type and location of stroke. Improvements in walking function occurred during rehabilitation as indicated by the median two-point increase in Functional Ambulation Categories score. Subjects with either lower motor selectivity function at baseline (Brunnstrom Scale Stages I–IV), ankle clonus, or lower ankle joint proprioception had substantially more weight-bearing asymmetry than those with better selectivity (Stages V–VI), no clonus, and normal ankle position sense.

Despite the study limitations, several key points that generally summarize and extend the findings of many studies of stationary standing ability after stroke can be extracted from the above findings:

1. Relatively severe disruption of stationary standing balance control generally exists after stroke in both the A-P and M-L directions of whole body motion. However, it appears that balance ability is disproportionately more affected in the frontal plane compared with the sagittal plane.
2. Over the time of 12 weeks of rehabilitation, M-L balance recovery was considerably more robust than A-P balance recovery, but this might reflect differences in the floor or ceiling effects of measuring performance and/or the specific interventions utilized.
3. Visual deprivation worsened balance performance overall, and this effect accompanied reduced ankle proprioception sense in 65% of subjects, but this dependency decreased for M-L balance during the time of rehabilitation, suggesting possible improved somatosensory integration.
4. The persistence of dynamic and weight-bearing asymmetries between the paretic and nonparetic sides and their worsening when cognitive resources are challenged suggests that automaticity (unconscious) of paretic limb weight-bearing support and use for balance control are common deficits after stroke that may precipitate lateral instability.
5. Similar to the studies of functional balance and disability discussed earlier, the observed recovery of functional mobility and motor selectivity score and residual deficits in controlling standing balance suggest that substantial compensations in sway regulation and functional balance performance are likely contributed by the nonparetic leg, which may be unable to completely compensate for insufficient paretic limb control.
6. There are indications that the standing asymmetry and lateral balance instability after stroke may be linked with visuospatial hemineglect (91,117), though this possibility requires further investigation.

Although considerable emphasis has been given to studying the quasi-static balance task of stationary standing, the ecological validity of such tests may be questionable in view of the more dynamic challenges of everyday balance requirements (123), which normally involve very different biomechanical solutions than those for stationary standing balance (124). Therefore, some caution should be used when attempting to extrapolate information about stationary standing performance after stroke to more dynamic balance situations. Nevertheless, measurements of stationary standing ability after stroke have shown associations with functional measures of balance and gait (90,99,110), suggesting they may provide some useful, though limited, information (123).

External Perturbations of Stance

Externally applied disturbances of standing balance involve mechanical perturbations applied to either the standing support surface or body that alters the COM–BOS relationship, requiring corrective responses from the balance control system to avoid falling. In addition, sensory perturbations of stance entail manipulations in one or more sensory information sources that may be used to sustain balance. Such studies have generally provided useful information about the balance control factors that may become impaired following stroke (muscle recruitment patterns, movement kinetics and

kinematics, and behavioral responses) and thus represent impairment level outcomes.

Mostly cross-sectional studies using external perturbations of stance in older adults with chronic stroke have primarily focused on unchanging BOS or feet-in-place responses. These studies have generally found absent, delayed, altered, or diminished paretic limb postural muscle activation patterns and movements as well as exaggerated compensatory reactions in the nonparetic lower limb that compromise balance (93,110,115,122,123,125–129). These observations support the prevalent reliance on compensatory strategies involving the nonparetic side of the body.

Longitudinal studies examining balance recovery using external perturbation approaches are quite limited. In one study, Kirker et al. (127) used electromyographic (EMG) recordings of hip abductor and adductor muscles and ground reaction force (GRF) measurements to characterize balance-related responses to motorized sideways pushes to the pelvis (2%–3% body weight) in 13 subjects with acute stroke receiving inpatient followed by outpatient rehabilitation. Tests were administered when subjects were first able to stand unsupported (median of 6 weeks after stroke) and serially for up to 38 weeks later. In comparison with normal control responses, four different patterns of hip muscle activation were found in participants with stroke, reflecting a gradation of paretic limb responses from none through progressively more appropriate and larger muscle activations and GRFs and, on the nonparetic side, none through normal or increased responses. Over time, nine subjects showed changes in hip muscle activation and GRFs that progressed toward normal response patterns. EMG latencies of paretic side hip muscles became shorter in seven subjects, but approached normal values in only three subjects. Functional mobility measures (Rivermead Mobility Index (81,82) and 10-m walk test) generally improved in most subjects with time of testing, but those with the most difficulty recruiting paretic-side responses initially used more compensatory involvement of the nonparetic side and had less recovery. However, this reliance on a compensatory balance strategy early on after stroke did not prevent the recovery of more appropriate muscle activation patterns later in recovery (after 21 weeks).

It has previously been mentioned that the lack of information on the active use of protective limb movements, such as stepping or reaching to contact a stable support surface to maintain balance, represents a gap in knowledge about standing balance recovery after stroke (123). This is striking because accumulating evidence has indicated the importance of stepping for dynamic balance recovery during ADLs (130). Moreover, healthy, community-living older adults at risk of falls have an increased reliance on stepping, rather than feet-in-place balance responses (2,54,130–137). Very limited information about perturbation-induced stepping has indicated that evoked steps were initiated primarily with the nonparetic limb following a lean and release postural perturbation in individuals with subacute stroke (121). In addition, increased lower-limb motor recovery scores and initial weight bearing on the nonparetic limb were associated with increased frequency of paretic limb stepping. An acute stroke case study using the same approach to train protective stepping over six sessions plus physical therapy showed short-term improvements in stance loading symmetry and faster speed of stepping (121,138). During inpatient stroke rehabilitation, increased fall rates were associated with increased use of external assistance and frequency of no step trials, lower foot-floor clearance, and delayed time to initiate stepping responses (139). Whereas these studies provide information about the types of changes in induced stepping especially in the acute stages of recovery after stroke, a more comprehensive understanding of the specific impairments in protective stepping performance among chronic stroke survivors that can be targeted for rehabilitation interventions to improve balance and prevent falls is needed.

Influence of Sensory Information on Balance

Studies manipulating sensory information to perturb standing balance with or without accompanying mechanical disturbances have mostly investigated the effects of visual deprivation or distortion. For example, sensory organization testing of 40 chronic poststroke subjects of at least a year's duration indicated greater balance difficulties with eyes closed on a sway-referenced support surface and when visual and vestibular information was incongruent with vestibular information intact (140). This might indicate that individuals with chronic stroke are excessively reliant on visual input (141), but it does not mean a neglect of the vestibular and proprioceptive information, rather a dependence on these two systems for balance control (142). The ability to select the appropriate sensory information for balance is impaired to a greater extent at 1 year than 1 month following a stroke (143). Impairments in the ability to reweight or integrate multisensory sources of information for standing balance, in addition to muscle weakness, also appear to contribute to A-P balance instability and acute falls during sensory organization testing after chronic stroke (129). Additional information is needed to better sort out whether such observations reflect impaired integration or weighting of multisensory information, compensatory substitution strategies, or other possible deficits in sensorimotor interactions for balance control after stroke and remain to be addressed (123).

Given the sensorimotor asymmetries that characteristically occur after stroke, Marsden et al. (144) examined the potential role of alterations in corticobulbar projections to brainstem output pathways involved in vestibular control of balance in 16 subjects with chronic middle cerebral artery stroke (mean = 31 months after stroke), two subjects with isolated corticospinal tract lesions involving the pons and medulla, and healthy control subjects. Vestibular-evoked balance responses consisting of frontal plane segmental displacements and M-L GRFs were determined after unilateral galvanic vestibular stimulation (GVS) whereas subjects stood with their eyes closed and equally loading both legs. Single-pulse transcranial magnetic stimulation (TMS) was

used to determine the motor-evoked potentials (MEPs) in the pre-activated tibialis anterior muscle while seated indicating corticospinal excitability. Compared with the controls, an abnormal interlimb difference in response symmetry was found in the stroke group despite equivalent load bearing between the limbs but in the presence of greater M-L sway. Head and pelvis displacements and the net horizontal GRF caused by GVS were higher after stroke. Individual GRFs were greater beneath the nonparetic limb compared with the paretic side, though the latter was comparable to the individual limb responses of controls. TMS-evoked MEPs indicated similar interlimb asymmetries for stroke subjects as well as delayed and lower paretic side responses compared to the controls. This TMS delay and GVS asymmetry were correlated ($r^2 = 0.60$) with no effect of lesion location (cortical and subcortical) or time after stroke on the GVS asymmetry. These results indicated that middle cerebral artery stroke disrupts the vestibular control of balance possibly by interrupting corticobulbar connections modulating brain stem balance areas. This perspective was supported by the results from the two subjects with discrete pyramidal tract lesions showing that the responses after a pontine stroke (i.e., above the lower pons) were comparable to middle cerebral artery strokes, but those accompanying a medullary stroke (i.e., below the vestibular nuclei) showed symmetrical GVS responses but asymmetrical TMS responses. Hence, these findings provide new insights pertaining to vestibular-mediated asymmetries of stance control that may contribute to the asymmetries of standing balance that have been consistently identified in most investigations of balance recovery after stroke.

Self-Produced Perturbations and Voluntary Recovery of Balance

Voluntary movements of the body segments and of the whole body exert challenges to sustaining standing balance because of their influences on the COM–BOS relationship as well as reactive forces acting on the body that must be counteracted to stabilize the segments and minimize their perturbation effects on balance. In many situations, voluntary movements are preceded and accompanied by anticipatory postural adjustments (APAs) that serve to minimize in advance the self-produced perturbations to balance induced by the goal-directed action or contribute to the evolving movement (10).

Predominantly cross-sectional studies of individuals with chronic stroke have generally found delayed and reduced APAs of the paretic lower limb muscles and increased activation of the nonparetic leg with reduced speed and amplitude of arm or leg movements that may be accompanied by difficulties with controlling balance (90,101,127,145–151). A longitudinal prospective study (90) determined changes in EMG activation patterns of leg muscles (bilateral hamstrings and soleus) during rapid nonparetic limb arm flexion movements performed while standing in 27 subjects with chronic stroke (mean = 32.7 months after stroke) undergoing a 4-week rehabilitation program. Overall, after a month of rehabilitation treatment, arm acceleration was increased, and EMG-onset latencies in bilateral hamstring muscles occurred earlier relative to arm movement onset and were larger in magnitude, indicating improvements in APA responses. The changes in onset timing and probability of muscle recruitment at posttest approximated the muscle activation patterns of healthy subjects observed previously (149). Across the group, these changes were accompanied by clinically meaningful improvements in functional balance and mobility. However, when subjects were stratified into subgroups based on functional balance scores (Berg Balance Scale, Clinical Outcomes Variables Scale, seven-m comfortable gait speed), 12 subjects with low initial balance scores, which improved at posttest, did not have improvements in paretic muscle activation whereas nonparetic-side APAs did improve. Another ten subjects showed an opposite trend whereby APA characteristics improved but functional measures did not. Respectively, these different patterns of recovery were consistent with the development of a compensatory strategy and true physiological recovery.

During natural speed voluntary leaning of the body as far as possible in different directions without moving the feet, hemiparetic subjects have difficulties in all directions and especially toward the paretic side (152). These problems with recovering weight-shifting ability have been examined in-depth longitudinally in 36 subjects who received inpatient rehabilitation beginning 10 weeks after first-time stroke (intracerebral infarct or hematoma). Voluntary frontal plane weight-shifting guided by visual COP feedback was quantified by COP displacements under each foot when subjects could first stand unsupported for at least 30 seconds and after 2, 4, 8, and 12 weeks later. Weight-shifting speed increased by 33% over the first 8 weeks and stabilized at a level that was slower than that of healthy control subjects. The imprecision of weight shifting continued to reduce by 25% over the 12 weeks of recovery and achieved normative values. Subjects retained a constant level of weight-transfer time asymmetry by being 23% slower toward the paretic leg compared with nonparetic-side transfers. Older age of greater than 65 years and the presence of visuospatial neglect were associated with a greater level of weight-shifting speed asymmetry but not with its recovery. Considering the coordinated interlimb hip abductor–adductor muscle control that normally underlies lateral weight transfer and its impairment after stroke (127,150,151,153), the persistence in weight transfer time asymmetry may be indicative of difficulties with weight shifting to either side, as has been emphasized in other studies (147,150,154,155).

Altering the BOS through stepping or by grasping a stable support surface occurs not only in reaction to an external postural perturbation but also can be engaged voluntarily in anticipation of a perceived threat to stability. Studies of voluntary stepping in individuals with chronic stroke have found that decreased weight bearing on the paretic limb prior to stepping was related to less propulsive force for forward momentum during paretic limb gait initiation (145). Reduced paretic limb propulsive force has also been reported to limit gait initiation speed when stepping with

either limb (156). The first step characteristics can be altered to a greater extent for nonparetic limb stepping when the paretic side is in single limb support (157). In reaction time stepping, step speed was observed to be slower in all step characteristics examined under single and dual task conditions for those with chronic stroke compared with controls (158). Moreover, mildly impaired stroke patients have difficulties with initiating and executing visually triggered step adjustments affecting balance control especially involving the medial direction where balance demands were the most challenging (159).

Falls

Stroke is among the leading risk factors for falls in older adults (160). Between 23% to 73% of community-dwelling older adults with chronic stroke fall once or more within four to six months after discharge from hospital (160,161). Community-based prospective studies have found that a history of stroke increases the risk of falling by two to sixfold (160,162,163) and when controlling for falls among older adults the rate is 1.77 times higher in the stroke population (164). Compared with healthy adults, this population has more than seven times the risk of experiencing a fracture (165).

Despite the contributions of multiple risk factors to falls accompanying aging and the complicating effects of stroke (e.g., environmental hazards, orthostatic hypotension, disorientation, and sedation), it is well recognized that those who fall present greater impairments in balance and mobility functions, which have been consistently found to be among the most important risk factors for falls (131,166–168). Cognition also plays an important role with more incidence of falls in those individuals with left hemiparesis (169,170) and a four-time greater risk of a fall in the first six months. In people with acute stroke (up to one month after stroke) and subacute stroke (one to six months after stroke), falls have been associated with balance and mobility impairments (95,161,171,172), visuospatial deficits, hemineglect (173), and cognitive deficits (95,172,174,175). People with chronic stroke (more than six months afterstroke) who have fallen reported that they were usually either walking or dressing when falls occurred, and they have attributed their falls to loss of balance, misstepping, foot drag related to tripping, or a lack of concentration and poor judgment (176). However, among individuals with chronic stroke, the relationship between balance factors and falls is unclear (92).

For people with chronic stroke living in the community, studies of functional balance and mobility have either found a relationship with falls (176–179) or no relationship (92,160,180,181). Part of the discrepancy in these findings appears to be related to whether or not fall prediction outcomes were focused on single fall events and/or multiple fall events (161,177,179–182). The level of stroke chronicity may also be an influential variable related to functional balance and falls (92,180,181). For example, a retrospective study of falls in 99 community-living subjects with chronic stroke (mean time poststroke = 4 years, range = 1 to 24 years) found that clinical measures of balance (Berg Balance Scale), mobility (gait speed), and cognitive status (Mini-Mental Status Exam) did not discriminate between fallers and nonfallers (92). A major conclusion was that routine clinical tests of balance may not test those aspects required to prevent falling and that more sensitive measures of balance that include large components of reactive dynamic balance are needed. At least for the chronic stroke population, this report, together with the other inconsistencies in the literature, raises some caution when using functional tests of balance and mobility to determine fall risk outcomes.

Currently, relationships between changes in motor control factors affecting standing balance after stroke (impairments and compensations) and the risk of falls are largely unknown. One study (183) investigated acutely induced falls into a support harness following standing-platform perturbations of balance in 44 subjects with single-episode chronic stroke (mean time poststroke onset, about 3.5 years) involving variable lesion sites who were not currently receiving rehabilitation. EMG activity from leg muscles, GRFs, and kinematic recordings were used to characterize postural balance responses with subjects classified as either fallers (required harness support to prevent falling in one or more trials) or nonfallers (no support needed). One-fourth of the subjects fell during the forward displacement trials, leading to a backward balance disturbance with 7% of subjects falling during posterior displacement trials. Comparison of balance responses for the anterior perturbations indicated slower paretic muscle activation timing for the fallers in the tibialis anterior, rectus femoris, and biceps femoris muscles, with longer intramuscular onset timing intervals bilaterally. At perturbation onset, the nonparetic side ankle was more dorsiflexed, the paretic hip more flexed, and the trunk position more anterior for the nonfallers compared with the fallers. At the completion of perturbation, the trunk position was more posterior, and the backward velocity was greater for the faller group compared with the nonfaller group. The muscle activation timing differences and differences in kinematics between the groups were consistent with the possibility that they directly contributed to the large number of fall episodes among the faller group. However, the muscle onset timing delays of approximately 20 to 35 ms and intramuscular delays of less than 20 ms were relatively small, making their potential to directly cause loss of balance somewhat uncertain. However, these changes might compound the overall balance stability deficit. Furthermore, the initial postural conditions adopted by the nonfallers likely provided them with a compensatory mechanical advantage that somewhat offset the backward falling tendency produced by subsequent movement of the platform.

Behavioral Factors

Behavioral factors influencing balance and mobility performance may also be an important determinant contributing to falls after stroke. Fall-related self-efficacy refers to the confidence an individual has in performing routine daily

activities without falling or losing balance (184). An increasing number of studies in this area have reported significant relationships between fall-related self-efficacy (measured by the Falls Efficacy Scale or Activities-specific Balance Confidence Scale) and balance and mobility (185–187) and falls (181,186). It is striking that though balance and mobility performance may not be a determinant of falls in some studies (92,181,186), fall-related self-efficacy is independently associated with balance, mobility, and falls in these reports. A recent longitudinal study following 98 participants with hemiparesis for one year after inpatient rehabilitation revealed balance confidence is lower than controls initially and remains lower than controls after one year (185). The improvement in balance confidence was influenced by the number of falls. Therefore, increased attention should be given to assessing and treating behavioral factors underlying fall-related self-efficacy associated with falls and fractures after stroke.

Site of Brain Lesion

To date, there have been relatively few studies that have examined the relationship between the specific location of the brain lesion causing stroke and the recovery of standing balance. The majority of information has addressed balance outcomes relative to the side of hemispheric stroke. In general, these reports have indicated that acute and more chronic problems with balance recovery are more marked for right hemispheric lesions compared with left-sided insults (189–194). Other studies, however, have not been able to confirm this general finding (99,140,195). Right hemispheric lesion effects on balance have been linked with hemispatial neglect manifested by lack of awareness or acknowledgement of objects or people on the side of the body opposite of the lesion (196). Right hemisphere neural networks are thought to be important for both spatial attention and postural awareness of verticality (196). The perception of visual verticality is often disrupted after stroke and might be an underlying component of balance impairment. For example, visual verticality was tested for 30 individuals with hemiplegia after a single hemispheric stroke within 45 days of stroke, and then at 3 and 6 months after stroke (197). Sixty percent of the participants had an initial inaccurate perception of verticality, and 39% of these recovered during the first three months after stroke. The evolution of visual verticality depended on the side of the lesion where recovery was better in left hemisphere-lesioned patients suggesting that poorer recovery after right-side stroke might be caused by the predominant role of the right hemisphere in spatial cognition contributing to the poorer recovery of balance.

Brain imaging studies (198) in healthy human subjects have implicated a network of cortical neurons activated by vestibular activity (inferior parietal lobe, temporal–parietal junction, posterior insula, and frontal eye fields) mainly in the right hemisphere of right hand-dominant individuals with neglect. This vestibular cortical network may also be involved with spatial orientation of the body relative to gravity (198). It may also play a more general role in representing the physical laws of motion by producing an internal model of gravity that estimates gravitational effects on the body and external objects (199). One such problem involves "the pusher syndrome," in which patients push toward the paretic side, especially while standing, and this may lead to falling (189). Vestibular cortical areas are frequently damaged after right middle cerebral artery stroke, resulting in neglect (140,191,200). Stroke lesions involving parietotemporal and parieto-insular vestibular cortical areas result in major difficulties with balance control (140,191,200). Thus, problems with multisensory integration of balance related information and/or reduced spatial awareness of vertical orientation may be major contributors to deficits in standing balance following stroke (see Chapter 18).

INTERVENTION APPROACHES

Interventions on balance control after stroke include various modalities and intensity of treatment. Some interventions emphasize a task-orientated approach to balance retraining, and others focus on the impairment level of the problem. This section addresses the results of recent intervention studies on standing balance after stroke and is categorized into five areas also found summarized in Table 25.1:

1. Training the neuromuscular system
2. Training using visual feedback
3. Somatosensory re-training
4. Impact of attention: implicit versus explicit training and cognitive strategies
5. External devices

Training the Neuromuscular System

Exercise programs that train the neuromuscular system take on many forms ranging from group, individual, functional training, or impairment-based approaches. Many of the recent research studies incorporated group or station exercises to improve balance in participants following a stroke. Whereas each study focused on a different structure of activities for the intervention, all incorporated functional tasks, such as step-ups, sit-to-stand, lunges, reaching, weight shifts, and walking activities. Others included various brisk-walking activities, obstacle courses, side stepping, marching or functional leg strengthening, and stretching. Some of the stations included tasks that specifically challenge standing balance by narrowing the BOS (foot placement), changing the sensory input (eyes closed, foam surface) or even perturbations by the instructor (93,201–210). Each program was supervised by a trained instructor who provided individually tailored modifications to the prescribed tasks so as to progressively challenge the individual capability of each participant. Varied sensorimotor challenges modified the difficulty level, complexity, and dosage utilized. These challenges allowed each participant the opportunity to develop effective strategies to deal with the many changing environmental conditions that may arise during daily balance tasks. Improvement in strength, static and dynamic balance, and occasionally

(*text continues on page 422*)

TABLE 25.1 Results of Recent Studies on Poststroke Balance Interventions

MUSCLE PERFORMANCE/MOVEMENT TRAINING (INDIVIDUAL OR GROUP STRATEGIES)									
				SIGNIFICANT OUTCOMES AND RESULTS RELATED TO BALANCE					
TYPE OF TRAINING	CITATION	SUBJECTS	STUDY DESIGN	BODY STRUCTURE/ FUNCTION	STATIC CONTROL	VOLITIONAL CONTROL	REACTIVE CONTROL	EFFICACY	COMMENTS
Aerobic with treadmill vs. usual care	Globas et al. (2012) (226)	N = 38 Chronic	RCT	↑ VO_2 ↑ Leg strength ↑ 6MWT	↑ BBS	↑ BBS ↑ RMI	NA	NA	Outcome focus on CV fitness
Aerobic vs. home stretching	Quaney et al. (2009) (227)	N = 38 Chronic	RCT	↑ VO_2	NA	↑ GUG	NA	NA	Trend in BBS Gains not retained
Balance trainer vs. usual care	Goljar et al. (2010) (324)	N = 39 Subacute	RCT		↑ BBS	↑ BBS, ↓ TUG	NA	NA	↑BBS, TUG in both groups
Balance training ex	Olawale and Ogunmakin (2006) (233)	N = 23 Chronic	Single cohort	NA	↑ BBS	↑ BBS	Falls—no change	NA	No control group
Body weight supported treadmill training (BWSTT)	Combs et al. (2010) (221)	N = 19 Chronic	Single cohort	NA	↑ BBS	↑ BBS	NA	↑ SIS, ↑ ABC	No control group
Body weight supported treadmill training with or without followed by manual gait training	Conesa et al. (2012) (220)	N = 103 Subacute	Single cohort (longitudinal follow-up)	NA	NA	↑ POMA	NA	NA	No control group
Body weight supported treadmill training 2 and 6 mos vs. home ex	Duncan et al. (2011) (222)	N = 408 Subacute	RCT	↑ FM-LE	↑ BBS	↑ BBS	NA	↑ SIS, ↑ ABC	Group differences at 6 but not 12 mos.
Circuit group training	English et al. (2007) (203)	N = 68 Subacute inpatient	NRCT	↑ 2MWT	↑ BBS	↑ BBS	NA	NA	↑ BBS both groups
Community based intensive motor training vs. usual care	Askim et al. (2010) (234)	N = 62 Subacute	RCT	↑ MAS	↑ BBS	↑ BBS	NA	↑ SIS	Both groups improved
Community group low intensity program	Cramp et al. (2010) (235)	N = 18 Subacute-chronic	Single cohort	↑ LE strength	↑ BBS	↑ BBS	NA	NA	No control group
Community-based group exercise	Eng et al. (2003) (202)	N = 25 Chronic	Single cohort	NA	↑ BBS	↑ BBS	NA	NA	No control group

Community-based ambulation training	Park et al. (2011) (225)	N = 25	RCT	NA	NA	NA	NA	↑ ABC	Two groups not time matched
Community program (adaptive physical activity)	Stuart et al. (2009) (236)	N = 93 Chronic	NRCT	↑ MI, ↑ 6MWT	↑ BBS	↑ BBS	NA	↑ SIS	Control group declined
Cycling with and without E-stim	Janssen et al. (2008) (228)	N = 12 Chronic	RCT	↑ strength ↑ 6 MWT	↑ BBS	↑ BBS	NA	NA	Both groups improved
Cycling + usual care vs. usual care	Katz-Leurer et al. (2006) (229)	N = 24 Subacute	RCT	↑ FM-LE	↑ PASS static	↑ PASS dynamic	NA	NA	Both groups improve but > cycling
Gait training with RAS	Hayden et al. (2009) (231)	N = 15 Subacute	Single cohort	NA	1 Limb stance	FRT no change TUG no change	NA	NA	No control group
Group agility/obstacle course, with stretching and strengthening	Macko et al. (2008) (205)	N = 20 Chronic	Single cohort	↑ MI ↑ 6MWT	↑ BBS	↑ BBS ↑ BI, ↑ SPPB	NA	↑ GDS, ↑ SIS	No control group
Group agility exercise vs. stretch/weight shift	Marigold et al. (2005) (93)	N = 61 Chronic	RCT	earlier onset muscle activity	↑BBS	↑ BBS ↓ TUG	↓ falls ↓ step reaction time	↑NHP, ↑ABC	Both groups improved; 1 yr. follow-up Fewer falls in agility group
Group balance	Michael et al. (2009) (237)	N = 7 Chronic	Single cohort	↑ VO_2 ↑ 6MWT	↑ BBS	↑ BBS ↑ DGI	NA	FES no change	No control group
Group balance	Mount et al. (2005) (206)	N = 4 Chronic	Case series	NA	↑ BBS	↑ BBS	NA	NA	No change in three cases for POMA
Home exercise program vs. education	Duncan et al. (2003) (201)	N = 92 Subacute	RCT	↑ LE strength ↑ 6MWT ↑ FM-LE	↑ BBS	↑ BBS	NA	NA	
Induced step training	Mansfield et al. (2011) (121)	N = 1 Subacute	Case report	↑ CMSA	↑ BBS ↓ Wt. bearing asymmetry	↑ BBS	↓ step duration and onset	NA	
Intensive exercise vs. self-initiated ex.	Langhammer et al. (2009) (325)	N = 75 Subacute	RCT	↑ MAS ↑ 6MWT	↑ BBS	↑ BBS ↓ TUG	NA	NA	Both groups improved
Lower extremity vs. upper extremity ex.	Pang and Eng (2008) (238)	N = 63 Chronic	RCT	↑ strength	↑ BBS	↑ BBS	NA	↑ ABC	Both groups improved
Mass practice strength training	Fritz et al. (2007) (211)	N = 8 Chronic	Case series	NA	↑ BBS	↑ BBS ↑ DGI, ↓ TUG	NA	↑ FES	
Mass practice	Vearrier et al. (2005) (208)	N = 10 Chronic	Single subject	NA	↑ BBS	↑ BBS	↓ Time to stabilize COP ↓ falls	↑ ABC	

(*continued*)

Table 25.1 Results of Recent Studies on Poststroke Balance Interventions (*continued*)

MUSCLE PERFORMANCE/MOVEMENT TRAINING (INDIVIDUAL OR GROUP STRATEGIES)									
				SIGNIFICANT OUTCOMES AND RESULTS RELATED TO BALANCE					
TYPE OF TRAINING	CITATION	SUBJECTS	STUDY DESIGN	BODY STRUCTURE/ FUNCTION	STATIC CONTROL	VOLITIONAL CONTROL	REACTIVE CONTROL	EFFICACY	COMMENTS
Sit to stand training + usual care vs. usual care	Tung et al. (2010) (230)	N =32 Chronic	RCT	↑ LE strength	↑ BBS ↑ Wt. distribution	↑ BBS LOS: ↑ Anterior control	NA	NA	↑ BBS both groups
Sliding rehabilitation machine + usual care vs. usual care	Byun et al. (2011) (326)	N = 30 Chronic	RCT with crossover	↑ LE strength ↑ MAS ↑ 6MWT	↑ BBS	↑ BBS ↓ TUG	NA	NA	
Speed dependent vs. steady speed treadmill	Lau et al. (2011) (223)	N = 26 Subacute	RCT	NA	↑ BBS	↑ BBS ↑ step length	NA	NA	↑ BBS both groups
Tai Chi vs. stretching	Au-Yeung et al. (2009) (218)	N = 136 Chronic	RCT	NA	NA	TUG no change ↑ COG excursion ↓ reaction time	NA	NA	
Tai Chi vs. group balance exercise	Hart et al. (2004) (204)	N = 18 Chronic	RCT	NA	BBS no change, Romberg	TUG no change	NA	↑ DHP	Control improved: Romberg, TUG, BBS
Task-oriented training (high intensity) vs. low intensity training	Outermans et al. (2010) (327)	N = 44 Subacute	RCT	↑ 6MWT	↑ BBS	↑ BBS, ↑ FRT	NA	NA	No group difference for BBS, FRT
Task-oriented resistance training	Yang et al. (2006) (210)	N = 48 Chronic	RCT	↑ LE strength	NA	↑ step test, ↓ TUG	NA	NA	
Yoga vs. usual care	Schmid et al. (2012) (219)	N = 37 Chronic	RCT	NA	↑ BBS	↑ BBS	↓ FOF		Both groups ↓ FOF
VISUAL FEEDBACK TRAINING									
Auditory and visual cueing vs. usual care	Chouhan and Kumar (2012) (232)	N = 45 Subacute	RCT	NA	NA	↑ DGI	NA	NA	Gains for auditory and visual cueing groups only
Balance control trainer-vertical movement	Lee et al. (2012) (328)	N = 40 Chronic	RCT	NA	↑ BBS	↑ BBS ↓ TUG	NA	NA	
Computerized dynamic posturography	Hakim et al. (2012) (242)	N = 1 Chronic	Case report	↑ Ankle ROM	↑ BBS ↑ LOS	↑ BBS ↓ TUG	NA	↑ABC	
Insole wedge and sensor + gait vs. gait training	Sungkarat et al. (2011) (243)	N = 35 Subacute-Chronic	RCT	NA	↑ BBS	↑ BBS ↓ TUG	NA	NA	

Kinesthetic ability trainer vs. usual care	Alptekin et al. (2008) (239)	N = 30 Chronic	RCT	↑ FM-LE	↑ static balance index and dynamic COP	↑ dynamic balance index	NA	NA	Both groups improved
Virtual reality + usual care vs. usual care	Cho et al. (2012) (252)	N = 22 Chronic	RCT	NA	↑ BBS	↑ BBS ↓ TUG	NA	NA	
Virtual reality vs. usual care	Jung et al. (2012) (251)	N = 21 Chronic	RCT	NA	NA	↓ TUG	NA	↑ABC	Both groups improve
Virtual reality + usual care vs. usual care	Kim et al. (2009) (250)	N = 24 Chronic	RCT	↑ Modified MAS	↑ BBS	↑ BBS	NA	NA	
Virtual reality + body weight supported treadmill training (BWSTT)	Walker et al. (2010) (249)	N = 6 Chronic	Single cohort	NA	↑ BBS	↑ BBS	NA	NA	No control group. Mixed results across subjects
Virtual reality + treadmill vs. treadmill	Yang et al. (2011) (248)	N = 14 Chronic	RCT	NA	↑ COP and max sway	↑ Sit to stand	NA	NA	No change in other COP measures
Visual feedback vs. usual care	Cheng et al. (2004) (240)	N = 52 Subacute	RCT	NA	COP	↑ direction control ML and AP	↓ Falls	NA	Decrease in falls not significant
Visual biofeedback on Balance master vs. usual care	Rao et al. (2013) (329)	N = 28 Subacute	RCT	FM-LE no change	↑ FM-B	NA	NA	NA	FIM gait and FM-B ↑ in both groups
Visual feedback on balance master	Srivastava et al. (2009) (244)	N = 45 Subacute-Chronic	Single cohort		↑ BBS increase balance index	↑ BBS ↑ LOS	NA	NA	No control group
Visual feedback posturography	Tsaklis et al. (2012) (245)	N = 9 Chronic	Single cohort	NA	↑ BBS ↓ COP velocity; ↓ COP sway area	↑ BBS ↑ COP AP	NA	NA	No control group. No change wt. distribution
SOMATOSENSORY RETRAINING									
Functional Electrical Stimulation (FES)	Robertson et al. (2010) (260)	N = 15 Chronic	Single cohort	↑ Toe clearance	NA	NA	NA	↓ABC	No control group
Multisensory input vs. neurodevelopmental (NDT)	Yelnik et al. (2008) (264)	N = 68 Subacute-Chronic	RCT	NA	↑ BBS, ↑ LOS	↑ BBS	NA	↑NHP	Both groups improved
Sensory training	Hillier and Dunsford (2006) (261)	N = 3 Chronic	Case series	↑ Sensation	↑ SLS	NA	NA	NA	Variable response across subjects
Sensory training vs. relaxation	Lynch et al. (2007) (262)	N = 21 Subacute	RCT	↑ Light touch	↑ BBS	↑ BBS	NA	NA	↑ BBS both groups
Sensory–visual exercise vs. ex without vision	Bayouk et al. (2006) (265)	N = 16 Chronic	RCT		NA	↓ COP AP ↑ Sit to stand	NA	NA	Sit to Stand improves in both groups

(*continued*)

TABLE 25.1 Results of Recent Studies on Poststroke Balance Interventions (*continued*)

TYPE OF TRAINING	CITATION	SUBJECTS	STUDY DESIGN	*SIGNIFICANT OUTCOMES AND RESULTS RELATED TO BALANCE*					COMMENTS
				BODY STRUCTURE/ FUNCTION	STATIC CONTROL	VOLITIONAL CONTROL	REACTIVE CONTROL	EFFICACY	
SOMATOSENSORY RETRAINING									
Tactile sensory training + usual care vs. usual care	Morioka and Yagi (2003) (263)	N = 26 Subacute	RCT	NA	↓ sway	NA	NA	NA	
Tongue-based biofeedback	Badke et al. (2011) (241)	N = 29 Chronic	Single cohort	NA	↑ BBS	↑ BBS, ↑ DGI, ↓ TUG	NA	↑ ABC ↑ SIS	No control group
Whole body vibration vs. placebo vibration	Brogardh et al. (2012) (272)	N = 31 Chronic	RCT	↑ 6MWT	BBS no change	BBS no change ↓ TUG	NA	↑SIS	↓ TUG and ↑ 6MWT in both groups
Whole body vibration + leg exercise vs. leg exercise	Lau et al. (2012) (270)	N = 82 Chronic	RCT	↑ LE strength 6MWT	↑ BBS	↑ BBS	NA	↑ABC	All outcome measures improved in both groups
Whole body vibration vs. music exercise therapy	van Nes et al. (2005) (271)	N = 53 Acute-subacute	RCT	↑ MI	↓ BBS ↑ Trunk control test	↓ BBS ↓ RMI	NA	NA	All outcome measures improved in both groups
IMPLICIT TRAINING OF BALANCE									
Implicit vs. explicate learning	Orrell et al. (2006) (282)	N = 24 Chronic/ healthy	RCT (single session)	NA	NA	NA	NA	NA	Explicit info detrimental to balance task
Upper extremity tasks training	McCombe Waller and Prettyman (2012) (280)	N = 9 Chronic	Single cohort	NA	↑ BBS	↑ BBS ↑ Velocity and directional control	NA	↑ ABC	No control group; Neurocom used
COGNITIVE STRATEGIES									
Mental practice + balance training vs. balance training	Hosseini et al. (2012) (284)	N = 30 Chronic	RCT	NA	↑ BBS	↑ BBS ↓ TUG	NA	NA	
Motor Imagery + gait vs. gait training	Cho et al. (2013) (CN) (283)	N = 28 Chronic	RCT	↑ FM-LE	NA	↑ FRT ↓ TUG	NA	NA	

EXTERNAL DEVICES									
AFO leaf spring vs. no AFO	Cakar et al. (2010) (289)	N = 25 Chronic	Single cohort	NA	↑ BBS	↑ BBS	Fall risk test improved	NA	No control group
Ankle foot orthosis vs. footwear alone	Pohl and Mehrholz (2006) (287)	N = 28 CVA 20; TBI 8. Subacute	RCT	NA	↑ weight bearing ↓ sway	NA	NA	NA	
Assistive device (canes) quad cane vs. single point cane	Laufer (2003) (285)	N = 30 Subacute, 20 controls	RCT	NA	↓ sway	NA	NA	NA	Both canes reduced sway
Bionic knee trainer	Byl (2012) (293)	N = 3 Chronic	Case series	NA	NA	TUG no change ↑ 5x sit to stand	NA	NA	↑ sit to stand at follow up
Robot-assisted device + usual care vs. usual care	Fisher et al. (2011) (291)	N = 21 Subacute	RCT	↑ 3 minute walk test	↑ Tinetti	↑ Tinetti	NA	NA	Both groups improved
Robotic knee orthosis	Wong et al. (2011) (292)	N = 3 Chronic	Case series	↑6MWT	↑BBS	↑EFAP	NA	NA	

Abbreviations: 6MWT, 6-minute walk test; ABC, activities-specific balance confidence scale; AFO, ankle foot orthosis; AP, anterior/posterior; BBS, Berg balance scale; BI, Barthel index; CoP, center of pressure; CV, cardiovascular; DHP, Duke health profile; DGI, dynamic gait index; EFAP, Emory functional ambulation profile; Ex, exercise; FES, falls efficacy scale; FM, Fugl Meyer assessment (LE, lower extremity; B, balance); FOF, fear of falling; FRT, functional reach; GDS, geriatric depression scale; GUG, get up and go (variation of TUG); LOS, limits of stability; MAS, motor assessment scale; MI, motricity index; ML, medial/lateral; NHP, Nottingham health profile; NRCT, nonrandom controlled trial; PASS, postural assessment for stroke; POMA, performance oriented mobility assessment; RAS, rhythmic auditory stimulation; RCT, randomized controlled trial; RMI, Rivermead mobility index; ROM, range of motion; SIS, stroke impact scale; SLS, single leg stance; SOT, sensory organization test; SPPB, short physical performance battery; Tinetti, Tinetti gait and balance; TUG, time up and go.

balance self-efficacy were reported in the studies. Only two studies included an assessment of reactive balance control. After agility training Marigold et al. (93) found that although both groups improved in the clinical outcome measures, the agility group had faster postural reflex onset in the paretic leg compared to controls and had less falls with platform perturbations after interventions. Reactive balance control improved as measured by the ability to step when released from a lean for an individual in the subacute phase after a stroke (121).

Two studies investigated the use of intense practice for improving balance with subjects at least 10 months after stroke (208,211). The training consisted of functional tasks, similar to those listed in the previous exercise studies. Training occurred for three to 6 hours per day for 10 days delivered in one-on-one sessions. Both studies showed improvement in balance with some retention up to three months after training. Although these studies did not use control groups, they support the feasibility of intense practice and the need to offer additional practice to maximize usefulness of treatment interventions.

Numerous studies have investigated the effectiveness of Tai Chi exercise on balance in various populations of older adults (212–216). The majority of the studies have reported improvements in balance and some studies reported changes in proprioception with Tai Chi in older adults (216,217). To date, only two studies have examined the effects of Tai Chi on stroke survivors (204,218). Each of these studies used a different form of Tai Chi for the 12-week duration. One of the studies found that the Tai Chi group did not improve their balance or walking compared to the control group; however, they did show improvements in quality of life (204). In the second study, the stroke group showed significant improvements over control group's limits of stability and reaction time but neither group showed improvement in mobility as measured by the Timed Up and Go. Similarly, Yoga has been used as an intervention to improve balance and showed improvements in balance and a decrease in fear of falling (219). Based on these limited studies, Tai Chi and Yoga appear to be beneficial but not significantly different than other exercise interventions.

Much has been written about treadmill training for gait in many different populations including stroke. Four studies have reported improvement in clinical measures of static and dynamic balance with treadmill training. The interventions varied in intensity and application (body weight, robotic trainer, progressive speed, early vs. late) but reported no difference in balance outcomes between groups or showed improvements with no control group (220–223), except with virtual reality treadmill training. Compared to traditional treadmill training, the virtual reality treadmill incorporating turns had improved stance symmetry and sway excursion during sit to stand. This is in contrast to two studies on walking interventions that showed improvement in balance self-efficacy as measured by the ABC and no change in the balance measure (224,225).

Other studies have investigated the effects of aerobic exercise (226,227), leg cycling (228,229), sit to stand (230), auditory stimulation walking program (231,232) or progressive structured exercise on poststroke survivors (93,201–203,205,206,225,233–238). Only three of these studies examined falls as an outcome measure and two had a decrease in falls (93,208) and one did not change the number of falls (233). Each of these studies included subjects of different stroke duration and different training duration and frequency but all reported improvement in some aspect of balance depending on the clinical balance measure used. The similarities in these interventions are that they require the individual to use their neuromuscular system to move and control their body in challenging tasks. The intensity, duration, and exact activity to produce the most improvement in balance has yet to be identified, but the system must be challenged to change.

Training Using Visual Feedback

Visual feedback training has typically utilized center of pressure trajectory information as feedback to the patient. Commercially available machines, custom computer programs, pressure mats, and electro-goniometers have been used for balance training after stroke to provide the online feedback about movement (239–246). All these studies showed improvement in center of pressure excursion, stability, or limits of stability, and one reported a nonsignificant reduction in falls (240). Most showed improvement in the clinical outcome measure they selected and one study reported an increase in the ABC (242). Use of a single group or unequal treatment intensities and lack of control conditions make it difficult to conclude the direct effect of the visual feedback on the reported changes.

Virtual reality and interactive video gaming have become more prevalent with advances in interactive media technology. A wide variety of applied technology methods have been developed and utilized from limited immersion with simple visual display using 2-D graphics with or without audio feedback to high-end total immersive virtual environments that utilize 3-D stereoscopic multisensory, multiple user experience (247). The potential benefit for these systems may be the ability to easily manipulate the task, safety, more fun, real-time feedback, and varied practice schedules. Virtual reality and interactive video games for balance training after stroke have utilized commercial devices and custom computer programs that offer limited immersion experience (248–252). These studies showed that participants tolerated the experience well and improved in the balance assessment measured. Small sample sizes and unequal treatment intensities limit understanding about the relative effectiveness of such training compared to real world practice.

Utilization of interactive gaming in the clinic has expanded. Application of appropriate games and understanding of the feedback provided will assist the clinician in effective utilization of this new technology into patient care. One study (253) in 2011 provided an analysis of games included in a commercially available gaming system. This analysis included tables of game description, impairments

targeted, and type of feedback provided in each game. Assessment of interactive programs is needed to appropriately match patient needs to selected training approaches.

Somatosensory Retraining

Diminished or altered sensation is a frequent impairment after stroke, and it has been related to reduced standing balance and mobility (98,129,182,254,255). Several studies have shown promising results using sensory retraining of the upper limb (256–259); however, there are relatively few studies that have investigated sensory training for standing balance. One study used functional electrical stimulation of the tibialis anterior muscle of the paretic leg during balance and mobility training and reported an increased toe clearance, but there was a decrease in the self-efficacy surrounding falls prevention measured by the ABC (260). More systematic sensory retraining of pressure detection, hardness, and texture identification under the foot has been reported in three studies (261–263). These studies of sensory retraining in the lower extremity reported encouraging results on changes in sensory measures but little impact on balance. Two of the studies showed improvement of sensory and balance measures over time in subjects with postacute stroke (261,262). However, only one of the studies found a difference in balance measures between the sensory training and control group (263). The positive findings from this study may be attributed to the increased standing time the sensory training group received.

Alteration of visual input is easily accomplished in the clinic by having the patient close their eyes or occluding his or her vision, and improvements in balance were shown in two studies (140,264). One study compared two balance training programs with and without visual cues (140). Compared to the vision-free group, fewer falls were observed in the vision-deprived group with improvement in static standing balance (140). The authors concluded that visual deprivation forces patients to increase their use of somatosensory and vestibular information and a reliance on visual information may be a natural compensatory strategy for dealing with impaired balance early on in the rehabilitation process.

Another simple way to manipulate sensory inputs in balance training is by using soft and firm surfaces. Bayouk et al. (265) used the same exercise program with two groups of chronic stroke survivors. One group performed the exercise with their eyes open; the second group performed the balance tasks with their eyes open and closed and on soft and firm surfaces. The group who performed the exercises with their eyes closed did better in the balance tasks and the 10-meter walk (265). Tilt boards, dimly lighted environments, and uneven or variously textured surfaces are other ways to manipulate sensory inputs in the clinic and challenge the patient to utilize or alternate their use of various sensory systems.

Whole body vibration (WBV) has recently emerged as an intervention that has positive effects on neuromuscular and sensorimotor systems by presumably activating muscles and stimulating sensory receptors (266–269). However, recent studies demonstrate equivocal results regarding the effectiveness of this approach. An investigation of the added benefit of WBV to leg exercises found that, although the treatment was well tolerated, there were no differences in outcomes with the WBV versus exercise alone (270). When WBV alone as an intervention was compared to exercise training to improve balance, gains were seen in balance outcomes that were no greater than exercise training (271,272).

Impact of Attention on Balance Training: Implicit Versus Explicit Training and Cognitive Strategies

Standing balance control requires the integration of multiple systems, the ability to adapt to changes in the task and environment, and some degree of attention (47,50,273). Cognitive deficits after a stroke can occur in the domains of language, orientation, attention, memory, information processing, executive function, and learning. Studies have shown that performance of a dual-task impacts balance in persons after stroke (47,274–276), suggesting that, after stroke, people utilize increased attention to maintain balance.

Current rehabilitation therapies typically involve using many complex and explicit instructions from the clinician on how to perform tasks and evaluation procedures. Recent work involving upper extremity tasks, suggests that this type of information is less helpful and may hinder implicit motor skill learning after stroke (277–279). In a recent study by McCombe Waller et al. (280), implicit training of balance function was investigated in a single cohort of participants after stroke receiving arm training in standing with no explicit cues related to postural control. Gains were found in functional and quantitative measures of balance control. The authors suggested that the improvements in postural control may result from the use of more "automatic" or unconscious processes for balance control given that the attentional focus was on performing the upper extremity task. It has been suggested that training with an attentional focus on postural control may, in fact, be disruptive to the unconscious control processes that subserve these often automatic postural actions (281). Orrell et al. (282) investigated implicit motor learning on a dynamic balance task with and without concurrent cognitive load. They found that all groups (healthy controls and persons after stroke) improved in the balance task, regardless of the task instructions. However, balance performance in the explicit learning poststroke group was impaired during secondary cognitive loading and not impaired in either the implicit learning poststroke group or the control groups. This suggested that providing explicit information may be detrimental to learning and execution of a dynamic balance motor task in some people after stroke. In summary, implicit training of postural control is an alternate intervention option for training balance function in the poststroke population in contrast to more traditional balance interventions that focus on isolated stability and weight shift training with explicit feedback.

Motor imagery has been used as an intervention whereby individuals evoke an imagination of a motor action to improve a particular task. Two studies that have examined motor imagery in conjunction with an existing therapy both showed improvements in postural control and balance (283,284).

External Devices

Assistive devices and lower extremity orthoses are frequently prescribed for individuals after stroke to help with ambulation. These devices have also been shown to increase postural stability (285,286). Canes decrease postural sway with some studies reporting that the quad is more effective in reducing sway (285). However, straight canes and quad canes do not appear to improve symmetrical weight bearing (285). The use of an ankle foot orthosis (AFO), on the other hand, does appear to increase symmetrical weight bearing, decrease postural sway initially, and improve balance, but this effect does not appear to be maintained over the long-term (287–289). One study utilizing a small lift under the stronger lower extremity reported an immediate improvement in symmetry of standing and postural control of individuals with hemiparesis (290).

In addition to external devices worn by patients as assistive devices, external devices have been developed that are used only in training. Recent advances in robotics have led to the development of untethered robotic devices for use in task-oriented training to improve balance control after a stroke (291–293). In one study, three patients used the robotic devices as part of training 1.5 hours at a time, two to four times a week for four weeks. Testing without the device after training showed gains in all three patients in gait parameters, Timed Up and Go, and the 5x's sit-to-stand outcomes (294). Similarly, a case study using a robotic knee orthosis involved three patients training for 18 sessions over a 6-week time period as part of task-oriented mobility training. All subjects demonstrated gains in both the Berg balance scale and the six-minute walk (292). In summary, canes, ankle foot orthosis, and lifts appear to be beneficial for improving standing balance in some situations by providing external support of body load and by increasing the BOS area; however, this may interfere with protective responses of the lower or upper limb (130). Newer robotic external devices worn during task-oriented mobility training show promise for improving balance control without the device after training.

Summary

The studies of standing balance rehabilitation after stroke presented in this section utilized a variety of intervention approaches. The common theme has been one of task-oriented practice under various environmental, sensory, motor, and cognitive challenges. Dosages varied between the studies from intensely concentrated one-on-one rehabilitation sessions to group activities held twice per week. Guidelines for effective standing balance training following stroke remain unclear. However, one might consider two simple straightforward modifications to augment current balance training programs. First, incorporate more training activities with vision occluded as a method to challenge an individual to increase their awareness and use of other sensory modalities. Second, minimize the amount of explicit information that is given during a treatment session to allow the person time to process through the implicit procedural learning system the balance strategies that work best for them.

PROTECTIVE STEPPING: A MODEL FOR LINKING DYNAMIC BALANCE CONTROL, FUNCTIONAL OUTCOMES, AND RISK OF FALLS

As discussed earlier in this chapter, falls and associated injuries related to problems with standing balance are common and are considered some of the most debilitating secondary complications accompanying stroke. The relationship between changes in balance control factors, functional balance, and mobility, and falls in chronic stroke is poorly understood. For example, a retrospective study (92) found that clinical measures of balance, gait mobility, and cognitive status were not associated with falls. A major conclusion was that routine clinical tests may not assess the aspects of balance required to prevent falls and that more sensitive measures of balance that include large components of reactive dynamic balance are needed (92). To a large extent, such current deficiencies in knowledge that limit the development of the most effective rehabilitation interventions to improve standing balance and prevent falls and related disabilities after stroke are likely caused by the lack of comprehensive approaches linking physiological measures of dynamic balance, functional performance, and falls.

The scarcity of information about the active use of limb movements, such as stepping or reaching to contact a stable support surface as a standing balance recovery mechanism after stroke appears to be importantly related to the foregoing observations.

From a biomechanical standpoint, stepping modifies the BOS in relation to the position and motion of the COM to maintain balance. Protective stepping may be initiated in anticipation of an impending loss of balance or fall or in reaction to sensorimotor events following external perturbations to balance. Contrary to traditional views, reactive stepping may be initiated well before the COM reaches the limits of the BOS (2). In addition, protective stepping shares many of the requirements of ongoing gait and therefore is an attractive framework for identifying physiological changes underlying impaired balance and mobility and falls among people with chronic stroke.

Measures of Protective Stepping Predict Future Falls in Healthy Older Adults

From our ongoing studies of generally healthy, community-living older adults at risk for falls, we have identified two

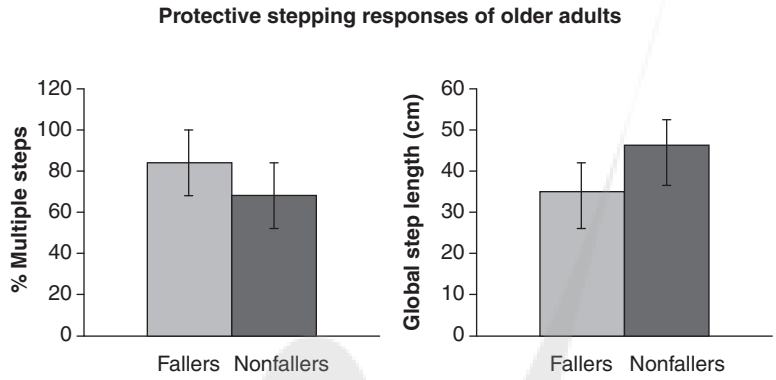

FIGURE 25.2 Group means 1 SD for prospectively identified healthy older fallers (n = 19) and nonfallers (n = 32) showing group differences between (left) first-step global length combining the A-P and M-L directions (two-sample t-test: $P = .003$) and (right) between the percent of the total balance perturbation trials with multiple recovery steps in response to lateral waistpulls K-W: ($P = .018$).

Abbreviations: A-P, antero-posterior; M-L, medio-lateral.

key performance markers of protective stepping that are predictive of prospectively identified falls, including the percentage of trials with multiple recovery steps and first-step global length combining the A-P and M-L directions (135). These measures reflect the effectiveness of stepping to arrest the motion of the COM at foot landing (137). We have previously demonstrated that the distance between the COM and the margin of the BOS, coupled with the COM velocity, is importantly related to effective balance recovery through stepping (2,295). These safety margins are smaller for older fallers than nonfallers (2,295). Hence, step placement relative to body position and motion is a fundamental means by which balance is maintained. Because stepping is often impaired in chronic stroke, we propose that multiple stepping behavior and impaired step length regulation (as well as other factors) will be importantly related to clinical assessments of impairments, functional performance, and falls.

Data from our previous studies of protective stepping using waist-pull perturbations of standing balance in 51 generally healthy, community-living older individuals (mean age 73.3 years) included subjects' prospective fall history for a period of 1 year after testing (135). Logistic regression analyses determined potential predictors of falls. Fall status was included as the dependent variable after dichotomization. Independent variables included percent total trials with multiple steps (rather than a single-recovery step) and first-step global length following multidirectional waist-pull perturbations that always induced stepping. Because controlling sideways balance during multidirectional stepping may be particularly problematic for older people (54,296–298) and is largely dependent upon hip joint abduction–adduction torques (296,298), we also evaluated clinical measures of isokinetic hip abduction (AB) torque (60 degrees through a range of motion of 0–30 degrees).

Overall, 74% (14 out of 19) of the fallers and 31% (10 out of 32) of the nonfallers used multiple steps in 100% of the trials (chi square: $P = .003$) in response to lateral perturbations. Figure 25.2 shows the percent total trials with multiple recovery steps used by the fallers and nonfallers (K-W: $P = .018$). The fallers also had a shorter (two-sample t-test: $P = .003$) first-step global length (34.0 cm 13.9 sd) than the nonfallers (46.1 cm 12.3 sd). Differences in hip strength further discriminated between the groups, whereby fallers produced lower peak hip AB torque than nonfallers (t-test: $P = .008$).

The percent trials with multiple steps were first entered into the single-variable regression model. Then, global-step length was added using a forward stepwise method. The percentage of trials with multiple steps was the strongest predictive value for falls (odds ratio = 6.160, $P = .005$). Fallers who used multiple steps in 100% of the trials were 6.2 times more likely to fall than individuals who did not always use multiple steps. Single variable analysis also showed that, for every decrease of 10 standardized units in step length, the odds of falling increased 2.0 times (odds ratio = 2.028, $P = .006$) and, for every decrease of 0.1 standardized units of peak isokinetic hip AB torque, the odds of falling increased 1.8 times.

The percent trials with multiple steps were combined with global-step length in the two variable models. This combination was not better in predicting fall status than the single-variable models. However, the percent multiple step-hip AB strength model was significantly ($P = .016$) improved over the percent multiple step model alone. Subjects who used multiple steps to recover their lateral balance 100% of the time and had lower peak isokinetic hip AB torque generation were 5.9 times more likely to fall.

We also determined the cutoff scores that provided the highest combination of sensitivity and specificity for predicting one or more falls. For example, in the protective stepping assessment, a cutoff score of 100% multiple steps resulted in 70.5% of the subjects being correctly identified as fallers or nonfallers, a sensitivity of 74%, and a specificity of 69%.

Protective Stepping Performance in Adults With Chronic Stroke Resembles Performance for Healthy, Older Fallers

The kinetic and kinematic characteristics of stepping following waist-pull perturbations of standing balance were evaluated in 10 independently ambulatory subjects with single-episode chronic stroke (mean age = 59.6 years). Three waist-pull trials at a single magnitude level (9 cm, 18 cm/s, 360 cm/s/s) were randomly applied in each of three directions:

- Straight forward (0 degrees)
- Diagonally forward at 30 degrees to the right (–30 degrees)
- To the left (+30 degrees)

Subjects were placed in a safety harness and instructed to react naturally to prevent falling. Overall, regardless of the direction of perturbation, subjects' first step was taken with their nonparetic leg in 66% of the trials. This indicated that they either selected to use and/or were limited to using their paretic leg more often for single-limb support rather than for relocating the BOS during the initial balance recovery step. It was anticipated that forward diagonal perturbations would involve stepping with the passively unloaded leg on the opposite side. This was mostly seen when the nonparetic leg (77% of trials) compared with the paretic leg (52% of trials) was unloaded. However, the use of the paretic leg was greater when that leg was passively unloaded compared to the straight forward perturbations (52% vs. 33%). This indicated that the perturbation direction may be a useful way to encourage forward stepping with the paretic leg.

The data shown in Figure 25.3 further indicates that, regardless of perturbation direction, subjects used multiple recovery steps in a high percentage of the total trials (pulls forward and toward paretic side = 70%, pulls straight forward = 83%, pulls forward and toward nonparetic side = 97%) that generally equaled and exceeded that of older fallers (83%) and occurred with a smaller magnitude of perturbation. Notably, steps taken in response to forward-diagonal waist-pulls toward the nonparetic side were almost always multiple recovery steps. This likely occurs because pulls to the nonparetic side cause passive loading of the nonparetic limb (and paretic limb unloading) that further complicates nonparetic limb stepping. In this case, subjects crossed over the midline of the body with a medially directed paretic limb step, which severely challenged their control of step landing.

In addition to the high incidence of multiple stepping responses, the initial global-step length (combined A-P and M-L directions; Figure 25.3) was shorter for paretic limb steps than for the step length identified for older fallers (Figure 25.2). These data from stroke subjects 13 years younger than the mean age of the older fallers suggest that they are at high risk of falling caused by impaired stepping performance.

To more fully determine the relationship between dynamic balance control and the functional impact of impairments in protective stepping and risk of falling, clinical assessments of balance and mobility and prospective fall data are needed. Falls are tracked through monthly postcards mailed in at the end of each month for one year after testing. For each reported fall, a follow-up telephone call is made to ask about precipitating factors, and, if any injuries were sustained, the medical care sought. The use of monthly mail-in reporting and follow-up is among the most rigorous approaches (299).

Implications and Importance

Application of this or other models to people with stroke will help to fill important deficiencies in knowledge, linking physiological measures of dynamic balance, functional performance, and falls. More elaborate applications of the framework would

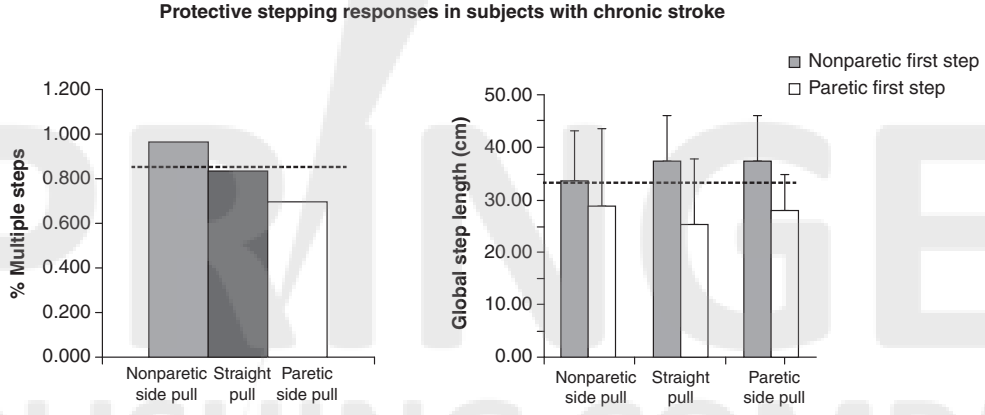

FIGURE 25.3 Means 1 SD for subjects with chronic stroke (n = 10) showing (left) the percent of the total trials with multiple recovery steps for each waist-pull direction and (right) the first-step global length (combined A-P and M-L displacement) for paretic and nonparetic limb steps for each direction of waist-pull perturbation. The broken horizontal lines indicate the levels of healthy elderly faller performance.

Abbreviations: A-P, antero-posterior; M-L, medio-lateral.

include assessing other potentially important factors such as changes in sensory systems, patterns of paresis, individuation of multijoint control, spasticity and joint mobility, response timing and multisegmental coordination, adaptive capacity, attention, and hemispatial neglect. Moreover, comprehensive approaches that attempt to link impairment level outcomes with functional and disability level outcomes, along with ecologically valid tests of dynamic balance recovery, will provide empirically grounded and evidence-based foundations for designing the most effective rehabilitation approaches to improving balance control, functional balance and mobility, and preventing falls.

RESEARCH FRONTIERS

This section provides a glimpse of selected research frontiers that have bearing on understanding the recovery of standing balance after stroke and on the development of the most effective rehabilitation interventions to enhance balance recovery and reduce related disabilities.

Cortical Control of Balance

A growing number of studies have begun to identify the involvement of cerebral cortical areas in the control of standing balance, a role that has been traditionally associated with spinal cord and brainstem systems. Using neural probes such as electroencephalography, positron emission tomography, or transcranial magnetic stimulation, studies of healthy individuals have identified contributions of cortical-mediated activity during standing (27), preceding or following external perturbation of stance (22–24,26,59,300), and accompanying anticipatory postural adjustments during voluntary tasks (25,29,30,33). Although understanding the role of cortical areas in regulating standing balance is still quite limited, this area of investigation is of obvious potential significance to balance recovery after cerebral stroke. Thus, balance-related cortical involvement likely influences several important aspects of standing regulation that may be impaired after stroke, including:

1. Response preparation, planning, and selection
2. Adaptive control mechanisms
3. Attention and other cognitive resources

A recent cross-sectional study, using event-related functional near-infrared spectroscopy examined the cortical involvement in balance recovery after hemiplegic stroke by determining longitudinal regional cortical activation (301). Cortical activation during external postural perturbations was studied in 20 postacute patients with subcortical stroke undergoing inpatient rehabilitation. Perturbation-related activation of the supplementary motor area (SMA) of the affected and unaffected hemispheres was significantly increased after intensive rehabilitation. The enhanced activity in the SMA of the unaffected hemisphere was associated with improved balance function as measured by the Berg balance scale. These findings suggested that the SMA plays an important role in postural balance control, and may be important for balance recovery after hemiplegic stroke. Additional information about the contributing roles of altered cortical mechanisms after stroke and their potential to be modified in the course of functional recovery by rehabilitation interventions such as those being applied to the upper limb (302–306) would be useful for developing the most effective balance intervention programs.

Changes in Skeletal Muscle

It is striking that there have been very few studies of fundamental physical and physiological properties of skeletal muscle after stroke, particularly as they relate to function and the recovery of balance and mobility. However, recent evidence from muscle biopsy (307) has indicated substantial structural and metabolic changes in muscle after stroke, including gross atrophy and shift to fast myosin heavy chain in paretic leg muscle that is associated with gait deficit severity. Evidence also suggests that inflammatory pathway activation and oxidative injury could lead to wasting, altered function, and impaired insulin action in skeletal muscle (307) (see Chapter 11 for further discussion).

Other work (308) using computed tomography to examine changes in muscle composition in 60 subjects with chronic stroke demonstrated 20% lower muscle cross-sectional area and 25% higher intramuscular fat area in the paretic thigh compared to the nonparetic thigh. In older adults without stroke, this low-density lean tissue (fat infiltration) is associated with lower physical fitness levels (309,310) and is implicated in muscle weakness (reduced contractile capacity) and reduced balance function (44,55,140,274,309–313). Few studies have examined the relationship between muscle structural changes and deficits in the paretic muscles. Muscle atrophy is evidence after stroke, and there is a correlation between quadriceps muscle atrophy and knee extensor torque deficits in the paretic limb (314). Importantly, exercise training can modify or reverse skeletal muscle abnormalities in people with chronic stroke (315). Ryan et al. (316) demonstrated the benefits of resistance training on skeletal muscle in participants 6 months after the stroke in a 12-week resistance training program. In the paretic limb, mid-thigh cross-sectional muscle area increased by 13%, maximum leg press strength increased 33%, and paretic knee extension increased by 56%, with a significant reduction in mid-thigh intramuscular fat.

Other changes in the paretic skeletal muscle properties that may contribute to balance deficits are decreased pennation angle (317,318), decreased muscle fiber length (317,318), and changes in tendon length (319,320). However, there are no studies examining the relationship between balance deficits and muscle property changes. Therefore, it would be important to determine the extent to which changes in skeletal muscle after stroke are contributing to balance problems. Further insights into this area could potentially shift or expand the focus of balance and mobility rehabilitation interventions by emphasizing the mitigating roles of muscle properties and mechanisms.

Balance Recovery: Physiological and Compensatory

Difficulty with identifying and understanding balance recovery following stroke is further complicated by the presence of what are commonly thought to be compensatory mechanisms or behaviors that often develop together with improvements in motor control factors that normally contribute to sustaining balance, thought to represent true physiological recovery. In practical terms, it is likely that the two recovery states and their overlap represent a continuum of available solutions that the balance system uses to sustain the COM position and motion within the actual or projected stability limits defined by the BOS conditions.

An intriguing parallel situation to the recovery of balance exists for the recovery of upper limb function in chronic stroke, whereby an individual's potential for functional recovery of limb use can be predicted from neurophysiological (TMS) and imaging (fMRI) measures of neural capacity (321). A major finding of this work was that, in subjects without TMS motor-evoked potentials (MEPs) and a hemispheric cortical asymmetry level that exceeded a critical cutoff value, no functional gains in arm motor recovery were possible with practice training. In contrast, those individuals for whom MEPs could be elicited and who had lower cortical asymmetry were capable of arm motor improvements with training. Thus, corticospinal tract integrity predicted the clinical potential for functional arm recovery in people at about three years after the time of stroke onset. One suggestion was that this approach can be used to help formulate goals for rehabilitation and identify patients for particular types of rehabilitation programs. The applicability of the findings with respect to true recovery and compensatory recovery processes is that those individuals identified to have residual neural capacity could be selected for programs emphasizing motor control factors whereas those with limited capacity might emphasize alternative compensatory solutions. If, as it appears, cortical areas are extensively involved in the control of standing balance (59,60), then a similar, though possibly modified, algorithm could be developed to assess the balance recovery process. Furthermore, from a recovery standpoint, evidence from animal models suggests that a time-limited window of neuroplasticity occurs after stroke where the greatest gains in recovery are likely to occur (322,323). Thus, the challenge for improving motor recovery and balance control following stroke is to determine how to optimally involve and modify residual and intact neuronal networks to enhance recovery from impairment and to develop compensatory strategies to improve function. To expand beyond the neural basis of recovery, it would also be informative to identify similar biological and physiological markers of skeletal muscle capacity and cognitive capacity after stroke to more fully capture the multifaceted nature of standing balance control problems. Overall, this line of investigation is an attractive and important research frontier for advancing the understanding and optimization of the functional recovery and rehabilitation of balance and mobility after stroke.

SUMMARY

The rapid expansion of recent scientific and clinical knowledge has driven the field of rehabilitation to an unprecedented level of growth and understanding. At the forefront of these efforts has been the increasing development of interdisciplinary approaches blending clinical, experimental, and technological expertise. Inherently, the complex and multifaceted nature of the human standing balance system and the challenges to balance rehabilitation will continue to require such integrated approaches to identifying the different factors contributing to balance problems and the means by which they can be effectively treated. In this chapter, we have synthesized current information derived from many of these different approaches. In doing so, we have attempted to identify those areas in need of additional information, areas where information is lacking, and some promising newer areas of inquiry.

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V

POSTSTROKE COMPLICATIONS AND THEIR TREATMENT

26

Secondary Prevention of Ischemic Stroke

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Survivors of a first-ever stroke or transient ischemic attack (TIA) are at high risk for recurrent stroke as well as myocardial infarction (MI) and mortality. Only a small proportion of patients with ischemic or hemorrhagic stroke will be eligible for acute therapy, and thus the greatest impact can be made through prevention. Recurrent stroke, whether symptomatic or silent, increases the morbidity and mortality associated with cerebrovascular disease. Assessment of stroke risk factors and etiology allows for tailored approaches to stroke prevention. It is critical to assess the cardiovascular risk profile and initiate aggressive management of vascular risk factors in all patients (1). Adequate treatment and risk reduction depends on a rapid and accurate classification of the cause of ischemic symptoms, regardless of whether they are transient or permanent (Table 26.1) (2–4).

THERAPEUTIC APPROACH

Large Artery Atherosclerosis

Extracranial Internal Carotid Disease

The benefit of carotid endarterectomy (CEA) was established by three prospective randomized trials: the North American Symptomatic Carotid Endarterectomy Trial (NASCET) (5), the European Carotid Surgery Trial (ECST) (6), and the Veterans Affairs Cooperative Study Program (7). These studies compared endarterectomy plus medical therapy with medical therapy alone. Among symptomatic patients with TIA or minor strokes and high-grade carotid stenosis (greater than 70%), there is overall a significant absolute (from 26.2% to 9% at 2 years) and relative risk (RR) reduction of recurrent stroke with a favorable number needed to treat (NNT = 17). Imaging of the carotid artery can be performed with a variety of modalities, including ultrasound, CT angiography, and MR angiography (Figure 26.1).

For patients with symptomatic carotid stenosis between 50% and 69% (moderate category), the results from NASCET demonstrated a lesser magnitude of benefit with CEA as compared to medical therapy (8). Patients over 75 years old, male, suffering from a recent stroke (rather than TIA), and with hemispheric symptoms are the ones deriving the greatest benefit from CEA. Intracranial stenosis, absence of leukoaraiosis, early surgery, and the presence of collaterals were also associated with better outcome (6,8). There was no significant benefit with surgery if the stenosis was less than 50%. More contemporary data have suggested that the benefit is greatest with early performance of surgery in an otherwise stable patient in view of the approximate 1% per day risk of stroke in the first 2 weeks (9). Emphasizing the importance of identifying symptomatic internal carotid artery stenosis, rapid-access TIA clinics can significantly reduce the risk of subsequent stroke, primarily by improving access to rapid carotid imaging and subsequent intervention (10–12). Stroke or TIA patients awaiting endarterectomy benefit from other maximal medical therapies to aggressively manage risk factors, notably antithrombotic medications and statins (1). After carotid revascularization, patients will continue to benefit from aggressive management of all other traditional cardiovascular disease risk factors.

However, in patients with complete carotid occlusion, CEA is not technically possible. Older (13) and recently completed trials (14) of extracranial–intracranial (ECIC) bypass surgery showed no benefit of surgery, even when perfusion failure was identified by advanced imaging techniques not readily available in most centers

The use of carotid artery stenting (CAS) has been investigated in multiple registry-based studies, as well clinical trials, because of the perceived lower perioperative morbidity, particularly as related to MI. The Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy (SAPPHIRE) trial randomized 334 patients to endarterectomy or stenting with the use of an embolic protection device (15). Most of the benefit was detected in the lower risk of MI for the stent compared with the higher surgical risk of endarterectomy. Two randomized, multicenter trials (EVA3S and SPACE) compared complication rates and long-term complications between CAS and CEA in patients with a symptomatic carotid stenosis of at least 60%. EVA3S aimed to show superiority; the study was stopped prematurely after the inclusion of 527 patients because of excessive stroke risk in the CAS cohort, despite the obligatory use of cerebral protection devices. The 30-day incidence of any stroke or death was 3.9% after endarterectomy and 9.6% after stenting; the RR of any stroke or death after stenting as compared with endarterectomy was 2.5 (95% CI, 1.2 to 5.1) (16). In contrast, SPACE aimed to show noninferiority between the two

TABLE 26.1 Ischemic Stroke Subtypes Atherosclerosis Risk in Communities Study

- Hemorrhagic stroke (17%)
  - Subarachnoid hemorrhage (41%)
  - Intracerebral hemorrhage (59%)
- Ischemic stroke (TOAST classification)
  - Cardioembolic (20%)
  - Large artery atherosclerotic (20%)
  - Small vessel disease (lacune) (25%)

Unknown/Cryptogenic (30%)

Source: From Refs. (2,4).

interventions and included 1,183 patients in the analysis. The rate of death or ipsilateral ischemic stroke from randomization to 30 days after the procedure was 6.8% with CAS and 6.3% with CEA (absolute difference 0.51%, 90% CI –1.89% to 2.91%) (17). The Carotid Revascularization Endarterectomy vs. Stenting Trial (CREST) enrolled both symptomatic and asymptomatic patients and demonstrated that CEA and CAS are equivalent at preventing the combined end point of stroke, MI, and death (18). In that trial CAS was associated with a higher risk of periprocedural stroke, while CEA was associated with a higher risk of MI. In subgroup analysis, patients over the age of 70 seemed to derive a greater benefit from CEA. The International Carotid Stenting Study (ICSS) was performed in Europe and enrolled patients with only symptomatic ICA stenosis. Similar to CREST, investigators showed similar increased rates of neurological complications in the CAS arm compared to CEA, with the overall results favoring CEA (19).

At present, CAS is recommended in selected patients in whom the stenosis is difficult to access surgically and patients with high surgical risk, radiation-induced stenosis, or restenosis after CEA. For patients with extracranial vertebrobasilar disease, medical treatment should be the first choice (antithrombotics, statins, and management of other risk factors). In exceptional circumstances, when patients continue to have symptoms despite maximal medical therapy, endovascular treatment of extracranial vertebral artery origin disease (20) may be considered.

Intracranial Atherosclerosis

High-grade symptomatic intracranial atherosclerosis (ICA) is associated with a high risk of recurrent ischemic stroke. In the Warfarin and Aspirin for Symptomatic Intracranial

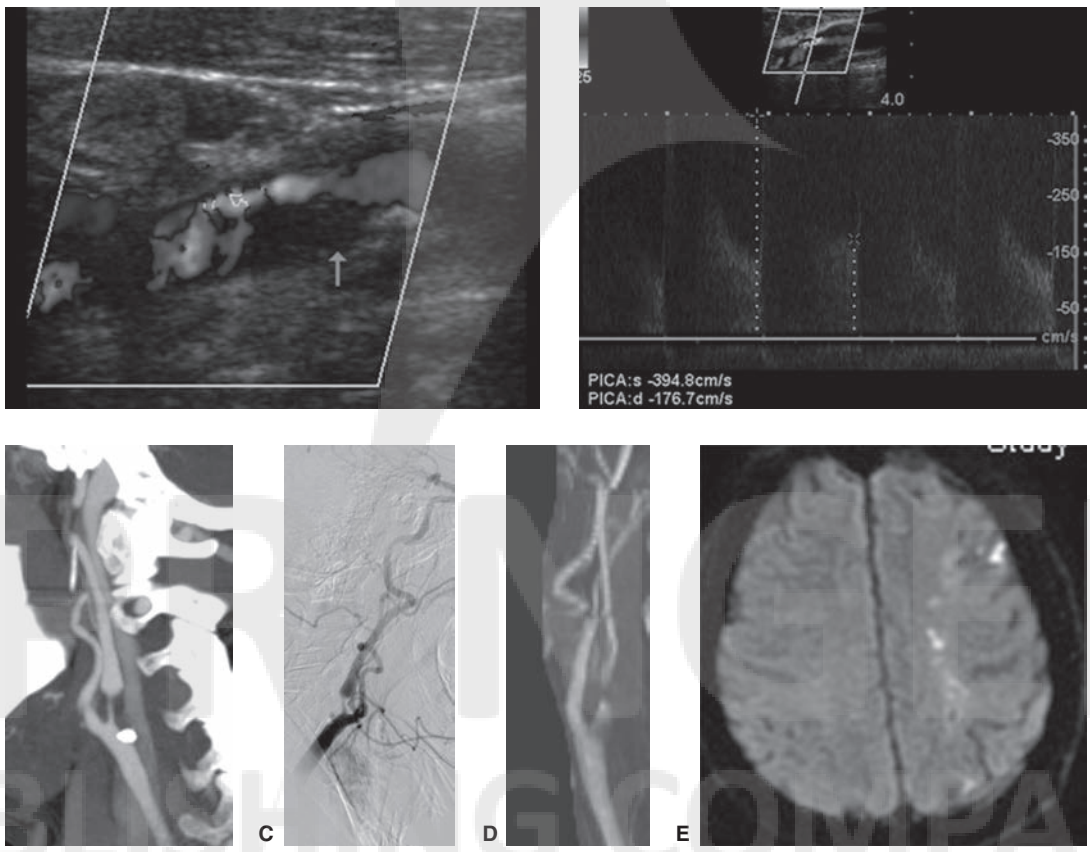

FIGURE 26.1 Imaging of symptomatic internal carotid artery atherosclerosis. (A) Carotid duplex showing plaque and associated elevated velocities (390 cm/s systolic and 177 cm/s diastolic). (B) CT angiography. (C) Digital subtraction angiography. (D) MR angiography. (E) MR image showing left hemispheric infarction.

Disease (WASID) trial, investigators compared high-dose aspirin (1300 mg daily) to adjusted-dose warfarin; the trial was stopped early because of an excess of mortality in the warfarin arm (21). Subgroup analyses in WASID identified those at high risk for recurrent stroke, including patients with stenosis greater than 70% and among patients with blood pressure (BP) that is not controlled to below 140/80 mmHg.

These high-risk subgroups were included in the Stenting and Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis (SAMMPRIS) trial in which patients were randomized to stenting and best medical therapy versus best medical therapy. The medical arm of the trial was novel in including a comprehensive program to reduce the low-density lipoprotein-cholesterol (LDL-C) to less than 70 mg/dL with high-dose statins, tight glycemic control, counseling on exercise and tobacco cessation by a nurse over the phone, target BP less than 140/80 mmHg (lower for diabetics), and treatment with dual antiplatelet agents, aspirin, and clopidogrel for 90 days (22). The SAMMPRIS trial was stopped early due to an excess number of new strokes in the stenting arm (23). Many of the new strokes occured in the posterior circulation and in the territory of perforating arteries, while the medical arm had a lower than expected stroke risk compared to historical baseline from WASID; on long-term follow-up, the risk of stroke remained higher in the stenting arm (24). Therefore, *at this time there is no clear role for routine intracranial artery stenting in the treatment of symptomatic arterial stenosis.*

Cardiogenic Cerebral Embolism

Patients with cardiac conditions such as atrial fibrillation (AF), valvular heart disease, acute MI, cardiomyopathy, patent foramen ovale (PFO) with atrial septal aneurysm, left ventricular dysfunction, and other structural diseases have an increased risk of presenting a first-time ever and recurrent stroke and/or TIA. These cardiac conditions are highly prevalent in the population at risk for stroke, though not all are associated with the same degree of recurrent stroke and not all require anticoagulation. These patients often have multiple vascular risk factors in addition to the cardiac source of embolism. In some cases, this potential dissociation can make the selection of an antithrombotic agent or a decision regarding an intervention complicated. Table 26.2 outlines antithrombotic treatment recommendations for cardioembolic stroke from the American Heart Association secondary prevention guidelines (1).

Atrial Fibrillation

More than 75,000 cases of stroke per year are attributed to AF. Multiple clinical trials have demonstrated the superior therapeutic effect of warfarin compared with placebo in the prevention of thromboembolic events among patients with nonvalvular AF (25). The efficacy of warfarin has an overall RR reduction of 68% (95% CI, 50 to 79). Warfarin has also been shown to be relatively safe and the optimal INR (international normalized ratio) range for anticoagulation appears to be 2.0 to 3.0 (26,27).

There is no evidence that combining anticoagulation with an antiplatelet agent further reduces the risk of stroke compared with anticoagulant therapy alone, though it does significantly increase the risk of bleeding (28). Novel anticoagulants have now entered the market and can be divided into direct thrombin inhibitors (dabigatran) and factor Xa inhibitors (rivaroxaban, apixaban). These three agents were shown to be statistically noninferior compared to warfarin and were associated with fewer complication rates (29–31). A major limitation of these agents, however, has been the inability to reverse their anticoagulant effect and the limited data on patients with renal dysfunction; dabigatran has also been associated with a possible increased risk of MI (32), and cannot be crushed to be administered through enteral means. The combination of aspirin and clopidogrel may be considered for warfarin-ineligible patients, with marginal reductions in absolute risk reduction in stroke compared to aspirin and associated higher hemorrhagic complication rates (33,34).

Exclusion of the left atrial appendage where many of the thrombi form in AF, with either an endovascular or external device, was an attractive alternative to treatment for patients ineligible for warfarin. Though the first trial proved the equivalency of warfarin to the Watchman device (35), a subsequent trial is ongoing and the device has not been FDA approved. An external device is available on a case-by-case basis as a humanitarian device exemption (HDE).

In general, the guidelines for prevention of stroke in patients with ischemic stroke or TIA recommend initiation of oral anticoagulation within two weeks of an ischemic stroke or TIA. In patients with large infarcts, hemorrhagic transformation of an ischemic stroke, or uncontrolled hypertension, additional delays may be appropriate.

Valvular Heart Disease

Rheumatic Mitral Valve Disease. Recurrent embolism occurs in 30% to 65% of patients with rheumatic mitral valve disease who have a history of a previous embolic event. Multiple observational studies have reported that long-term anticoagulant therapy reduces the risk of systemic embolism in patients with rheumatic mitral valve disease (1).

Mitral Valve Prolapse. Mitral valve prolapse (MVP) likely reflects a normal variant rather than a single disease process. Despite years of research, the symptomatology and significance of MVP remain controversial (36). No randomized trials have addressed the efficacy of selected antithrombotic therapies for this specific subgroup of stroke or TIA patients.

Patent Forament Ovale

PFO is a congenital cardiac atrial defect that may provide a conduit for peripheral venous clots to be shunted to the cerebral arterial circulation. The prevalence of PFO is approximately 25% (37). Patients with PFO-associated strokes tend to be younger and are less likely to have traditional

TABLE 26.2 Recommendations for Patient With Cardioembolic Stroke Types

RISK FACTOR	RECOMMENDATION	CLASS/LEVEL OF EVIDENCE
Atrial fibrillation (AF)	Anticoagulation with adjusted-dose warfarin (INR range 2.0–3.0) is recommended for patients with ischemic stroke or TIA with persistent or paroxysmal AF.	Class I, Level A
Valvular heart disease	Long-term warfarin therapy is rational with adjusted dose (INR 2.0–3.0) whether or not AF is present.	Class IIa, Level C
Rheumatic mitral valve disease	Antiplatelet agents should not be added to warfarin, to avoid additional bleeding risk.	Class III, Level C
	For patients who have a recurrent embolism while receiving warfarin, adding aspirin (81 mg/day) is suggested.	Class IIa, Level C
Mitral valve prolapse (MVP)	Long-term antiplatelet therapy is reasonable.	Class IIa, Level C
Mitral annular calcification (MAC)	Antiplatelet therapy may be considered for patients with MAC not documented to be calcific.	Class IIb, Level C
	For patients with mitral regurgitation resulting from MAC without AF, antiplatelet therapy or warfarin may be considered.	Class IIb, Level C
Aortic valve disease	Antiplatelet therapy may be considered for patients who do not have AF.	Class IIa, Level C
Prosthetic heart valves	Oral anticoagulants are recommended for patients with modern mechanical valves (INR 2.5–3.5).	Class I, Level B
	For patients with mechanical valves who have an ischemic stroke or systemic embolism despite adequate therapy with anticoagulants, adding 75–100 mg/day of aspirin (INR 2.5–3.5) is rational.	Class IIa, Level B
	Anticoagulation with warfarin (INR 2.0–3.0) may be considered in patients who have bioprosthetic valves.	Class IIb, Level C
Acute MI and left ventricular thrombus	For patients with ischemic stroke caused by an acute MI in whom LV mural thrombus is identified by cardiac imaging, oral anticoagulation is reasonable (INR 2.0–3.0) for at least 3 months and up to 1 year.	Class IIa, Level B
	Aspirin should be used concurrently for the patient with ischemic coronary artery disease during oral anticoagulant therapy in doses up to 162 mg/day.	Class IIa, Level A
Cardiomyopathies	In this group of patients, either warfarin (INR 2.0–3.0) or antiplatelet therapy may be considered for prevention of recurrent strokes.	Class IIb, Level C
Patent foramen ovale (PFO)	Antiplatelet therapy is reasonable to prevent a recurrent stroke.	Class IIa, Level B
	Warfarin should be used in patients with other indications for oral anticoagulation.	Class IIa, Level C
	PFO closure may be considered for patients with recurrent cryptogenic stroke despite medical therapy.	Class IIb, Level C

risk factors such as hypertension, hypercholesterolemia, or smoking (38,39). PFO can be detected by transthoracic echocardiography using agitated saline injection, though transcranial Doppler with agitated saline injection may be superior (40). The diagnosis of a hypercoagulable state or deep venous thrombosis in the lower extremities in conjunction with the presence of PFO raises the suspicion of a causal role in stroke (41). There has not been a definitive study to establish best medical therapy in the absence of venous thrombus in the young. However, the PICSS study showed no benefit from warfarin in a group of older, conventional stroke patients enrolled in the WARSS trial (42). The question of optimal management remains unresolved. The CLOSURE I trial, and other recently completed trials, have not demonstrated the benefit of percutaneous closure on stroke prevention (43–45); in these trials the overall risk of recurrent stroke is small, particularly among those for whom the PFO is most likely to be causal. Indices have been proposed to identify those in whom PFO is most likely to be causally related to stroke; in most instances these are young patients without stroke risk factors (46). These same patients are at low risk of recurrent stroke.

Noncardioembolic Stroke or TIA

Recently published trials have contributed to the large body of evidence supporting the benefit of antiplatelet agents for stroke prevention in patients with history of noncardioembolic ischemic stroke or TIA. In a meta-analysis of 21 randomized trials comparing antiplatelet therapy with placebo in 18,270 patients with prior stroke or TIA, antiplatelet therapy was associated with a 28% RR reduction in nonfatal strokes and a 16% reduction in fatal strokes (47). In cryptogenic stroke there is often a high suspicion for undetected AF, particularly among patients with infarcts in the cortical surface or cerebellum. Recent data with prolonged rhythm monitoring for up to 30 days with a surface monitor, or for longer periods with an implantable monitor, have demonstrated detection rates for AF that are approximately 30% across multiple studies (48). At many institutions patients with cryptogenic stroke will be discharged with one of these monitors if they are eligible for warfarin and were detected with AF, although the clinical significance of such rare and difficult-to-detect AF remains to be tested.

Antiplatelet Agents

Aspirin

Two randomized controlled trials have demonstrated that aspirin in doses ranging from 162 to 300 mg/day administered within 48 hours of ischemic stroke reduced the rate of recurrent stroke within 2 weeks (49). In the long term, multiple clinical trials have shown the benefits of aspirin compared to placebo at reducing the risk of stroke.

Clopidogrel

The CAPRIE trial randomized patients with stroke, MI, or peripheral arterial disease to clopidogrel versus aspirin. Overall there was a 0.8% absolute risk reduction in stroke, MI, or vascular death in favor of clopidogrel, with much of the benefit among the peripheral arterial disease outcomes (50). The CAPRIE trial, however, was not powered to detect treatment differences within patient subgroups

Overall, the safety of clopidogrel is comparable to that of aspirin, and it has clear advantages over ticlopidine, which is rarely used because of the risk of neutropenia. A few cases of thrombotic thrombocytopenic purpura have been described with clopidogrel.

Addition of Clopidogrel to Aspirin for Prevention of Vascular Events

The double-blind, randomized study Clopidogrel and Aspirin versus Aspirin Alone for the Prevention of Atherothrombotic Events (CHARISMA) randomized 15,603 subjects with cardiovascular disease or multiple risk factors to either 75 mg of clopidogrel plus a low dose of aspirin (75–162 mg) or a placebo plus aspirin (51). Thirty-five percent of subjects (n = 4320) qualified because of a history of cerebrovascular disease within 5 years of enrollment and there was no significant difference in risk of nonfatal ischemic stroke (1.9% vs. 2.4%, $P = .10$) or intracerebral hemorrhage (ICH).

In the Management of Atherothrombosis with Clopidogrel in High Risk Patients with TIA or Stroke (MATCH) trial (52), the combination of dual antiplatelet agents was not associated with an overall decrease in the risk of ischemic stroke compared to clopidogrel alone, particularly when considering the risk of hemorrhage. Patients with a prior stroke or TIA plus additional risk factors (n = 7599) were allocated to 75 mg of clopidogrel or combination therapy with 75 mg of clopidogrel plus 75 mg of aspirin per day up to 6 months from their initial stroke. There was no significant benefit of combination therapy compared with clopidogrel alone in reducing vascular events, death-related vascular events, or rehospitalization secondary to ischemic events. The risk of major hemorrhage was significantly increased in the combination group compared with clopidogrel alone, with a 1.3% absolute increase in life-threatening bleeding. The combination of aspirin and clopidogrel was further tested in the secondary prevention of small subcortical strokes trial, where there was an overall increase risk of mortality in the aspirin and clopidogrel arm compared to aspirin alone (53). In the long term, there is no proven indication for the combination of aspirin and clopidogrel over a single agent for noncardioembolic stroke.

The combination of aspirin and clopidogrel over shorter periods has gained significant attention in the acute setting for minor stroke and TIA. In the recently completed Clopidogrel in High-Risk Patients with Acute Nondisabling Cerebrovascular Events (CHANCE) trial (54,55), aspirin and clopidogrel for 21 days followed by clopidogrel monotherapy versus aspirin alone, reduced the risk of ischemic stroke at 90 days without an increase in hemorrhage. Further confirmatory trials are ongoing and must be completed and reviewed before this can be adopted as the standard of care.

Aspirin and Dipyridamole

Several trials have evaluated the efficacy of aspirin in combination with dipyridamole. The European Stroke Prevention Study (ESPS-2) randomized 6602 patients with prior stroke or TIA into 3 groups: (a) 50 mg/day of aspirin plus 400 mg/day of extended-release dipyridamole, (b) aspirin alone, (c) extended-release dipyridamole alone, and (d) a placebo. The risk of stroke was significantly reduced by 18% on aspirin alone, 16% with dipyridamole alone, and 37% with a combination of aspirin plus dipyridamole. The combination was superior to aspirin alone in reducing recurrence of stroke (23%) and 25% superior to dipyridamole alone (56). The effect of the combination was further confirmed in a later clinical trial (57), while the combination seems to have similar efficacy to clopidogrel alone (58). The most common side effect of dipyridamole was headache, which can represent an adherence issue during treatment. Bleeding was not significantly increased by dipyridamole.

Aspirin, a combination of aspirin and extended-release dipyridamole, and clopidogrel all remain accepted options

for initial therapy for patients with noncardioembolic ischemic stroke and TIA; therefore, the selection of an antiplatelet agent should be individualized on the basis of patient risk factors, tolerance, and other clinical characteristics.

Hypercoagulable States

Inherited coagulation disorders such as antithrombin III, protein C or proteins S deficiency, prothrombin gene G20210A mutation, or Factor V Leiden (FVL) may contribute to strokes in pediatric or young populations. These abnormalities rarely contribute to stroke in adults and can be overinterpreted if only measured during acute stroke, when levels can be temporarily affected by the active thrombotic event (59).

Hypercoagulability may be a symptom of an underlying malignancy, and diagnostic studies should be performed to exclude this as a possible underlying cause.

The strongest link between a thrombophilic disorder and stroke is the association between antiphospholipid (APL) antibodies and stroke in young adults (less than 50 years of age) (60). The Antiphospholipid Antibodies in Stroke Substudy (WARSS/APASS) was the first study to compare randomly assigned warfarin (INR 1.4 to 2.8) with aspirin (325 mg) for the prevention of a second stroke in patients with APL antibodies. Patients with both lupus anticoagulant and anticardiolipin antibodies had a higher event rate (31.7%) than patients negative for both antibodies (24%), but this was not statistically significant (61). Antiplatelet agents appear reasonable as first-line therapy. For patients with stroke or TIA who meet the criteria for APL antibody syndrome, oral anticoagulation with a target INR of 2 to 3 is recommended.

Sickle Cell Disease

Sickle cell anemia is an autosomal recessive genetic disease that causes production of a defective form of hemoglobin, hemoglobin S (HbS). The central nervous system manifestations of vaso-occlusive crises include cerebral infarction (children), hemorrhage (adults), seizures, TIA , cranial nerve palsies, meningitis, sensory deficits, and acute coma. Ischemic strokes are common in children, and they tend to be recurrent. These patients are often maintained on transfusion programs to suppress HbS. A retrospective multicenter review of sickle cell disease (SCD) patients with stroke showed that a reduction of HbS to less than 30% was associated with a reduction in the rate of recurrence at 3 years from more than 50% to 10%. Exchange transfusions in children who have already had a stroke are often performed, though the data are more limited than for the primary prevention scenario (62).

Cerebral Venous Sinus Thrombosis

Cerebral venous sinus thrombosis (CVST) results from occlusion of a venous sinus and/or cortical vein and is usually caused by a partial thrombus or an extrinsic compression. CVST can be caused by a multitude of factors, including hypercoagulable state, extrinsic compression of the venous system, infection, dehydration, pregnancy, and oral contraceptives. CVST has highly variable clinical manifestations (alteration of consciousness, seizures, focal neurologic deficits, and headache), making its diagnosis a challenge. Magnetic resonance (MR) venography or computed tomography (CT) venography is used to confirm the diagnosis.

Observational data and recent guidelines suggest that both unfractionated heparin (UFH) and low molecular weight heparin (LMWH) are safe and effective in acute cerebral venous thrombosis followed by oral anticoagulation for three to six months (63). Anticoagulation is recommended, even in patients with hemorrhagic venous infarcts. The novel anticoagulants have not been well studied in cerebral venous occlusive disease.

Arterial Dissections

Dissection, a tear in the subintimal layer of a large artery, is most common in the internal carotid artery as it enters the petrous bone and the vertebral arteries as they course through the foramen transversarium. Intracranial dissections are less common. Dissections lead to ischemic strokes through artery-to-artery embolism or by causing significant stenosis and occlusion of the proximal vessel (64). Dissections can also cause a pseudo-aneurysm, creating a source for thrombus formation. Intracranial dissections can cause subarachnoid hemorrhage when the dissection becomes subadventitial. Although the treatment is unproven, patients are often treated with intravenous heparin followed by oral warfarin for three to six months. There has not been a trial comparing this approach to antiplatelet therapy (65). The duration of therapy is based on the period of anticipated high risk and the natural history of the vessel repair. No studies have examined the safety and efficacy of therapy using different durations of anticoagulation. For patients with recurrent ischemic events, long-term anticoagulation may be considered.

CONVENTIONAL MODIFIABLE STROKE RISK FACTORS

Hypertension

Hypertension is one of the most common global diseases. Because of the associated morbidity and mortality and the cost to society, hypertension is an important public health challenge. Hypertension is the single most important risk factor for stroke and also causes "silent" infarcts, which contribute to cognitive dysfunction (66,67). There is a continuous association between both systolic and diastolic BPs and the risk of ischemic stroke (68).

Seven published randomized controlled trials with a combined sample size of 15,527 participants with ischemic stroke, TIA, or ICH focused on the relationship between BP reduction and the secondary prevention of stroke and other vascular events (69). The patients were followed up for two to five years. Treatment with antihypertensive drugs was associated with significant reductions in all recurrent strokes,

nonfatal recurrent stroke, MI, and all vascular events. The overall reductions in stroke and all vascular events were related to the degree of BP lowering achieved, but whether a particular class of antihypertensive drug offers a particular advantage for use in patients after ischemic stroke remains uncertain.

Blood pressure management is recommended for both prevention of recurrent stroke and prevention of other vascular events in persons who have had an ischemic stroke or TIA. Benefit has been seen with an average reduction of approximately 10/5 mmHg. The optimal drug regimen remains uncertain; however, the available data support the use of diuretics and the combination of diuretics and an angiotensin converting enzyme (ACE) inhibitor (1). In patients with history of MI, a beta-blocker and ACE inhibitor are recommended. In patients with mild hypertension with increased cardiovascular risk, an ACE inhibitor or a calcium channel blocker were not found to be superior to low-dose thiazide diuretic therapy. However, in clinical trials ACE inhibitors provided better outcomes than placebo. The SPS3 trial recently completed its BP arm and demonstrated a trend toward lower stroke with tighter BP control (<130 mmHg) compared to up to 150 mmHg among lacunar strokes (70).

Diabetes

Diabetes mellitus is a chronic disease that requires conscientious longitudinal medical attention. Diabetes mellitus and age were the only significant independent predictors of recurrent stroke in a population-based study of stroke (71), and it is a strong determinant for the presence of multiple lacunar infarcts in two different stroke cohorts (72).

Most of the available data on stroke prevention in patients with diabetes are on the primary rather than secondary prevention of stroke. Intensive treatments to control hyperglycemia, hypertension, dyslipidemia, and microalbuminuria have demonstrated reductions in the risk of cardiovascular events (73).

Thiazide diuretics, beta-blockers, ACE inhibitors, and angiotensin II receptor blockers (ARBs) are beneficial in reducing cardiovascular events and stroke incidence in patients with diabetes (74). ACEIs and ARBs are preferred because they have been shown to reduce albuminuria and favorably affect the progression of diabetic nephropathy. More meticulous control of lipids is also recommended among diabetics, with an LDL-C of goal as low as 70 mg/dL (75).

Glycemic control has been shown to reduce the occurrence of microvascular complications (nephropathy, retinopathy, and peripheral neuropathy) in several clinical trials and is recommended in multiple guidelines of both primary and secondary prevention of stroke and cardiovascular disease (75). Analysis of data from randomized trials suggests a continual reduction in vascular events with the progressive control of glucose to normal levels. Diet, exercise, oral hypoglycemic drugs, and insulin are recommended to reach glycemic control.

Dyslipidemia

The impact of lipid abnormalities on ischemic stroke has been somewhat controversial, although mounting evidence supports aggressive management for secondary prevention. The guidelines of the American Heart Association and the NCEP Adult Treatment Panel III (ATP III) define *hypercholesterolemia* as a blood cholesterol concentration of greater than or equal to 240 mg/dL. Desirable cholesterol concentrations are less than 200 mg/dL.

The 2011 American Heart Association/American Stroke Guidelines for prevention of recurrent stroke make the following recommendations for lipid management in ischemic stroke and TIA patients (1):

1. Follow the national Cholesterol Educational Program III (NCEPIII) guidelines for patients with stroke or TIA who have elevated cholesterol (Table 26.3)
2. Administer statins and aim for a cholesterol-lowering goal of LDL-C lower than 100 mg/dL for those with CHD (coronary heart disease) or symptomatic atherosclerotic disease, or LDL-C lower than 70 mg/dL for very high risk persons with multiple risk factors

TABLE 26.3 LDL Cholesterol Goals and Cut Points for Therapeutic Lifestyle Changes (TLCs) and Drug Therapy in Different Risk Categories

RISK CATEGORY	LDL GOAL	LDL LEVEL AT WHICH TO INDICATE LIFESTYLE CHANGES	LDL LEVEL AT WHICH TO CONSIDER DRUG THERAPY
CHD or CHD risk equivalents	<100 mg/dL	>100 mg/dL	>130 mg/dL (100–129 mg/dL drug optional)
2+ risk factors	<130 mg/dL	>130 mg/dL	10-year risk 10%–20% >130 mg/dL 10-year risk <10% >160 mg/dL
0–1 risk factors	<160 mg/dL	>160 mg/dL	>190 mg/dL (160–189 mg/dL drug optional)

3. Consider administration of statins for ischemic stroke or TIA patients with atherosclerotic stroke but no preexisting indications for statin therapy.

The Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) trial was a randomized, double-blind study designed to determine if 80 mg/day of atorvastatin or placebo would reduce the risk of fatal or nonfatal stroke in patients with no known CHD who had a stroke or TIA 30 days earlier and within the previous 6 months (76). The trial randomized 2365 subjects to atorvastatin and 2366 to placebo. There were no significant differences between the two treatment groups in the incidence of serious adverse events. However, there were 55 hemorrhagic strokes in the atorvastatin treatment group and 33 in the placebo group. Myalgia (5.5% vs. 6.0%), myopathy (0.3% vs. 0.3%), and rhabdomyolysis (0.1% vs. 0.1%) did not differ in the atorvastatin or placebo treatment groups (76).

The SPARCL results provide evidence that 80 mg/day of atorvastatin administered to patients with stroke or TIA and without known CHD reduces the risk of stroke and cardiovascular events, despite a small increase in the risk of hemorrhagic stroke.

Smoking

Smoking increases the risk of ischemic stroke in a dose-dependent fashion. In the Women's Health Initiative study (WHI) of 39,783 patients, smoking fewer than 15 cigarettes a day had a RR of 1.93 for total hemorrhagic stroke. This risk increased to a risk ratio of 3.29 for women who smoked more than 15 cigarettes per day. The risk of ICH and subarachnoid hemorrhage were also increased in this population (RR 2.67, 4.02, respectively). On average, smoking doubles the risk of stroke (77).

Patients should be approached during their acute hospitalization regarding the importance of a smoking cessation program. The use of nicotinic patch, alone or in combination with bupropion, may be considered. The potential risk for a reduction in seizure threshold associated with bupropion use may be a concern in patients with large cortical strokes.

Alcohol Intake

The role of alcohol is controversial. Studies are difficult to conduct because of multiple socioeconomic variables. Meta-analysis of multiple studies indicates that heavy alcohol consumption (>60 grams per day) increases the individual's risk for all stroke subtypes, especially intracerebral and subarachnoid hemorrhages, and is also correlated with increase in the incidence of hypertension (78). Therefore, alcohol cessation is an important intervention for heavy drinkers.

MODIFIABLE RISK FACTORS EXCLUSIVE TO WOMEN

Oral contraceptive pills (OCPs) are a very common method of birth control globally, but the risk of stroke with OCPs—especially in conjunction with factors such as smoking, hypertension, genetic predisposition to thromboembolism, and migraine—has a major impact in secondary stroke prevention. Preparations with a high estrogen content (150 mcg) have been associated with both arterial and venous thromboembolism, and the third-generation OCP, containing gestodene or desogestrel and the same low dose of estrogen, has been associated with an increase in the risk of venous thromboembolic disease (79). In heavy smokers over the age of 35 and in women with previous thromboembolic events, OCPs are contraindicated.

Migraine with aura is an independent risk factor for stroke, particularly for young patients (80). There is also evidence that the risk of stroke is high during the peripartum and postpartum periods, with an increased risk up to 12 weeks from delivery (81). There is no definite guideline for the use of antiplatelet/antithrombotic therapy in stroke prevention for women with a history of pregnancy-related stroke.

SUMMARY

Stroke and TIA have great impact on the global public health, affecting millions of people of varied ethnicity, age, gender, and socioeconomic status and causing serious disabilities that affect the quality of life of these people. Therefore, stroke prevention is an important field of secondary prevention considering both conventional and population-specific risk factors. Modifiable risk factors such as hypertension, diabetes, smoking, physical inactivity, obesity, and dyslipidemia should be aggressively managed to prevent recurrent stroke and first MI. Diagnostic evaluation for an etiology should be thorough, with a particular emphasis on symptomatic internal carotid artery disease and AF due to the high risk of recurrence.

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27

Prevention of Deconditioning After Stroke

Frederick M. Ivey and Richard F. Macko

Stroke is associated with profound cardiovascular deconditioning (1). Peak fitness levels for individuals with history of stroke are approximately half that found in age-matched sedentary controls, indicating significant functional aerobic impairment (2–4). Low fitness levels compromise the capacity of stroke patients to meet the elevated energy demands of hemiparetic gait (5–7), and this diminished physiological fitness reserve capacity limits basic activities-of-daily-living (ADL) capacity, contributing to activity intolerance and subjective fatigue (8,9). Poor fitness also increases atherothrombotic risk after stroke by impacting elements of the cardio-metabolic syndrome (10,11) and promoting insulin resistance (12,13).

Whether poststroke fitness reductions are primarily because of premorbid conditions, direct effects of the stroke itself, or poststroke physical inactivity remains unclear. All are likely contributors, but understanding the relative contribution of each will require further research into biological and etiological mechanisms (1). Whatever the case, the need to address stroke-related decrements in fitness is gradually emerging as a clinical care priority in mainstream practice. For example, the Commission for Accreditation of Rehabilitation Facilities (CARF) International has newly revised best-care standards for stroke, applicable to all health care facilities (www.carf.org). These include plans for prevention of physical inactivity and physical deconditioning as a cornerstone for improving cardio-metabolic health and preventing recurrent stroke events. The information presented in this chapter should serve to advance the rationale for promoting the CARF model throughout the international health care system. This clinical care model must continue to develop, working toward full and broad implementation in such a way as to efficiently combat the devastating health consequences of aerobic deconditioning after stroke.

Hemiparetic body composition abnormalities affect multiple physiological systems, contributing to poor fitness (14) and the high prevalence of insulin resistance (12,13) in this population. Secondary biological abnormalities include unilateral gross muscular atrophy (15,16), increased intramuscular area fat (15,16), and a shift toward a fast-twitch muscle fiber type (17–19). These unilateral tissue changes are pronounced, with implications for both disability and worsening cardio-metabolic risk. Additionally, accelerated hemiparetic osteoporosis coupled with heightened fall risk predisposes to serious fractures (20). All stroke-related body composition and metabolic abnormalities are worsened by physical inactivity and advancing age. The first section of this chapter defines the profile of diminished physiological fitness reserve and details some of the underlying body composition and tissue-level abnormalities. We discuss the clinical relevance of these findings in terms of functional impairment and risk factor profiles.

Stroke survivors retain capacity for physiological adaptation to an exercise training stimulus. A variety of different exercise training modalities have been used to safely improve cardiovascular fitness after stroke (3,21–25). Increasing evidence from randomized studies further shows that structured exercise programs, particularly those employing task-repetitive locomotor training, can improve sensorimotor function even years after stroke (23,26–29). Hence, several exercise regimens are successful at both increasing fitness and improving gait patterning to reduce the energy costs of hemiparetic gait. This may ultimately improve mobility function and basic ADL capacity after stroke. The second section of this chapter reviews the physiological and functional effects of exercise after stroke. Although further research is needed to optimize exercise design, new evidence regarding dose intensity and health benefits of exercise after stroke is presented. Importantly, stroke participants can tolerate and benefit from higher-intensity exercise models, including treadmill (TM) training for maximal aerobic benefit (25), and aggressive strength training models, which have the capacity to dramatically affect leg skeletal muscle both on the paretic and the nonparetic sides (30).

The third section rounds out the chapter by providing general guidelines for implementing exercise programs after stroke. Goals should be oriented toward a multiple-physiological systems approach intended to improve fitness, sensorimotor function, and cardiovascular-metabolic health and to prevent or reduce deleterious body composition abnormalities that accompany disuse while aging with the chronic disability of stroke. The high prevalence of residual neurological deficits, as well as medical and cardiovascular comorbid conditions, presents unique safety and

feasibility issues related to implementation of exercise programs after stroke. Thus, recommendations are provided for initial medical evaluation to optimize safety and overcome the barriers to exercise participation. We reference some evidence-based protocols and exercise progression formulas that have proven successful in research settings and touch upon some future research directions that are likely to influence the practice of exercise to best promote health and wellness after stroke.

CARDIOVASCULAR HEALTH AND FITNESS AFTER STROKE

Cardiovascular health and fitness are integrally linked to exercise behaviors. To gain perspectives on the health impact of physical deconditioning following stroke, exercise behaviors must be considered across the phases of recovery. Conventional subacute stroke rehabilitation primarily focuses on optimizing basic ADL skills and functional independence, and preventing complications that can hinder recovery during the crucial early subacute stroke period (31). It is not clear that conventional rehabilitation systematically provides an adequate exercise stimulus to reverse the profound physical deconditioning and associated hemiparetic muscular atrophy that worsen neurological disability and cardiovascular health profiles in this sedentary population. In one study, cardiac monitoring of conventional physical therapy during the subacute stroke recovery period revealed that less than 3 minutes per session reached an aerobic intensity of 40% of measured heart rate reserve (HRR) (32). This level represents the lowest target for exercise in usual cardiac rehabilitation care. A large metropolitan catchall area in the United States reported that after a stroke, the typical patient attends a mean of 9 ± 5 outpatient physical therapy visits. The same study went on to say that therapy usually ended entirely between 30 and 180 days after stroke (3). These findings suggest that conventional physical therapy during the subacute recovery phase provides an inadequate exercise stimulus to address the domains of physical and metabolic deconditioning.

Measuring Fitness Levels After Stroke

Several studies have measured cardiovascular fitness levels using open circuit spirometry after stroke (Table 27.1). Although exercise testing strategies have been diverse, the general finding has been dramatically lower peak VO_2 levels in stroke survivors, contrasting with age-matched elderly controls who are physically inactive but otherwise healthy. Individuals in their 60s are expected to have peak oxygen levels ranging between 25 and 30 mL/kg/min depending on a number of factors (33). Thus, the mean peak oxygen consumption level in stroke patients averages

TABLE 27.1 Studies on Peak Aerobic Fitness After Stroke

STUDY	SUBJECTS	TESTING DEVICE	MEAN VO_2 PEAK (ML/KG/MIN)
Potempa et al. (22)	42 chronic stroke, 43–72 years	Cycle ergometer	15.9
Fujitani et al. (35)	2–49 months poststroke (n = 30), 53.6 years	Cycle ergometer	17.7
Rimmer et al. (36)	35 chronic stroke, 53 ± 8 years	Cycle ergometer	13.3
Mackay-Lyons (32)	29 subacute, 65 ± 14 years	Treadmill 15% BWS	14.4
Duncan et al. (3)	92 subacute, 69 ± 10 years	Cycle ergometer	11.5
Kelly et al. (37)	17 subacute, 61 ± 16 years	Semi-recumbent cycle	15.0
Chu et al. (21)	12 chronic, 62 ± 9 years	Cycle ergometer	17.2
Ivey et al. (2)	131 chronic, 64 ± 7 years	Treadmill full BWS	13.6
Ivey et al. (38)	46 chronic, 63 ± 9 years	Treadmill full BWS	14.1
Tomczak et al. (39)	10 chronic, 54 ± 3 years	Modified recumbent cycle ergometer	17.7
Billinger et al. (40)	11 chronic, 61 ± 12 years	Total-body recumbent stepper	16.6
Rimmer et al. (4)	55 chronic, 60 ± 10 years	Cycle ergometer	13.0
Severinsen et al. (41)	48 chronic, 68 ± 9 years	Cycle ergometer	16.3
Billinger et al. (42)	62 chronic, 62 ± 12 years	Cycle ergometer or total-body recumbent stepper	15.6
Baert et al. (43)	33 subacute, 59 ± 11 years	Cycle ergometer	18.1
Tang et al. (44)	47 chronic, 67 ± 7 years	Treadmill GXT	16.5

Abbreviations: BWS, body weight support; GXT, graded exercise test.

approximately half that of age-matched individuals. This is partially a function of the extremely high energy cost of hemiparetic gait contributing to diminished physiological fitness reserve (34).

Functional Consequences of Reduced Fitness After Stroke

The extremely low levels of peak oxygen-consuming capacity found in stroke survivors can compromise functional mobility and are below the level required for some basic activities of daily living. The human body at rest consumes roughly 3.5 mL/kg/min of oxygen or 1 metabolic equivalent (MET) (45). The MET calculations associated with various forms of activity (46,47) reveal that light instrumental activities of daily living (IADLs) generally require approximately 3 METS of oxygen consumption, whereas more strenuous ADLs require approximately 5 METS or 17.5 mL/kg/min. Notably, published MET values for different activities do not take into account neurological disability, which may be associated with even higher energy requirements for gross motor activities as a result of biomechanical inefficiency (7).

The impact of low fitness on function after stroke is best illustrated when peak fitness values are considered in the context of the range of energy expenditure necessary to perform daily activities (Figure 27.1) (2). Whereas peak values for age-matched healthy individuals far exceed the approximated ADL range, the exhaustion value falls somewhere in the middle of the zone for most stroke patients (Figure 27.1) (2). Thus, many stroke patients must work to complete exhaustion to achieve the middle of the established ADL range, making mid- to upper-level ADLs either impossible or unsustainable for extended time periods.

Of course, low fitness levels have consequences beyond functional impairment. In a seminal study involving more than 60,000 participants, Hooker et al. (48) demonstrated that cardiorespiratory fitness was an independent predictor of first-time stroke. Whether these findings extend to recurrent stroke awaits further research, but, until proven otherwise, it is prudent to assume that low fitness is a prominent factor in recurrent risk as well. Further, low fitness levels have been found to correlate with impaired metabolism (38) and reduced cerebral blood flow (49) in chronically disabled stroke survivors, indicating the central relevance of conditioning status to general health in this population.

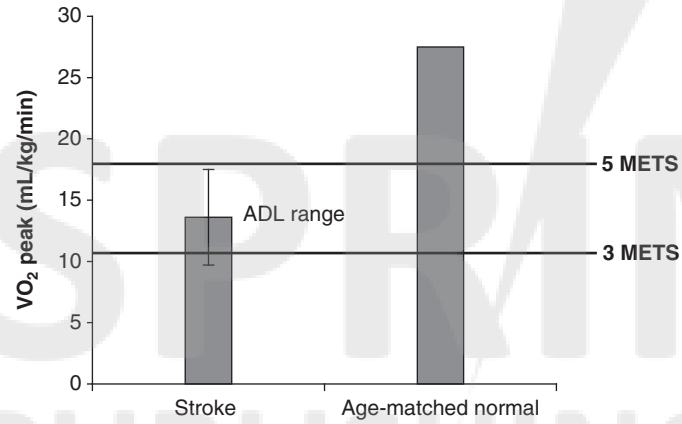

FIGURE 27.1 Peak aerobic fitness levels of N =131 chronic stroke patients relative to the energy requirements for activities of daily living.

Source: Reproduced with permission from *Topics in Stroke Rehabilitation*.

Mechanisms Underlying Poststroke Deconditioning

Although consensus has emerged that stroke leads to extreme deconditioning, the underlying biological mechanisms have not been systematically investigated. The disability of stroke is widely attributed to brain injury alone, and the diminished fitness attributed to reduced "central" neural drive. However, there are a number of changes in skeletal muscle and surrounding tissues that propagate disability and contribute to low fitness levels, including gross muscular atrophy, muscle fiber type shift, tissue inflammation, and altered vasomotor function, as discussed in the following sections.

Role of Muscle Atrophy

In stroke patients, reduced muscle mass plays a role in the ability to use oxygen. The level and quality of metabolically active tissue partially accounts for the amount of oxygen a person can utilize. Ryan et al. (14) confirm a strong relationship between thigh muscle mass by dual energy x-ray absorbtiometry (DEXA) and peak VO_2. In this study, VO_2 was related to the lean muscle mass of both thighs, with lean mass predicting more than 40% of the variance in peak aerobic fitness (14).

Stroke patients have reduced lean tissue mass that is related to the degree of neurological disability. Bilateral mid-thigh CT scans are used to illustrate the severe atrophy caused by chronic hemiparesis (Figure 27.2; 15). There is extreme gross muscular atrophy in paretic leg mid-thigh CT scans, showing 20% lower muscle area compared to the nonparetic thigh. The findings of exaggerated muscle erosion on the paretic side have been confirmed by a study utilizing serial CT measurements from the knee to the hip, enabling the calculation of muscle volume bilaterally (16). Intramuscular area fat is 25% greater in the paretic thigh compared to the nonparetic thigh (15,16), and is linked to elements of the metabolic syndrome and their associated complications (50). Therefore, the significance of stroke-related body composition abnormalities extends beyond poor fitness and function in this disabled population.

Unilateral Muscle Fiber Type Changes

Cellular changes in skeletal muscle may also contribute to poor fitness and worsening cardiovascular disease (CVD) risk after stroke. Prior studies of hemiparetic muscle reveal variable findings related to altered fiber type proportions,

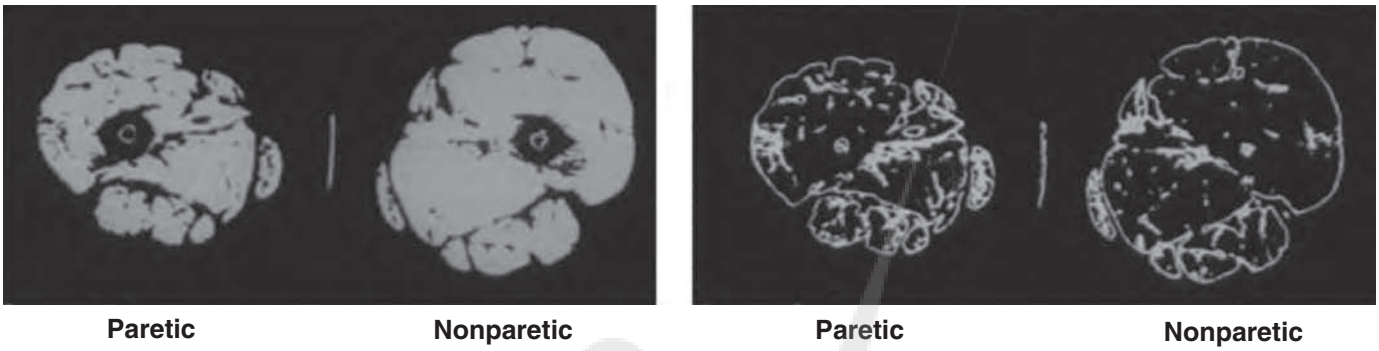

FIGURE 27.2 Bilateral CT scan illustrating muscle atrophy and elevated intramuscular area fat on the paretic side.

Source: Reproduced with permission from *Topics in Stroke Rehabilitation*.

loss of type I muscle fibers, fiber atrophy, and reduced oxidative capacity (18,19,51–54). A slow-to-fast fiber type conversion has been reported (17,18,53). Skeletal muscles are composed of fibers that express different myosin heavy chain (MHC) isoforms. Slow (type I) MHC isoform fibers have higher oxidative function, are more fatigue resistant, and are more sensitive to insulin-mediated glucose uptake. Fast (type II) MHC fibers are recruited for more powerful movements; they fatigue rapidly and are less sensitive to the action of insulin (55). Routine ATPase staining of paretic leg muscle biopsies shows elevated proportions of fast type II fibers in the paretic leg of stroke survivors (Figure 27.3) (2).

Similar findings are reported in the hemiparetic upper extremity (53). Further, densitometric analysis of MHC gel electrophoresis analyzing bilateral vastus lateralis biopsies shows significantly elevated proportion of fast MHC isoforms in the paretic versus nonparetic leg (17). These findings contrast with the relatively equal proportions of slow and fast MHC fibers found in vastus lateralis of individuals without stroke (53). Interestingly, a shift to fast MHC composition in the paretic muscle is also seen in animals and humans after spinal cord injury (56). This suggests that neurological alterations may be partially responsible for the shift of muscle phenotype. A switch to fast MHC can occur with muscle unloading or disuse. The relative inactivity after stroke could also facilitate these changes. The shift to fast MHC is in contrast to the changes seen in normal aging, where fast MHC fibers are preferentially lost through denervation and slow MHC fiber density increases (57). Hence, this shift after stroke is an abnormal muscle molecular phenotype that would be expected to result in a more fatigable, insulin-resistant muscle.

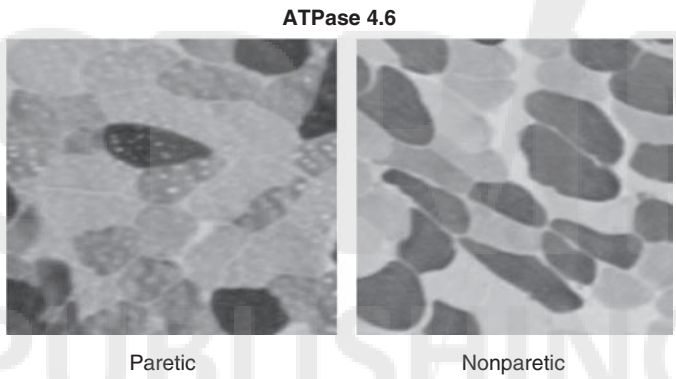

FIGURE 27.3 Fiber-type shift on paretic side.

Source: Reproduced with permission from *Topics in Stroke Rehabilitation*.

Inflammatory Pathway Activation in Hemiparetic Muscle

The molecular mechanisms underlying muscular atrophy and insulin resistance after stroke are not fully understood. Bilateral biopsies from the vastus lateralis muscle of chronic stroke patients reveal a nearly three-fold increased tumor necrosis factor-alpha mRNA expression in the hemiparetic leg muscle, compared to age-matched nonstroke controls (58). In addition, there is a significant 1.6-fold increased TNF-alpha mRNA expression in the nonparetic leg muscle of stroke patients compared to controls (58), evidence of a bilateral or systemic process conferring more widespread inflammatory effects. Immunohistochemical studies further show that TNF-alpha localizes to interfascicular space as well as the muscle fascicle, suggesting that increased inflammatory cytokine production may arise from both muscle and surrounding adipocytes (2). The clinical significance is that TNF-alpha blocks insulin signaling and mediates muscle atrophy (59–62). Thus, inflammatory mechanisms may contribute to both muscular atrophy and insulin resistance after stroke, thereby both lowering fitness and elevating recurrent stroke risk.

Myostatin Elevation in Hemiparetic Muscle

Myostatin is a key negative regulator of muscle mass in humans and animals (63,64), having direct and indirect influences on several other molecular regulators of atrophy and hypertrophy. In a recent study, vastus lateralis biopsies of the paretic and nonparetic muscle were used for

measurement of myostatin gene expression by Real-time (RT)-PCR (30). Myostatin mRNA expression levels were 40% higher in the paretic than nonparetic muscle ($P = .001$) at baseline and decreased by 49% in the paretic muscle ($P < .005$) and 27% in the nonparetic muscle ($P = .06$) after a 3-month resistive exercise training program. This is significant given myostatin's established role as an inhibitor of skeletal muscle growth. The reduction in myostatin was greater in the paretic than nonparetic muscle ($P < .001$) by repeated analysis of variance (ANOVA) measures (30). Thus, the increased myostatin mRNA in the paretic thigh and reduction with resistance training imply an important regulatory role for myostatin after stroke.

Hemiparetic Osteoporosis

Hemiparetic osteoporosis is a clinically important body composition abnormality that is linked to duration of immobility, muscular atrophy, and poor cardiovascular fitness after stroke (65–67). Osteoporosis is more severe in the upper than lower extremity, but fracture risk is greater for the hip (65). Hip fracture risk is reportedly 7-fold elevated in the first year after stroke, and 15% projected across 5 years (20), and is increased 7-fold for each 2 standard deviation decrease in femoral neck bone mineral density (68). Paretic leg femoral neck bone density declines up to 14% within a year after stroke (69)—a period in which up to 73% experience a fall (70). Hence, exercise strategies to improve both balance and bone health may serve as important adjuncts to best medical care. Despite the established role of exercise as an adjunct to best medical care for treatment of osteoporosis (71), few studies have systematically examined the potential for exercise to improve balance and bone health after stroke. Three studies with positive outcomes on falls (72–74) used repetitive functional tasks, which most likely improved motor coordination, movement speed, and strength (72). In 2008, Eng et al. (65) published a review paper indicating that randomized trials support the use of exercise training to reduce fracture risk after stroke, but that further studies are required to draw definitive conclusions. Most recently, Pang and Lau (75) showed that tibial bone geometry improved more in TM exercise trainers than controls after stroke.

Impairments in Blood Flow

Findings of unilaterally impaired paretic leg blood flow in chronic stroke identify yet another clinical feature related to reduced cardiovascular fitness and enhanced CVD risk. When resting and postischemic reactive hyperemic blood flow was compared between the affected and unaffected legs of stroke patients, results showed 32% and 35% reductions, respectively (76). These results were replicated in a more recent trial from our laboratory (77). Of equal or greater importance were the findings that middle cerebral artery blood flow is reduced on the ipsilesional side of the brain (49). Importantly, both peripheral and cerebral blood flow dynamics can improve with regular progressive fitness training after stroke (49,77), and arterial function has been shown to improve subsequent to strengthening exercises in community-dwelling stroke survivors (78).

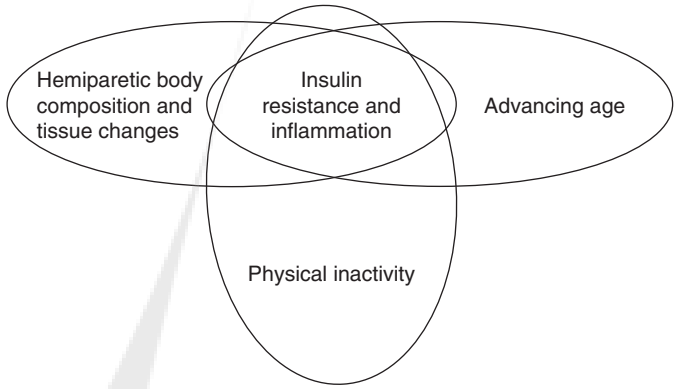

FIGURE 27.4 Interacting features in the stroke population that combine to produce elements of the metabolic syndrome.

Clinical and Metabolic Consequences of Paretic-Side Tissue-Level Changes

The skeletal muscle, bone, and vasomotor regulatory abnormalities on the paretic side may contribute to worsening cardiovascular risk by propagating physical inactivity, insulin resistance, and the metabolic syndrome. Kernan et al. (12,79) originally identified a high prevalence of insulin resistance during the subacute stroke recovery period. Subsequent findings in chronic stroke reveal an extremely high prevalence of abnormal glucose metabolism (13). In a chronic stroke study involving more than 200 volunteers, 35% screened had documented diabetes by medical history. Additionally, fasting and postload hyperglycemia were highly prevalent in those who are not identified as diabetic by medical history. The findings suggest that the rate of abnormal glucose metabolism may be as high as 80% in chronic stroke (13). This is clinically relevant given that impaired and diabetic glucose tolerance prospectively predict two- to three-fold increased risk for recurrent cerebrovascular events (80). Figure 27.4 depicts some contributors to poststroke metabolic syndrome and their interaction with one another.

We now know that the metabolic status of stroke survivors can be beneficially impacted by TM exercise training, as evidenced by highly significant reductions in insulin area under the curve during oral glucose tolerance testing as well as improved diabetes status in 58% of participants (38). A recent paper in stroke also shows that resistive training can improve insulin sensitivity by 31% in as little as 3 months (81).

PHYSIOLOGICAL AND FUNCTIONAL EFFECTS OF EXERCISE AFTER STROKE

This section provides an overview of evidence that several exercise modalities can improve health, fitness, and functional outcome categories after stroke. Our focus is on exercise programs involving the lower extremities or

whole body, consistent with the mission of improving mobility function, fitness, and metabolic health, and countering the secondary body composition abnormalities that occur as a consequence of stroke and physical inactivity. In practical terms, this approach primarily engenders elements of aerobic training by incorporating larger muscle groups that are more effective to provide a cardiovascular exercise stimulus to improve metabolic health, consistent with consensus statements for exercise recommendations in high CVD risk populations (10). Where such information is available, the specific exercise intensity and progression formula are described, as these may affect the nature and temporal profile of exercise-mediated adaptations. We include recent advances in the application of resistance training in stroke survivors, which provide evidence of strength gains and paretic leg performance capacity without deleterious increases in spasticity. Preliminary steps have also been taken in the direction of alternative therapies such as tai chi (82,83) and yoga (84,85) that may hold promise in the rehabilitation of those with stroke. There is a growing emphasis on community-feasible and home-based exercise models, which may afford opportunities to better disseminate health and function, promoting training programs to larger numbers of stroke survivors. Finally, efforts to capture the recent trends in stroke exercise rehabilitation related to intervening earlier, more aggressively, and more creatively (e.g., with family support) are also ongoing.

Exercise Training for Cardiovascular Fitness After Stroke

Several exercise modalities have been shown to increase cardiovascular fitness in stroke survivors. A synthesis of these studies suggests that approaches to exercise training may necessarily vary as a function of neurological deficit severity, baseline fitness levels, and the time phase of recovery after stroke (Table 27.2) (26). Moreover, differing elements of training prescriptions and their progression (e.g., aerobic intensity, training velocity, repetition) may further determine the nature of exercise-mediated outcomes. Table 27.2 summarizes some of the more widely cited exercise intervention studies measuring impacts on peak aerobic capacity. Note that the work of Globas et al. (25) (Table 27.2) showed that higher than previously observed relative increases in peak aerobic capacity may be possible by placing a greater emphasis on TM training intensity progression. Other evidence is also now available to demonstrate that stroke survivors benefit from higher-intensity exercise training protocols (86).

Notably, a gain in peak fitness of as little as 1 MET (3.5 mL/kg/min) prospectively predicts 17% to 29% lower nonfatal and 28% to 51% fatal cardiac events in men (92), and, as stated previously, fitness level predicts first-time stroke risk (48). Therefore, the gains reported in the studies listed in Table 27.2 are clinically important. Beyond goals of improving function after stroke, tertiary stroke prevention and CVD risk factor modification should be a major objective of exercise in this population (10). In high CVD risk nonstroke populations, exercise has been shown to improve a number of physiological factors linked to stroke and cardiac event risk, including insulin sensitivity (93), hemostatic and inflammatory markers (94,95), and indices of vascular endothelial dependent vasomotor reactivity in coronary and peripheral circulations (96). Other health benefits include improved lipid profiles (97) and improved autonomic tone, which is linked to lower cardiac mortality (98). Exercise is established as an adjunct to best medical care in management of obesity, dyslipidemia, diabetes, and hypertension, strongly supporting a role for exercise to address cardiovascular comorbidities in stroke survivors. Exercise improves insulin and glucose areas under the curve during oral glucose tolerance test after stroke (38), with postload insulin response having previously been identified as a predictor of stroke risk (99).

Effects of Exercise on Sensorimotor Function After Stroke

Approximately 75% of stroke survivors are left with residual deficits that persistently impair function. In particular, sensorimotor deficits impairing gait and balance limit functional independence and promote a sedentary lifestyle with subsequent physical deconditioning. Until recently, the window for motor recovery with conventional rehabilitation was widely considered to be only three to six months, with little functional improvement thereafter (100,101). Seminal studies in rehabilitation of the paretic upper extremity now inform us that task-repetitive training can improve arm motor function in chronic stroke, and that the functional gains are associated with brain plasticity (102). A similar paradigm shift is taking place in our understandings of brain plasticity and lower-extremity motor control.

Increasing clinical and experimental data provide evidence that exercise has the potential to improve selected motor performance outcomes, even years after stroke, and that the functional improvements are associated with mechanisms of neuroplasticity (89,103,104). Table 27.3 presents some examples of exercise intervention studies producing significant improvements in basic ADL-related functional parameters in subacute and chronic stroke patients (26).

Exercise Intervention Strategies After Stroke Using Multiple Modalities

Although a comprehensive review of the exercise literature in stroke is beyond the scope of this chapter, details related to some of the more widely cited studies are provided in the following paragraphs. Efforts were made to select several representative studies that employ diverse training modalities, including cycle ergometry, recumbent stepper training, water-based exercise, home- and community-based therapies, resistance (strength) training, and TM training, as well

TABLE 27.2 Exercise Intervention Studies and Their Impact on Peak Aerobic Fitness

STUDY	DESIGN/POPULATION	INTERVENTION	+ VO_2 PEAK
Potempa et al. (22)	Randomized/chronic stroke	10 weeks cycle training 3×/week versus passive range of motion	Treatment: +13%[a] Control: +1 %
Rimmer et al. (36)	Randomized/chronic stroke	12 weeks on a variety of aerobic (30 minutes) and strength equipment (20 minutes) 3×/week versus delayed entry controls	Treatment: +8%[a] Control: –10%
Macko et al. (87)	Noncontrolled/chronic stroke	6 months treadmill (TM) exercise 3×/week	Treatment: +10%[b]
Duncan et al. (3)	Randomized/subacute stroke	12 week in-home therapist-supervised program emphasizing strength, balance, endurance (cycle) versus usual care	Treatment: +9%[a] Control: +1%
Chu et al. (21)	Randomized/chronic stroke	8 weeks water-based aerobics up to 80% HRR versus upper-extremity functional exercise	Treatment: +23%[a] Control: +3%
Macko et al. (23)	Randomized/chronic stroke	6 month progressive TM training 3×/week versus attention controls (stretching)	Treatment: +17%[a] Control: +3%
Pang et al. (88)	Randomized/chronic stroke	Community-based UE versus LE exercise 3×/week 19 weeks	Treatment (LE):+11%[a]
Ivey et al. (38)	Randomized/chronic stroke	6 months TM exercise 3×/week	Treatment: +15%[a] Control: –3%
Luft et al. (89)	Randomized/chronic stroke	6 months TM exercise 3×/week	Treatment: +18%[a] Control: –3%
Tang et al. (90)	Matched control/subacute stroke	Cycle ergometer training 3×/week until discharge	Treatment: 23%[b] Control: 13%[b]
Rimmer et al. (4)	Cluster assignment/chronic stroke	14 weeks: Cycle ergometer or recumbent stepper 3×/week	Moderate intensity: +4% Low intensity: +6% Conventional: +3%
Letombe et al. (24)	Randomized/subacute stroke	4 weeks of adapted physical exercise training	Treatment: +20%[a] Control: 8%
Ivey et al. (49)	Randomized/chronic stroke	6 months TM exercise 3×/week	Treatment: +19%[a] Control: –4%
Gjellesvik et al. (91)	Noncontrolled pilot	Uphill TM walking	Treatment: +12%[b]
Globas et al. (25)	Randomized/chronic stroke	3 months TM exercise 3×/week	Treatment: +29%[a] Control: –4%

[a]Significant between groups across time.
[b]Significant within group.

Abbreviations: HRR, heart rate reserve; LE, lower extremity; UE, upper extremity.

as multi-modal therapy and other alternative interventions. Clearly, much work remains to be done in elucidating the optimal exercise formula for producing maximal gains in fitness and function to delay disability and cardiovascular morbidity/mortality after stroke.

Cycle Ergometry and Recumbent Stepper Training

A seminal study conducted by Potempa et al. (22) compared 10 weeks of adapted bicycle ergometer exercise with a control intervention consisting of passive range of motion exercise in chronic stroke patients. Results showed a significant between-group difference in VO_2 peak change over time, with the bicycle ergometer group (n = 19) achieving 13% gains compared to no change for controls (n = 23). Though Fugl-Meyer sensorimotor scores were positively correlated with gains in peak VO_2, neither of the treatment groups showed significant differences in functional outcome scores. This study showed that aerobic exercise using cycle ergometry is feasible and improves fitness in chronic hemiparetic stroke, but provided no clear evidence that cycle exercise could improve neuromuscular function or functional mobility. Since then, a few studies have been conducted examining the effects of cycle ergometry after stroke (4,90), but none have produced conclusive findings that this form of intervention improves functional outcome. However, the use of a recumbent stepper device (Nu Step) has shown promise for improving poststroke function, with gains observed in the Berg Balance Scale (118).

TABLE 27.3 Exercise Intervention Studies and Their Impact on Selected Functional and Physical Performance Outcomes

STUDY	DESIGN/POPULATION	INTERVENTION	FUNCTION
Hesse et al. (105)	Noncontrolled/subacute and chronic stroke	5 weeks 5×/week. Off partial weight support TM walking	*Rivermead mobility* Treatment: +110% *Gait velocity* Treatment: +250%
Potempa et al. (22)	Randomized/chronic stroke	10 weeks cycle training 3×/week versus passive range of motion	*Fugl-Meyer index* Treatment: no change Control: no change
Duncan et al. (106)	Randomized/subacute stroke	12 weeks home-based. Theraband, walking, or bike for 20 minutes versus usual care	*10-m gait velocity* Treatment: +37.3% Control: +12.3% *6-minute walk* Treatment: +28% Control: +17%
Teixeira-Salmela et al. (107)	Noncontrolled/chronic stroke	10 weeks aerobic + strength training 3×/week	*30-m gait speed (m/s)* Treatment: +21.2%
Rimmer et al. (36)	Randomized/chronic stroke	12 weeks on a variety of aerobic (30 minutes) and strength equipment (20 minutes) 3×/week versus delayed entry controls	*Exercise time* Treatment: +29% Control: +15%
Katz-Leurer et al. (108)	Randomized/acute stroke	8 weeks cycle ergometer 2×/week at 60% HRR versus usual care	*Postintervention walk distance* Treatment: 143 m Control: 108 m *Stair climbing* Treatment: 26 n Control: 18 n
Eng et al. (109)	Noncontrolled/chronic stroke	8 weeks community-based 3×/week aerobic stepping, stretching, functional LE strengthening (chair rise)	*12-minute walk* Treatment: +9.5% *10 m walk speed* Treatment: +14.4% (self-selected) +9.3% (fastest)
Duncan et al. (3)	Randomized/subacute stroke	12 week in-home therapist-supervised program emphasizing strength, balance, endurance versus usual care	*10-m gait velocity* Treatment: +25.7% Control: +18% *6-minute walk distance* Treatment: +26% Control: +15%
Chu et al. (21)	Randomized/chronic stroke	8 weeks water-based aerobics up to 80% HRR versus upper-extremity functional exercise	*Self-selected gait speed (m/s)* Treatment: +16.1% Control: +2.9%
Eich et al. (110)	Randomized/subacute stroke	6 weeks 5×/week harness secured and minimally supported TM walking (30 minutes) plus physiotherapy (30 minutes) versus physiotherapy alone (60 minutes)	*10-m walk* Treatment: +78% Control: +36% *6-minute walk* Treatment: +84% Control: +51%
Macko et al. (23)	Randomized/chronic stroke	6 months progressive TM training versus attention controls (stretching)	*6-minute walk* Treatment: +30% Control: +11% *WIQ distance* Treatment: +56% Control: +12%
Pang et al. (88)	Randomized/chronic stroke	Community-based UE versus LE exercise 3×/week 19 weeks	*6-minute walk* Treatment (LE): +19.7%

(*continued*)

TABLE 27.3 Exercise Intervention Studies and Their Impact on Selected Functional and Physical Performance Outcomes (*continued*)

STUDY	DESIGN/POPULATION	INTERVENTION	FUNCTION
Pang et al. (111)	Randomized/chronic stroke	Community-based UE versus LE exercise 3×/week 19 weeks	*Wolf motor function* LE: 0% UE: +7% *Fugl-Meyer assessment* LE: +2% UE: +12% *Dynamometry (grip strength)* LE: +2% UE: 17%
Yang et al. (28)	Randomized/chronic stroke	Dual task-based exercise program (walking while manipulating 1 or 2 balls) versus attention control (3×/week for 4 weeks)	*Walking speed* Dual task: +35% Control: –13%
Noh et al. (112)	Randomized/chronic stroke	Aquatic therapy versus conventional therapy (3×/week for 8 weeks)	*Berg balance* Treatment: +18% Control: +5%
Macko et al. (113)	Noncontrolled/chronic stroke	Adaptive Physical Activity Program (APA, featuring group mobility, balance and stretching exercises in hospital gym 2×/week for 2 months)	*Short physical performance battery* Treatment: +56%
Combs et al. (114)	Noncontrolled/chronic stroke	Body-weight-supported TM training (24 sessions over 8 weeks)	*Berg balance* Treatment: +10%
Galvin et al. (115)	Randomized/acute stroke (very disabled)	Family-mediated exercise therapy (FAME; family member gets trained to deliver progressive leg training at bedside) versus usual care	*6-minute walk* FAME: +242% Control: +102% *Berg balance* FAME: +102% Control: +34% *Barthel index* FAME: +57% Control: +25%
Park (29)	Randomized/subacute stroke	Community-based ambulation training versus usual PT care	*Walking speed* Treatment: +41% Control: +11% *6-minute walk* Treatment: +40% Control: +15%
Duncan et al. (116)	Randomized/subacute stroke	Early- and late-onset body-weight-supported TM rehabilitation versus PT-supervised home exercise (3×/week for 12 to 16 weeks). Outcome measures 1 year after stroke	*6-minute walk* Early LT: +59% Late LT: +63% HE: +67% *Walking speed* Early LT: +62% Late LT: +63% HE: +64% *24-hour step count* Early LT: +58% Late LT: +61% HE: +78%
Hill et al. (117)	Delayed entry/chronic stroke	Lower-extremity strength training (8 weeks, 3×/week)	*6-minute walk distance* Treatment: +4% *Time up and go* Treatment: +7%
Schmid et al. (85)	Randomized/chronic stroke	Yoga-based rehabilitation (2×/week for 8 weeks)	*Berg balance* Treatment: +12% Control: +4%

Water-Based Exercise

Chu et al. conducted a water-based exercise study lasting 12 weeks (21). Those in the experimental group exercised for one hour, three days per week, in a swimming pool. The patients were progressed to 30 minutes of water aerobics at 80% HRR, with the remainder of time consisting of stretching and warm-up/cool-down. Although this study had a very small sample size (7 treatment and 5 controls), the intervention produced large relative gains in peak aerobic capacity (23%), perhaps arguing for strong consideration of this form of intervention for stroke survivors. A higher level of baseline fitness and function may have influenced results and confounded interpretation relative to other experiments in the field of poststroke exercise rehabilitation. Aquatic therapy has also been shown to improve balance, forward and backward weight-bearing abilities of the affected limbs, and knee flex or strength (112). However, a recent Cochrane review concluded that the few randomized studies done to date in this area provide inconclusive evidence regarding whether aquatic therapy reduces stroke disability (119), and that better and larger studies are required.

Home- and Community-Based Therapies

Duncan et al. (106) were the first of the randomized studies to utilize a home-based intervention model. The program consisted of 36 sessions of 90-minute duration over 12 to 14 weeks. Subjects in the usual care group had services as prescribed by their physicians. All sessions for the exercise group were supervised by a physical or occupational therapist at home. Components of the program were range of motion and flexibility, strengthening, balance, upper-extremity functional use, and endurance training (riding a stationary bike for 30 minutes). Both the intervention and usual care groups improved in strength, balance, upper- and lower-extremity motor control, upper-extremity function, and gait velocity. Gains for the intervention group exceeded those in the usual care group in balance, endurance, peak aerobic capacity, and mobility. The study was important in demonstrating the practical utility of home-based interventions compared to the more frequently applied hospital-based intervention programs for improving fitness and function after stroke. However, it should be noted that there was still a high level of supervision despite the study being home-based. More recently, Duncan and colleagues showed that a home-based intervention supervised by physical therapists compares favorably to more intensive hospital-based body-weight-supported TM rehabilitation in terms of adaptations in walking speed, 6-minute walk distance, and 24-hour activity across the subacute phase of stroke recovery (116). Additionally, trials have been conducted to determine the effectiveness of community-based ambulation training after stroke (29,120–123), with some success shown in improving basic functional outcome measures. However, Langhammer et al. observed advantages for TM training compared to walking outdoors with respect to walking speed, stride symmetry, and 6-minute walk distance (121). Whatever the modality, returning to independent community ambulation is a challenging rehabilitation goal (123).

Resistance (Strength) Training

Several systematic reviews of outcomes related to progressive strength training after stroke show great promise for this form of rehabilitation intervention (124–127). Of the original eight studies conducted during or before 2007, three (128–130) were randomized controlled trials (RCTs), with the remainder being single-case time-series analyses (131) or single-group pre–post trials (132,133). Since then, seven important strength training studies (four randomized) have been added to the mix (30,117,134–138), thereby broadening our understanding of the extent to which this intervention can affect a diverse array of outcome categories in this population. Wide variation was found in the frequency and duration of the training programs as well as type of equipment used. Studies had participants training anywhere from 2 to 5 sessions per week with a total intervention period ranging from 4 to 12 weeks. Several of the studies used isokinetic dynamometers for training (Cybex or Kin-Com) (131,132), with the remainder using weight machines, hand weights, and a purpose-built static dynamometer. Training was originally primarily targeted to larger muscle groups of the lower limb, with the exception of one study exercising wrist extensors and upper-limb flexors (131). Harris and Eng recently published a meta-analysis demonstrating that strength training can also improve upper-limb function without increasing tone or pain for individuals with stroke (127). All of the studies that measured strength reported significant increases with large effect sizes. Two of the single-group pre–post studies (132,133) and one RCT (128) measured effects of the training on spasticity by Hoffman reflex, stretch reflex, Achilles tendon jerk, the pendulum test during knee flexion, electromyography (EMG) in the quadriceps and hamstring groups, and the modified Ashworth scale. None of the studies reported increases in spasticity after a resistance training exercise program. All measured the effects of training on at least one functional outcome. Generally, walking speeds were significantly increased with this form of training, with effect sizes ranging from 0.5 to 1.5. The RCT with the largest walking speed effect size (128) focused training on the hip, knee, and ankle of each patient's paretic limb. Collectively, this small group of clinical trials provides preliminary evidence that progressive resistance strength training can be effectively used to improve strength and function without a concomitant increase in spasticity after stroke. Interestingly, a few studies now show that beyond strength and ambulatory function adaptations, this intervention type may be effective for mental health (134,137), perceived participation (138), and paretic-side skeletal muscle hypertrophy (30). With regard to the latter point, evidence now shows that progressive lower-extremity strength training, provided it is intense enough, can cause large increases (+15%) in both paretic and nonparetic thigh muscle volume measured by serial CT scanning from the knee to the hip. Further, this muscle volume increase

coincides with reductions in skeletal muscle myostatin, a primary inhibitor of muscle growth (30).

Treadmill-Based Training Approaches

Based on pioneering studies of hind limb stepping recovery in despinalized cats, variants of treadmill (TM)-based training have emerged to promote locomotor learning after stroke (139,140). A biomechanical basis for this approach is supported by findings that TM walking improves reflexive gait patterning in hemiparetic patients (141,142). The facilitation of gait patterning with TM is well characterized for both body weight support (BWS) (141) and self-supported full-weight-bearing TM exercise conditions (142). TM produces a 50% improvement in interlimb stance to swing symmetry ratios, 30% improvement in impulse symmetry, and improved timing of quadriceps activation compared to overground walking in hemiparetic stroke patients (143). TM-based training also provides the task repetition that animal and human studies suggest is requisite to mediate motor learning and neuroplasticity (144). Randomized studies show that the benefits of TM training translate into improved overground walking, and can be extended to more severely impaired subjects using BWS strategies (145). TM-based training can also be combined with progressive aerobic exercise to improve both fitness and ambulatory function (23), as discussed in the following sections. There is currently a greater appreciation for the importance of more aggressively advancing TM training intensity (146–151) and duration (152,153) in the context of affecting health outcomes after disabling stroke. Aerobic fitness gains can be almost double the average normally seen with close attention to TM intensity progression details (25).

Partial Body Weight Support Treadmill Training

Partial BWS TM training has received much investigation, particularly as a means to provide a physiological gait training stimulus to more impaired subjects across earlier phases of stroke recovery (141). This approach utilizes a suspensory harness to progress patients from 30% to 40% BWS to full-weight-bearing TM walking, typically with 1 to 2 therapists facilitating stepping and truncal stability across 4 to 6 weeks. Early studies by Hesse et al. provide evidence that BWS TM training may restore gait in severely affected nonambulatory patients (141,145). Subsequent randomized studies confirm that BWS TM training is better tolerated and more effective than full-weight-bearing TM to improve gait and balance function in more severely hemiplegic patients, specifically that subset with lower gait velocities (<0.2 m/s) and poorer balance (Berg scores < 15 points) (154,155) and in advancing age. The latter finding may be explained by the significantly lower oxygen demands of BWS TM training—a finding that brings into question whether BWS using current protocols provides adequate aerobic intensity for metabolic health benefits (156).

Despite some positive results, a Cochrane review found no significant effects from BWS TM training except greater walking speed in those already ambulatory (157). Whether BWS TM or other TM-based training strategies are more effective than conventional therapy in durably improving function or fitness after stroke remains unclear (158). However, few studies have systematically investigated the training parameters or conditions to BWS TM training outcomes. One promising avenue is that BWS TM training at higher velocities may be more efficacious to improve walking velocity during the subacute stroke period (159). These findings have spurred important clinical trials investigating the relative benefits of BWS TM training across the subacute versus chronic stroke phases (114,160–165). However, the results published by Duncan et al. cast doubt on the relative utility of this intervention model during stroke recovery (116).

Full Body Weight Support Treadmill Training

Although partial BWS TM training may be an effective means for initiating training, particularly for those with greater gait impairment (154), this form of training has not traditionally utilized aerobic progression formulas (156). Thus, based on studies of exercise rehabilitation in the frail elderly, we have studied the profile of fitness and mobility function gains across six months of progressive full BWS TM aerobic exercise training in stroke survivors with chronic hemiparesis (23). This is a much longer therapeutic duration than is typical for most stroke rehabilitation programs. Our results show that the time profile of cardiovascular fitness gains with regular TM exercise training are progressive and nearly equal across the initial three months and the third to sixth months of training (Figure 27.5) (23). There is no evidence of

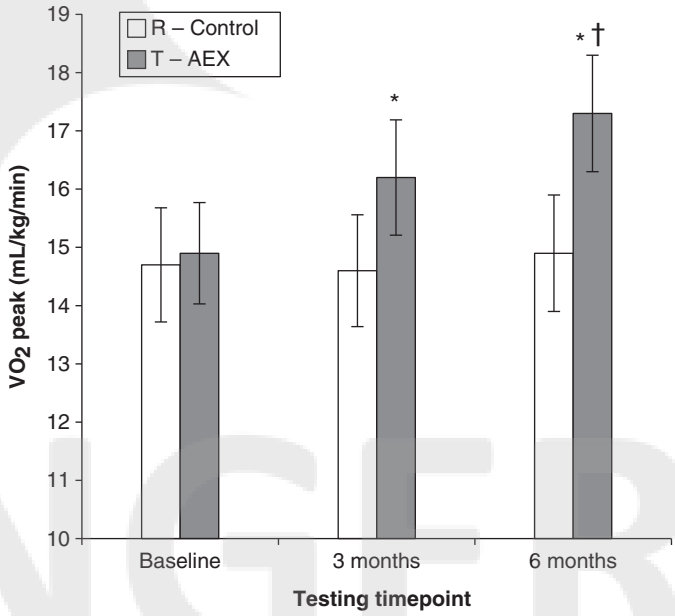

FIGURE 27.5 Progression of improvement in VO_2 peak across 6 months with progressive full BWS TM training in chronic hemiparetic stroke patients.

*$P < .05$ within group.
†$P < .01$ between groups.

Source: From Ref. (23). Macko RF, Ivey FM, Forrester LW, et al. Treadmill exercise rehabilitation improves ambulatory function and cardiovascular fitness in patients with chronic stroke: a randomized, controlled trial. *Stroke*. 2005;36(10):2206–2211.

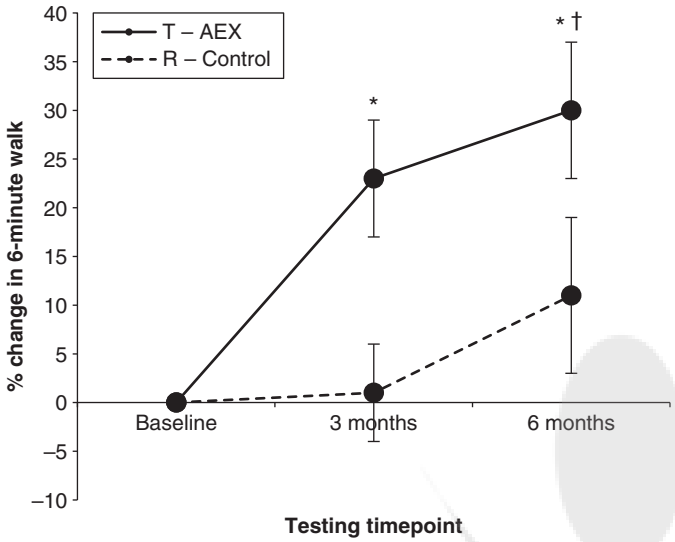

FIGURE 27.6 Progression of improvement in 6-minute walk distance across 6 months with progressive full BWS TM training in chronic hemiparetic stroke patients.

* $P < .05$ within group.
† $P < .05$ between groups.

Source: From Ref. (23). Macko RF, Ivey FM, Forrester LW, et al. Treadmill exercise rehabilitation improves ambulatory function and cardiovascular fitness in patients with chronic stroke: a randomized, controlled trial. *Stroke*. 2005;36(10):2206–2211.

plateau, suggesting that training even beyond six months may produce further benefits in peak fitness levels. In addition, full BWS TM exercise also improves 6-minute walk performance and self-reported indices of functional mobility across 6 months, with greater gains in 6-minute walk occurring within the initial 3 months of training (Figure 27.6) (23).

Notably, prospective studies show a plateau in mobility recovery within 3 months after stroke in 95% of hemiparetic patients receiving conventional rehabilitation care (101). Our findings in a randomized study show that TM training improves both fitness and mobility function long after conventional rehabilitation care has ended and that the duration of exercise therapy to optimize these outcomes is at least six months. Again, greater than previously observed improvements with TM training may be possible by aggressively tailoring progression formulas such that participants are challenged to the greatest extent within any given disability level (25,148). Results from studies of TM training after stroke support incorporating long-term exercise after stroke, consistent with public health recommendations for sustained regular exercise to improve fitness and cardiovascular health for all Americans (10).

Multi-Modal and Alternative Approaches to Stroke Exercise Rehabilitation

A trial involving primarily African American stroke survivors utilized a multi-modal intervention (36). A delayed-entry controlled design was used to provide training to all 35 participants. Outcome testing included measures of peak VO_2, strength, flexibility, and body composition. The 3×/week training protocol consisted of the following components: cardiovascular endurance (30 minutes), muscle strength and endurance (20 minutes), and flexibility (10 minutes). Results showed significant time increases by group interactions for the following measures during cycle ergometer fitness testing: VO_2 peak, time to exhaustion, and maximal workload. This was among the first randomized exercise studies in stroke to show significant between-group effects for muscular strength and endurance as well as improvements in body composition (body weight, BMI, total skinfolds). Other multi-modal exercise therapies have also been successful after stroke (72–74), particularly in the context of falls prevention.

Several additional alternative approaches to stroke rehabilitation have been tested within the past five years, including split-belt TM training (166), TM locomotor training with leg weights (167), elliptical machine training (168), dual-task exercise training (28), balance training (169), Lokomat robotic training (170,171) and virtual reality-based training (172). Although data are somewhat preliminary at this time, some have shown promise for restoring health and function in this population. One of the more interesting discoveries to come to light in recent years is the capacity for multiple exercise modalities to improve cognitive function and mental health after stroke (173–177). Animal studies preliminarily indicate that this may partially be a function of exercise-induced increases in brain-derived neurotrophic factor (BDNF) levels (178).

Community- and Home-Based Intervention Strategies

Numerous behavioral and psychosocial issues associated with chronic disability and aging influence exercise adherence and can serve as barriers to participation following stroke (179,180). Limited access and labor intensity of individualized conventional stroke therapies further constrain resources for poststroke exercise programs. Although both home- and rehabilitation center-based programs have been studied, the safest and most effective settings and behavioral strategies to best disseminate exercise programs to stroke survivors are unknown. Group exercise programs feasible for conduct in the community setting have recently been investigated to increase access (113), while providing a socially reinforced model for structured physical activity across the chronic stroke period.

A seminal Canadian study by Pang et al. (88,111) was the first to examine effects of community-based exercise programs on bone health and mobility outcomes in older individuals with chronic stroke. Individuals with remote stroke (>1 yr) who could walk 10 meters independently (with or without walking aids) were randomized to 19 weeks of three 1-hour sessions per week of an Arm Exercise Group or a program that included brisk walking, sit-to-stand exercises, stepping onto low platforms walking obstacle course, and partial squats and toe rises to improve strength. The latter program significantly increased VO_2 peak by 9%, extended 6-minute walk distance by 20%, and improved paretic leg strength, but not Berg Balance Scores. However, most subjects had milder balance deficits, whereas that subset with moderate deficits did not successfully progress their exercise intensity.

Notably, this intervention prevented the declines in femoral neck bone mineral density that occurred in the Arm Group and increased distal tibial trabecular bone mineral content on the paretic side. This shows that community-based exercise programs can improve fitness, walking capacity, leg strength, and bone health for older individuals with milder chronic deficits (88,111).

Based on models of task-oriented exercise and social learning to facilitate exercise behaviors in the frail elderly, an adaptive physical activity (APA) program with gymnasium and home components was designed to improve mobility and ADL function for chronic stroke patients (113). Group exercises targeting improved gait and balance were utilized to enhance social support, with a parallel home regimen to build self-efficacy for habitual physical activities. Two months of the APA program improved Berg Balance, 6-minute walk distance, and Barthel index scores in 20 older subjects with chronic hemiparetic deficits (113). Tuscany Regional Health Authorities have established APA programs at 11 community sites in a 30 × 30 km region of Italy where health services outcomes are tracked. These findings provide proof of concept that community-based exercise programs improve mobility and basic ADL function and can be implemented in geographically defined regions to improve outcomes for older chronic stroke patients.

Progress continues to be made in the area of home and community rehabilitation after disabling stroke (115,181,182). Of particular note are recent attempts to incorporate family members into the rehabilitation programs (115,182). Evidence now shows that family involvement may be critical to optimizing patient recovery (115). Also, the study by Duncan et al. strongly suggests that home physical therapy (PT) care may be equal to or surpass more complex interventions delivered in hospital settings (116).

STRATEGIES FOR DESIGNING EXERCISE PROGRAMS IN STROKE SURVIVORS

Goals of Exercise Training

Structured exercise programs should be considered for all stroke survivors. As detailed in the prior section, a number of randomized studies now demonstrate that various exercise modalities can significantly improve cardiovascular fitness after stroke. Although fundamental questions remain regarding how to optimize the exercise prescriptions, the magnitude of VO_2 peak gains that are attainable with exercise after stroke is considered clinically significant in terms of both functional capacity and cardiovascular health promotion (92). Risk factor modification is a second major objective of long-term exercise after stroke. Cardiovascular fitness and metabolic health are integrally linked and modifiable by exercise training, which may translate into reduced recurrent stroke risk and cardiovascular events in this population (10). Individuals aging with the chronic disability of stroke are further subject to body composition abnormalities that are propagated by sedentary lifestyle, worsening rehabilitation outcomes, and cardiovascular risk. The interrelated goals for improving fitness and preventing the body composition complications of physical inactivity constitute a multiple physiological systems model defining the targets of exercise therapy after stroke (Figure 27.7).

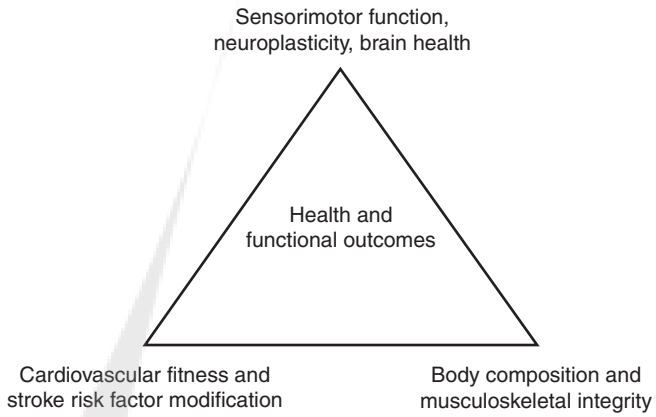

FIGURE 27.7 Multiple physiological systems that define the targets of exercise after stroke.

Intrinsic to this model is an emerging recognition that exercise can improve function by leveraging principles of motor learning even years after stroke. Emerging clinical and experimental data show that task-repetitive training can mediate functionally relevant motor learning in both the paretic upper and lower extremity (141,142). Conversely, lack of practice or "disuse" can propagate disability at a musculoskeletal and central nervous system level. Habitual daily physical activity patterns are a determinant of outcomes that warrant attention as an adjunct to any structured exercise program in the long-term care of stroke survivors. Hence, an objective of exercise therapy is improving the sensorimotor function that translates into improved daily activity profiles and quality of life across the continuum of stroke care. Motor learning strategies can be combined with aerobic training in a clinically appropriate way to improve the multiple physiological systems that determine functional and health outcomes, as shown in Figure 27.7.

The planning of exercise programs for stroke patients should be initiated early on with specific education to participants and family regarding the clinical relevance of exercise to functional recovery, cardiovascular health, and stroke risk factor modification. Most stroke survivors and many health care providers outside the field of rehabilitation care are unaware that both lower- and upper-extremity motor function can be improved by structured motor learning-based exercises even years after the initial stroke event (23,183). That physical inactivity is an independent risk factor for stroke and "disuse" leads to deconditioning, which worsens disability and stroke risk, are understated health concerns that should be reinforced across the phases of rehabilitation care. Patients should be informed that consensus statements strongly recommend exercise as an adjunct to

medical treatment for optimal management of hypertension, dyslipidemia, obesity, insulin resistance, and diabetes, all of which are elements of the cardio-metabolic syndrome and highly prevalent after stroke.

Medical Evaluation and Safety Issues Related to Exercise

As a result of the high incidence of medical and cardiovascular comorbid conditions that can influence exercise participation, evaluation for an exercise program should begin with a medical history and physical and cardiopulmonary examination. Medical exclusions for exercise after stroke are consistent with ACSM criteria for high CVD risk subject (33). In brief, exclusion criteria that have been systematically employed for exercise research include symptomatic heart failure, unstable angina, peripheral arterial occlusive disease, chronic pain syndromes, dementia or severe aphasia (operationally defined as incapacity to follow two-point commands) (27), and other medical conditions that preclude participation in low-intensity aerobic exercise, consistent with the 2012 ACSM guidelines. Using these eligibility criteria along with entry exercise tests, our safety data tracking across more than 10,000 TM aerobic training sessions and more than 400 peak exercise tests in chronic hemiparetic patients reveals no study-related serious adverse events. Analyses from a randomized study reveal only occasional minor musculoskeletal complaints reported by these deconditioned patients across six months of progressive TM aerobic training at an expected rate not different from controls performing supervised stretching exercises and low-intensity walking (23).

However, cumulative experience in safety of exercise after stroke is limited to research studies with very small sample sizes. These are inadequate to identify the full scope of medical or neurological factors that could complicate different exercise training approaches in the diverse stroke population. In one study, Rimmer et al. reported transient stroke symptoms, a seizure, and a hypotensive response during exercise testing (36), whereas other analyses of full-weight-bearing TM exercise revealed no serious training-related adverse events (23). However, hemiplegic arm and major hemisensory deficits predicted higher noninjurious fall risk, prompting our use of safety harnesses for subjects with specific deficit profiles. A further consideration is that strenuous exertion, such as that accompanying peak exercise testing, can precipitate arrhythmias and lower blood pressure in predisposed individuals with cardiac disease (33). Hence, exercise testing should be approached with caution in subjects with hemodynamic carotid stenosis or recent large territorial brain infarction. Although no exercise safety data yet exist, these conditions are known to markedly impair cerebral autoregulation, reducing capacity to compensate for drops in systemic blood pressure (10). Until more information is available, best clinical judgment and appropriate cardiopulmonary assessment should be used to guide the timing and design of exercise testing and training poststroke.

Exercise in Subacute Stroke Period

Structuring exercise programs after stroke presents unique safety and feasibility questions. Clinical research has not yet resolved basic questions regarding when to start structured exercise, nor shown which training modality(ies) or dose intensity are optimal across the phases of stroke recovery. Implementing exercise during the subacute stroke period is further complicated by the greater deficit profiles (101,141,154), high prevalence of cardiac comorbid conditions (184,185), and medical problems such as autonomic deconditioning and pain syndromes that are common and known to affect rehabilitation care (27). These factors limit patients' activity tolerance, forcing clinicians to weigh the feasibility of adding further exercise to already demanding early intensive rehabilitation. However, delay can be costly. Inactivity produces rapid declines in fitness and muscle mass that could worsen the functional aerobic impairment already present in the early stroke period (32).

Conventional rehabilitation does not likely provide adequate exercise intensity to reverse deconditioning after stroke (31,32,186). However, practice patterns differ considerably, as can the physical efforts and cardiopulmonary response to exertion during rehabilitation in different stroke patients (185). One practical approach is to assess the exercise intensity of usual physical therapy, focusing on upright and transitional movements that produce greatest exertion (31). Heart rate monitoring and ratings of perceived exertion (RPE) scales can be used for this purpose. If the aerobic component of usual rehabilitation care is considered deficient, therapists can consider adding low-intensity exercise, based on the cardiopulmonary safety profile, tolerability, and rehabilitation needs for each patient. Although the long-term benefits of starting specific exercise modalities early after stroke is not yet established, BWS TM training is better tolerated by individuals with greater gait deficits (154), and can provide an aerobic stimulus if properly administered (105). Hence, BWS TM training or other modalities to facilitate exercise in more disabled subjects warrant consideration early on.

Exercise Programs and Barriers to Participation in Chronic Stroke

For exercise programs to be successful across the chronic phase of stroke, a thorough pre-exercise entry evaluation, including assessment of barriers to exercise, is important (10). Numerous factors can interrupt the continuity of health-promoting exercise programs when transitioning from subacute to the chronic phase of stroke. Whereas most stroke survivors desire and would participate in regular exercise if available, a number of common psychosocial and behavioral factors can become formidable barriers. Stroke patients have a poor self-efficacy for exercise, which predicts reduced free-living physical activity and exercise behaviors in chronic stroke patients (10,179). An important and often ignored component of poor self-efficacy for

exercise and ADL function after stroke is fatigue (9,187). Nearly half of stroke survivors report fatigue as a factor that interferes with daily function, and reduces confidence to participate in regular exercise (9). Hence, evaluation using validated instruments, such as the Fatigue Severity Scale (9), can be used to identify this common barrier in the pre-exercise evaluation. Similarly, depression after stroke is common and could impede exercise participation (188). Because some studies show that exercise can improve mood after stroke, pre-exercise evaluation of depression and tracking using validated scales is advised. Another factor related to poor self-efficacy for exercise after stroke is inadequate outcome expectations. Most stroke patients are unaware that exercise can be undertaken to improve fitness, health, and function even years after a disabling stroke. Further, physician recommendations influence exercise patterns in aging and disability populations and are historically underutilized to promote exercise in the chronic stroke phase. Collectively, these findings are consistent with social learning theories to promote exercise behaviors in aging and chronic disease and highlight the importance of education and behavioral strategies to overcome barriers.

Important additional barriers are lack of resources, social isolation, and limited family support to sustain successful exercise programs in the chronic phase of stroke. Assessment of family and psychosocial support in the context of resources for maintaining exercise programs is advised (106). In practical terms, most stroke patients have limited access to exercise facilities or community programs that can provide the social support and oversight to successfully implement evidence-based exercise programs. Moreover, the efficacy and viability of long-term home exercise programs after stroke is unknown. These issues underscore the importance of rehabilitation health professionals partnering with primary medical care providers to jointly increase access to community and home services promoting exercise, health, and wellness after stroke.

Recent advances in home- and community-based exercise programs supporting this model are promising (88,106,109,113).

Selecting Exercise Training Formulas

By the time most individuals have reached the chronic phase of stroke, gait deficits are less pronounced, and subsequently, exercise-training capabilities are different. Most have achieved some degree of ambulatory function and may not require BWS or more dependent modalities for training. The gains in function often enable patients to participate in more rigorous and longitudinal exercise programs that have the potential to maintain and improve fitness and function while aging with the disability of stroke. Exercise modalities appropriate to deficit severity can optimally be implemented according to specific aerobic progression formulas based on cardiopulmonary exercise testing that can enhance safety and cardiovascular-metabolic health effects, as outlined in the following sections.

Exercise Testing Poststroke

Epidemiological studies show that 75% of stroke patients have CVD (184,185). Although uncommon, exertion-related myocardial events are possible in individuals with pre-existing cardiac disease and sedentary lifestyle (33). Further, many stroke patients have marked activity intolerance, particularly older individuals and those with greater gait deficits, which predict lower fitness levels after stroke. Exercise testing has revealed previously undiagnosed or asymptomatic coronary artery disease in 20% to 40% of stroke survivors (34) and provides information regarding the cardiopulmonary response to exertion that can be used to optimize safety and customize design of the aerobic exercise prescription. Therefore, submaximal effort or symptom-limited maximal effort exercise testing is recommended when clinically feasible to evaluate the cardiopulmonary safety and toleration of stroke patients of strenuous physical exertion before starting exercise training. Treadmill testing and training recommendations are summarized in Tables 27.4 and 27.5.

The selection of exercise testing modality may be influenced by many clinical factors, such as deficit profile, rehabilitation goals, or planned congruence with anticipated training modality. Because exercise testing can provide a reliable and valid means for quantifying fitness gains with training for both TM and bicycle testing modalities in hemiparetic stroke patients (22,189), congruence in testing and training modalities is recommended. There are no studies in stroke patients to discriminate between choices of submaximal versus symptom-limited peak effort exercise protocols. The term "peak effort," rather than maximal exercise test, is employed here because most stroke patients do not achieve full criteria for VO_2 max by open circuit spirometry testing (189). Peak exercise testing provides the most useful information for aerobic exercise in high-risk populations. Peak exercise heart rates are most accurate and have proven useful in the design of heart rate (HR) training progression in accordance with the Karvonen Formula. For high cardiac risk patients, training should be conducted at least 10 beats

TABLE 27.4 Treadmill Exercise Tests

TEST	PURPOSE
Zero-incline TM tolerance test	Acclimatize to TM; select speed for stress test
Screening TM exercise stress test	Identify cardiopulmonary response to strenuous exertion. Screen for underlying cardiac abnormalities
VO_2 peak exercise test	Measure peak oxygen-consuming capacity with open circuit spirometry as an outcome variable on a separate day from the screening TM exercise stress test

TABLE 27.5 Suggested Exercise Testing Protocol for Stroke Survivors

1. Start at 0.1 mph and increase to velocity determined from zero-incline TM test.
2. Fastest comfortable walking velocity maintained at no incline for initial 2 minutes, then:
   - Milder gait deficits: advance to 4% incline for next 2 minutes, then increase incline 2% every minute thereafter (velocity constant) to peak volitional exertion.
   - Moderate-to-severe deficits: advance to 2% incline for next 2 minutes, then increase incline by 2% every 2 minutes thereafter, with velocity held constant.

per minute below the exercise intensity that produces systolic blood pressures higher than 250 mmHg or diastolic blood pressure higher than 115 mmHg, ST segment depression of more than 1 mm, or other significant ECG or clinical cardiopulmonary intolerance (33). These criteria may best be revealed using peak exercise protocols.

Little is published regarding use of submaximal exercise to design aerobic prescriptions after stroke or exercise planning for stroke patients who cannot undergo exercise tests. Peak exercise testing may not be feasible or desired for some patients, particularly those less than 1 month poststroke, a period within which cerebral autoregulation is likely to be most impaired. In a seminal American Heart Association (AHA) consensus statement, submaximal exercise testing was recommended using predetermined endpoints of 70% of age-predicted maximum HR, consistent with practice in postmyocardial infarction patients (10). A period of ECG telemetry monitoring is recommended for those stroke patients deemed at high cardiac risk and who cannot undergo any exercise testing (33). Although no studies have yet established the efficacy in stroke, low-intensity exercise at increased training duration and/or frequency has been recommended for cardiac patients without an entry exercise test. Such guidelines extrapolated from cardiac patients may be useful until further data are available for stroke patients considered at high cardiac risk.

General Guidelines for Exercise Training and Progression

Treadmill Aerobic Training

The target training parameters used in chronic stroke patients from our laboratory (27) consist of three 40- to 45-minute sessions per week of TM walking at 60% to 70% of HRR, where target heart rate is calculated with the Karvonen Formula:

Heart rate reserve (HRR)
= Maximum heart rate – Resting heart rate

Target heart rate = (HRR × training %) + Resting heart rate

Creating a zone of 60% to 70% simply requires performing the calculation twice to come up with an upper and lower limit for the desired range. Training intensities of up to 80% HRR are now shown to be efficacious and safe in this population (25). Training is initiated conservatively at 40% of HRR for durations of 10 to 15 minutes and advanced as tolerated. Discontinuous training epochs consisting of three to five minutes TM walking with similar duration interval rests are used in those highly deconditioned or more severely disabled patients incapable of continuous training. Total training duration is then advanced as tolerated toward the target. Handrail support is used, and 5-minute TM warm-up and cool-down periods at approximately 30% of HRR are phased into each workout as participants develop the necessary endurance for longer bouts of training. Regression analyses of clinical factors related to training safety reveal that arm hemiplegia (inability to grasp TM handrail for support) and presence of major sensory deficit are associated with increased risk of falls during TM training. Although such events are uncommon and of low impact, we use suspensory safety harnesses (Biodex Medical, Shirley, NY) in a nonweight-bearing fashion to eliminate the risk of fall injury in our patients. Heart rate is monitored continuously by two-lead ECG (Polar Electro, Woodbury, NY), and blood pressure recordings are taken before, at the midpoint, and at the conclusion of each exercise session to ensure safety and to document the intensity of the training session.

Progression of training workload is determined biweekly by monitoring each patient's gait, HR response, and patient-reported level of fatigue at the end of a training session. If no gait instability, exaggerated HR response (HRR > 80%), or extreme fatigue is noted (Borg Perceived Exertion used as adjunct to rate tolerability), an increase in training speed by 0.1 mph increments is prioritized to reach the target training intensity. Increase in TM grade (1% increments) is utilized secondarily to achieve target aerobic intensity for those individuals who do not tolerate further TM velocity progression to meet this goal. Training duration is typically advanced approximately 5 minutes every 2 weeks, as tolerated, to arrive at a total 45 minutes of training by the third month of training. For those completing intermittent bouts of exercise, only duration is altered in order to progress to one continuous bout of 15 minutes.

Bicycle Aerobic Training

Potempa et al. achieved aerobic fitness gains after stroke using a bicycle ergometer training protocol (22). In this case, subjects exercised on an adapted cycle ergometer for 30 minutes 3 times per week. The intervention period lasted a total of 10 weeks. In the first 4 weeks, the training load was increased from 30% to 50% of maximal effort to the highest level attainable by the subject. The highest training load was then maintained for the final six weeks of training. Although this protocol resulted in fitness gains, sensorimotor function was not improved using this adapted bicycle ergometry protocol.

Resistive/Strength Training

A diverse array of equipment and RT exercise progression protocols have been used successfully in stroke (30,117,134–138). From the standpoint of building muscle mass, muscle strength, and muscle endurance, our group has emphasized a high-repetition, relatively high-intensity lower-extremity training format (30,81). This is accomplished through a series of exercises performed on three separate Keiser K-300 lower extremity air-powered machines utilizing pneumatic resistance (leg extension machine, leg curl machine, leg press machine). Because of the large discrepancy in strength and function between the paretic and nonparetic legs after stroke, limbs are always exercised separately on each Keiser machine. This ensures the maximum degree of stimulus on each side. Participants perform 2 sets of 20 repetitions on each leg on each machine (3 × 4 sets = 12 sets total, 12 × 20 repetitions = 240 repetitions). Each unilateral set of 20 is conducted with the goal of achieving at least one instance of muscle failure (sometimes more), such that the participant must lower the pneumatic resistance to achieve 20 repetitions. Generally, the initial weight is set at a level that will cause muscle failure somewhere between the 10th and 15th repetitions. The weight is then lowered gradually, enabling the participant to achieve additional repetitions up to the 20th. If necessary, the weight is lowered a second, third, or fourth time to achieve 20 repetitions. Often, during the initial stages of training, arriving at the ideal weight is a matter of trial and error, meaning that several training sessions are required for participants to fully comprehend what is being asked of them and to consistently train at the level of difficulty and intensity described here. Once the participant is performing 16 to 20 repetitions at a given weight, it is left to the discretion of the trainer on when and how much to advance the weight for the next set/session. Ideally, the trainer progresses the weight to a level that again causes the first incidence of muscle failure between the 10th and 15th repetition. Having more than the usual number of repetitions per set also imparts the added benefit of producing a cardiovascular effect with more prolonged elevations in heart rate and breathing. As with TM aerobic exercise implementation, consistent and careful monitoring of vital signs is essential for safety.

SUMMARY AND FUTURE RESEARCH

Reduced cardiovascular fitness is commonly observed after stroke, with physiological and functional consequences. More work is needed to fully elucidate the precise causes and consequences of this decline, but preliminary evidence points to several noteworthy biological correlates. Specifically, changes to paretic side extremities, including muscle atrophy, muscle fat accumulation, fiber type alteration, hemodynamic impairment, reduced capillary density, and increases in inflammatory markers, may both contribute to and be compounded by reductions in cardiovascular fitness. Moreover, there are systemic disturbances in metabolism and respiration that are exacerbated with sedentary living and the accompanying fitness decline. Hence, preventing and reversing the deconditioning trend after stroke is of paramount importance. Despite encouraging developments over the past few years, more is needed to ensure that cardiovascular/metabolic deconditioning becomes a focal point for poststroke care in mainstream clinical practice.

Fortunately, exercise training models have demonstrated high efficacy for addressing many deconditioning-associated issues in stroke. Degrees of training response to any given exercise stimulus, provided it is implemented carefully with optimal and safe progression in mind, is often comparable to that observed in healthier, nonstroke aging populations. A variety of exercise protocols show promise as a potent stimulus for improving fitness and associated physiological and functional outcomes in stroke-disabled individuals. Although the body of evidence for exercise-induced adaptation in stroke is still somewhat limited, substantive progress has been made in showing the extent to which exercise can be used to improve VO_2 peak, sensorimotor function, systemic metabolism, peripheral hemodynamics, cerebral hemodynamics, muscle tissue quantity, muscle biology, tissue inflammation reduction, pulmonary function, and cognition. Larger randomized research studies aimed at effective exercise prescription and informing best practice in stroke rehabilitation are essential to the advancement of stroke recovery.

There remains a significant practice gap, with many basic questions regarding the practice and effects of exercise after stroke left unanswered. The optimal training modalities and dose intensity of exercise, and how these may relate to deficit profiles or time since stroke, are unclear. Although selected CVD risk markers have improved, there are no long-term data to determine whether exercise reduces recurrent stroke, cardiovascular events, or progression of insulin resistance to diabetes. Future research could consider the promising findings from bench and clinical studies in nonstroke populations that exercise improves cognitive function, depression, and alters neural growth factors that could improve brain health in aging and mediate brain plasticity linked to motor learning. In practical terms, many of the recommended safety and training approaches for stroke patients are borrowed from the cardiac literature. These should be empirically tested in stroke patients—a population that in many ways is clinically and biologically unique. Further studies in community translation and systematic strategies to overcome barriers to longitudinal participation are needed to better realize the benefits of exercise after stroke.

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28

Medical Complications After Stroke

Lalit Kalra

Patients with stroke are at risk of developing a wide range of medical complications that have the potential of causing death or delaying successful rehabilitation. Several studies have shown that medical complications may be the primary cause of hospital-related death in more than 50% of stroke patients and may contribute to death in an even larger proportion (1). The timing of deaths in stroke is bimodal: the first peak occurs in the first week, predominantly as a direct consequence of brain damage; and the second peak occurs several weeks later, mainly as a result of potentially preventable medical complications such as infection, venous thromboembolism, or cardiac disease (1–5). Medical complications not only increase mortality during inpatient care, but have also been shown to have a significant effect on long-term mortality. A study of nearly 600 patients has shown that the presence of one or more medical complications during hospitalization was associated with a hazard ratio for mortality ranging from 2.67 in the initial cohort to 8.93 in patients who had survived for three or more years, after adjusting for age, gender, initial stroke severity, stroke subtype, comorbidity, and disability at the time of discharge from hospital (6).

Medical complications have also been associated with increased disability and poor functional outcome in stroke patients. The scope of intensive therapy is limited in patients suffering complications during rehabilitation, which may result in longer hospital stays, increased resource use, and institutionalization (4,7). Mortality-adjusted data analysis from the RANTTAS trial, which excluded patients who died at three months after stroke, showed that serious medical events during hospitalization were associated with a four-fold increase in residual severe disability, independent of stroke severity and other variables (5). The length of hospital stay for rehabilitation is directly proportional to the number of medical complications suffered by patients, and 7% to 17% of stroke patients undergoing rehabilitation need to be transferred back to acute care settings, which further increases the overall cost of stroke management (4,8). It is, therefore, both inaccurate and misleading to view inpatient stroke rehabilitation as a medically quiescent process that does not require ongoing medical input.

FREQUENCY AND TYPE OF MEDICAL COMPLICATIONS

Medical complications are known to be common in patients with stroke, but estimates of their prevalence in rehabilitation settings differ significantly, ranging from 27% to 96% in various studies, with a median of 75% (9). Complications appear to be more frequent in patients with severe strokes (94%) compared to patients with mild or moderate deficits (16%) (7). Prevalence of complications is higher (75%–85%) in studies that include acute patients and in studies that have used rigorous and prospective methods for data collection (9). The type of medical complications also varies with patient characteristics and management settings. The commonest medical complications seen in rehabilitation settings are infections (particularly of the chest or bladder), falls, deep vein thrombosis (DVT) and thromboembolism, pain, loss of skin integrity and/or pressure sores, and other mobility-related problems, such as musculoskeletal pain or limb edema. During rehabilitation, patients with stroke are also more susceptible to exacerbations of pre-existing cardiac, vascular, and metabolic diseases, which are frequently present in this population. A list of frequently encountered medical complications is given in Table 28.1, which is by no means exhaustive.

The wide variation in estimating the frequency and types of medical complications that people with stroke experience during their rehabilitation (Table 28.2) reflects the methodological problems and inherent biases encountered in undertaking such studies (9). Earlier studies have either incorporated a retrospective case ascertainment design (2–4,10) or prospective analysis of patients selected for intervention studies (5,7), with different criteria for patient selection, definition of complications, timing of assessments, and duration of follow-up. The retrospective identification of complications from case notes is further influenced by the diagnostic criteria used, interobserver bias, and the standard of notekeeping. Most studies have recorded only symptomatic complications that occurred during the inpatient stay, which will be influenced by reporting bias and duration of observation (11). Very few studies have investigated the

TABLE 28.1 Medical Complications Reported in Stroke Patients

Infections	Aspiration pneumonia, chest infections, urinary tract infection, sepsis, cellulitis, *Clostridium difficile* enteritis
Mobility-related problems	Falls, fractures, musculoskeletal pain, edematous limbs, DVT in calf, thigh or axilla, PE, loss of skin integrity, breaking skin, pressure ulcers, urinary retention or incontinence, constipation, diarrhea
Comorbidity	Angina, myocardial infarction, congestive cardiac failure, atrial or ventricular arrythmias, cardiac arrest, hypertension, hypotension, poor diabetic control, hypoglycemia, ischemic colitis, exacerbation of chronic lung disease, peripheral vascular disease
Others	Noncardiac pulmonary edema, gastrointestinal bleeding, dehydration and electrolyte imbalance, renal impairment, anemia, malnutrition

prevalence of complications in a defined representative sample of stroke patients from a fixed time point early in the course of their disease, using prespecified objective criteria for identifying complications, prospective data-collection methods, and regular follow-up.

THE DETERMINANTS OF MEDICAL COMPLICATIONS

The incidence and frequency of complications in stroke rehabilitation are influenced by several factors. Most studies show that the frequency of complications increases with age of patients and the severity of neurologic or functional deficits (Table 28.3). Prestroke disability, urinary incontinence, vascular risk factors such as diabetes and hypertension, markers of poor nutritional status (e.g., hypoalbuminemia), and length of hospital stay also identify patients at higher risk of developing infections (8,10,11). Factors that predict transfer to acute medical facilities from rehabilitation settings include elevated admission white blood cell counts, low admission hemoglobin levels, greater neurologic deficit, and a history of cardiac arrhythmia (8).

The relationship reported in some studies between increased length of hospital stay and increased prevalence of complications raises important issues. It remains unclear whether prolonged hospitalization is a cause or a result of stroke-related complications, but it is likely that complications are both a cause and an effect of prolonged hospitalization. The setting in which patients are managed also has an important influence on the frequency and type of complications. Kalra et al. (7) have shown that although there are no differences in the frequency of complications between generic and specialist settings, there is a significant difference in the type of complications between the two settings. This difference may be one of the reasons for better outcomes and shorter lengths of hospital stays reported in specialist settings. It is likely that patients cared for in a dedicated stroke unit are under more scrupulous observation by experienced staff and may experience fewer severe or life-threatening complications, whereas less-severe complications may appear to be more frequent simply because of better recognition and documentation in case records (10). This explanation is supported by a study on processes of care on specialist units, which showed that patients on a stroke unit were monitored more frequently than those in general units and that more patients received antipyretics, measures to reduce aspiration, and early nutrition (12). Complications were less common in the specialized setting, with fewer patients suffering from chest infection or dehydration, which was associated with reduced mortality, fewer instances of institutionalization, and shorter length of hospital stay. Similar findings have been reported from the most recent Stroke Unit Trialists Collaboration meta-analysis of medical complications data from seven trials, which included 3327 patients and showed significantly lower complications arising from immobility and infections in patients managed on specialist units (13).

SPECIFIC MEDICAL COMPLICATIONS

Aspiration and Pneumonia

Aspiration and swallowing impairment are common after stroke; a recent meta-analysis has shown that their incidence ranges from 51% to 55% on clinical tests and 64% to 78% on videofluoroscopy or other instrumental tests (5). Dysphagia is associated with a three-fold increase in the risk of chest infections, which increases to eleven-fold in those with definite aspiration (14). Large stroke registries across the world have shown pneumonia to be the single most important cause of death in the entire stroke population, accounting for 23% of deaths in the Japanese registry (15) and 31% in the German Stroke Registers Study (1). In addition, as many as two out of three stroke patients who appear to be able to swallow safely on clinical assessment have been shown to aspirate using instrumental diagnostic techniques (16). Aspiration is associated with a higher risk of chest infections and mortality (17).

Although aspiration is common after stroke, not all patients who aspirate will develop chest infections. It is likely that there are several mechanisms that protect the lower airways, ranging from physical processes that clear the airways of the aspirated material, to cellular and immunological processes that combat infection. Of these, voluntary expiration and cough are particularly important for maintaining the patency of airways. Cough, whether voluntary or reflex, generates high expiratory flows with laminar flow in the smaller airways, which dislodge and eject foreign material from the pulmonary system. The relationship between cough and aspiration has not been explored in detail, but the few studies available

TABLE 28.2 Frequency of Medical Complications Reported in Different Studies

	DOBKIN ET AL. (3) (N = 200)	DROMERICK ET AL. (4) (N = 100)	KALRA ET AL. (7) (N = 245)	DAVENPORT ET AL. (10) (N = 607)	JOHNSTON ET AL. (5) (N = 279)	LANGHORNE ET AL. (11) (N = 311)	ROTH ET AL. (8) (N = 1029)	BAE ET AL. (6) (N = 579)
Study design	Retrospective	Retrospective	Retrospective	Retrospective	Prospective	Prospective	Prospective	Prospective
Study setting	Rehabilitation	Rehabilitation	Rehabilitation	Rehabilitation	Acute and rehabilitation	Rehabilitation	Rehabilitation	Acute and rehabilitation
Centers	Single center	Single center	Single center	Single center	Multicenter	Multicenter	Single center	
Complications								
Chest infection	2%	7%	12%	12%	10%	22%	4%	11%
Urinary tract infection	7%	44%	25%	16%	11%	24%	31%	8%
DVT	2%	4%	5%	3%	2%	2%	4%	
Pulmonary embolism	2%	0%	1%	1%	1%	1%	1%	
Skin breaks								
Pressure sores	2%		3%	18%	5%	21%	4%	1%
Falls		25%		22%		25%	11%	
Cardiac events					8%		5%	1%
GI bleeding					5%		3%	3%
Pain (excl. painful shoulder)			31%	8%		34%	14%	
Total	**40%**	**96%**	**60%**	**59%**	**85%**	**85%**	**75%**	**27%**

TABLE 28.3 Common Risk Factors for Poststroke Complications

RISK FACTOR	OR (95% CI)
Complications	
Age	2.4 (1.6–3.8)
Stroke severity	4.6 (2.7–7.9)
Premorbid disability	2.7 (1.7–4.3)
Urinary incontinence	8.5 (5.6–13.0)
Diabetes	1.9 (1.1–3.4)
Hypertension	1.8 (1.3–2.6)
Hypoalbuminemia	1.7 (1.2–2.5)
Length of stay >30 days	12.9 (7.7–22.0)
Specialist unit management	0.6 (0.4–0.9)
Transfer to acute facilities	
Elevated admission white blood cell counts	1.9 (1.3–2.8)
Low admission hemoglobin	1.9 (1.3–2.7)
Greater neurologic deficit	2.5 (1.4–4.4)
History of cardiac arrythmia	1.8 (1.2–2.7)

Source: Data from Davenport et al. (10), Roth et al. (8), and SUTC (13).

show that absent or weak cough in stroke patients is associated with a higher incidence of aspiration and chest infections (18,19). Several aerodynamic measures of voluntary cough are impaired in stroke patients compared to nonstroke control subjects, and in aspirating compared to nonaspirating stroke patients (19). More recent studies suggest that stroke patients also have impaired reflex cough, increasing the likelihood of aspiration (20). The final common pathway for the production of effective cough is the ability to generate high intra-abdominal pressure by strong contraction of the abdominal muscles. Recent studies have shown diaphragmatic involvement on the affected side, disruption of cortico-respiratory neuronal outflow, and decreased expiratory muscle excitation from the affected hemisphere in patients with stroke (21). It is quite likely, but remains unproven, that the impairment of expiratory muscle function may impair voluntary cough efficacy and contribute to increased susceptibility to chest infections after stroke.

The CNS modulates the immune system through humoral and neural pathways, and it has been suggested that stroke may induce an immunodeficient state at the time of maximal deficit by affecting hypothalamic pituitary adrenal (HPA) axis activity and resulting in impairments of the sympathetic nervous system and various neurohumoral mechanisms (22). Experimental studies have shown long-lasting depression of cell-mediated immunity, reduced spleen cellularity and response to mitogens, and increased production of inflammatory factors on sympathetic stimulation in stroke models. This is supported by findings of reduced peripheral blood lymphocyte counts, impaired T- and natural killer cell activity, reduced mitogen-induced cytokine production, rapid increase of circulating cytokines in plasma, and sympathoadrenomedullary activation with infection in stroke patients.

Despite several studies showing strong associations between dysphagia and chest infections, there are few intervention trials of antibiotics used to prevent chest infections. A meta-analysis of 5 studies that included 506 stroke patients showed that preventive antibiotic therapy reduced infection rate from 36% to 22% overall (relative risk, 0.58; 95% confidence interval, 0.43–0.79), but there was no effect either on mortality or the likelihood of good outcomes (23). Major limitations in existing literature include small studies based on the assumptions of high frequencies of chest infections (30%–45%), much higher than those encountered in clinical practice; inclusion of nondysphagic stroke patients in whom the risk of aspiration and pneumonia is significantly lower than in those with dysphagia and more severe stroke (typical of those undergoing rehabilitation); and very short treatment duration. In addition, end points were inconsistent and consisted of infarct size and bladder temperature rather than mortality or chest infections. The use of antibiotics is associated with increased risk of serious adverse events such as *Clostridium difficile* and methicillin-resistant staphylococcus aureus colonization, which were not addressed.

Existing guidelines have evidence-based recommendations on the assessment, positioning, and feeding of acute stroke patients to prevent chest infections, but there is not enough evidence to support a clear strategy for antibiotic use for prevention (24). The current policy is to adopt a "wait and watch" approach for identifying early signs of chest infection and treat aggressively with appropriate antibiotics if any of these are present. Additional risk factors for aspiration and chest infection in patients undergoing rehabilitation include age over 65 years, speech or cognitive impairment, stroke severity and residual disability, decreased level of consciousness, brainstem strokes, and multiple infarcts (25); patients identified at high risk should be monitored closely for early signs of aspiration and chest infection. Preventive measures to reduce chest infections include assessment for dysphagia, aspiration risk, and cough; positioning and regular suctioning, dietary modifications, and dental and oral hygiene. It should be emphasized that nasogastric tubes or percutaneous gastrostomies do not reduce the risk of aspiration in dysphagic patients. For further reading on the management of dysphagia, see Chapter 14.

Cardiac Complications

Cardiac disease is not only a risk factor for stroke but also a common complication encountered during stroke rehabilitation. As stroke and heart disease share several risk factors, a recent stroke may be caused by a concomitant acute myocardial infarction, valvular heart disease, heart failure, or arrhythmias—and these conditions may also be exacerbated by stroke. The involvement of the right insula in stroke is of particular importance in predisposing to cardiac complications, because of its rich connections with the limbic system and involvement with autonomic control (26). The

occurrence of serious cardiac events and nonstroke vascular death in stroke patients varies between 1.1% to 2.1%, and most of these events tend to occur in the first two weeks after stroke (27,28). Factors that predispose to the risk of cardiac disease in recovering stroke patients include stroke severity, diabetes, congestive heart failure, and a prolonged QTc interval (28).

Cardiac arrhythmias are the commonest complication after stroke and include atrial fibrillation, supraventricular tachycardia, ventricular ectopic beats, and ventricular tachycardia (29). Cardiac arrhythmias can lead to hemodynamic instability, increase the risk of cardiac death, and be associated with cerebral and systemic thromboembolism. Subclinical ECG abnormalities in stroke patients are frequent, but their relevance to outcomes remains controversial. Of these, only prolongation of the QTc interval has been independently associated with ventricular arrhythmias and vascular death (30).

A systematic review of myocardial infarction in stroke patients suggests a 2% incidence for both myocardial infarction and nonvascular death in stroke patients (27). A subthreshold increase in cardiac enzymes is more common and thought to be indicative of brain-induced myocardial damage (myocytolysis) (31). Worsening of congestive heart failure is frequently seen in stroke patients, largely because of iatrogenic complications such as fluid overload or changes in medications. Occasionally, congestive heart failure may be precipitated by new-onset myocardial infarction or arrhythmia. Very rarely, patients with severe strokes may develop Takotsubo syndrome, a characteristic cardiomyopathy with left ventricular apical ballooning. Takotsubo syndrome is usually self-limiting, but has been associated with sudden death, congestive heart failure, and recurrent thromboembolism (32).

Identification of high-risk patients and surveillance on the stroke unit can help to prevent such complications. As these complications may be life threatening, patients may need to be transferred to acute facilities with intensive monitoring and specialist input as appropriate to their needs.

Falls

Falls during rehabilitation are common, and a high prevalence has been reported in many studies (Table 28.1). In a study by Davenport et al., falls were the most common individual complication and occurred in 22% of patients (10). An even higher proportion of falls during the hospital stay was reported by patients discharged from rehabilitation, with nearly 46% claiming to have fallen at least once during their hospital stay and 73% experiencing a fall within the first six months of discharge (33). In most instances, these falls are benign; soft-tissue damage or need for further investigations is seen in about 10% of fallers and only 1% to 3% of patients who fell suffered a fracture as a result of the fall. An important consideration is falls occurring in patients receiving anticoagulation for secondary-stroke prevention while undergoing rehabilitation. Despite falls being a relative contraindication to anticoagulant therapy because of percieved risks, Stein et al. have shown that although falls in patients on anticoagulation were as frequent as in nonanticoagulated patients undergoing rehabilitation, the risk of injury, major bleeding, or intracranial hemorrhage was comparable to those not receiving anticoagulation (34).

The great paradox of rehabilitation is that most therapy activity is geared toward increasing mobility in stroke patients; yet patients who have some ability to mobilize are most prone to falling (11). The main reason for falls is stroke-related disability, with most patients losing balance while attempting to undertake basic activities such as transferring, walking, or reaching. Factors associated with increased risk of falls include age, severity of stroke deficit, neglect, cognitive impairments, comorbidity, and a tendency to "push" from the unaffected side (35). Patients who have had one fall are at a greater risk of suffering further falls. The Berg balance test has been suggested as a reliable, objective test for identifying potential fallers in rehabilitation settings, but its use in clinical practice remains to be validated (36).

The greatest risk of falling in rehabilitation settings is during unsupervised activity, but it may neither be feasible to monitor patients on a 24-hour basis nor desirable to lower their optimism and perceptions of recovery by severely restricting activity. The answer may lie in effective therapy techniques and strategies to prevent falls, good communication with patients to provide a clear understanding of stroke-related problems and their abilities, safe environments, toileting programs, and use of aids and technology. Individuals with evidence of balance difficulties, neglect, seizures, cognitive impairments, or use of CNS-depressant medication are at high risk and these risks should be minimized by careful attention to environment and medication (9). The use of hip protectors as shock absorbers to prevent fractures after a fall has been advocated in stroke patients and supported by a pooled analysis of 15 trials, which has shown benefit in the older patient (37). However, there must also be acceptance, by both patients and professionals, of the small element of risk of falling, which is inherent to promoting independence and self-confidence in stroke patients undergoing rehabilitation.

Urinary Dysfunction

The most frequently occurring urinary problems associated with stroke are frequency, incontinence, retention, and infection. Urinary incontinence has a reported incidence ranging from 37% to 79% (9) and is one of the most commonly encountered medical complications in rehabilitation settings. Elderly patients with stroke can have pre-existing difficulties with micturition, which are worsened even by mild strokes. Any urinary problem can adversely affect self-esteem and motivation of patients, leading to delayed discharge from hospital, increased caregiver burden after discharge, or institutionalization. Patients who are incontinent on admission to rehabilitation suffer additional complications and have greater morbidity, both during their hospital stay and at three months after stroke (38). Many stroke

patients who are initially incontinent regain continence in two weeks, but 15% to 20% patients may have persisting problems at six months after stroke (39). The main predictors of incontinence in the 935 patients included in the Copenhagen Stroke Study were age, severity of stroke, diabetes, and pre-existing functional comorbidity (39). Factors associated with increased risk of urinary tract infections included older age, a history of prior stroke, greater stroke severity, use of beta-blockers or antidepressants, and a postvoid bladder residual of greater than 150 mL.

Several mechanisms contribute to incontinence in stroke patients (40). Patients may present with incontinence because of impairments of bladder function resulting from an "uninhibited bladder" and/or hyperreflexia from disrupted neuromicturition pathways. Other patients have normal bladder function but may still be incontinent because of stroke-related motor, cognitive, and language deficits. In some patients, incontinence may result from bladder hyporeflexia caused by concurrent neuropathy associated with age or diabetes or from concurrent medications, which are unrelated to the acute stroke. In addition, there may be many nonphysiological factors that contribute to increased prevalence of reported incontinence in stroke patients. These include other stroke-related problems such as depression, apathy, confusion, or speech difficulties, which may affect the desire or the ability to communicate voiding needs. Some patients who are dependent on caregivers for transfers and mobility may find it difficult to void in a socially appropriate manner. Lack of caregiver support may also make it difficult for stroke patients to use the toilet quickly enough. Medications (such as diuretics) can increase the frequency of the need to void, whereas others (such as those with anticholinergic effects, and beta-blockers in particular) can increase confusion or affect the autonomic nervous system, leading to incontinence or retention.

There are a wide range of interventions, including bladder training, continence nurse practitioner care, pharmacological treatments, and sensory–motor biofeedback techniques, to manage continence in stroke patients. Many of these behavioral and pharmacotherapy interventions are supported by small studies, but the heterogeneity in patient populations, study design, and times of enrollment between studies limits their ability to influence practice (41). There are no large well-designed randomized controlled trials that provide conclusive evidence of benefit, and no single treatment has been shown to be superior to any other in improving continence. In the absence of conclusive evidence, a stepwise approach beginning with behavior intervention, progressing to medication only if these measures fail, and considering surgical interventions as a last resort has been recommended (36).

The use of indwelling catheters in patients with incontinence is an important issue in stroke management. It is generally believed that early use of indwelling catheters will inhibit regaining continence in stroke patients, and that the use of indwelling catheters should be limited to patients with incontinence who cannot be treated with other means, patients with urinary-outlet obstruction, severely impaired patients with skin breakdown in whom frequent bed or clothing changes would be difficult or painful, and patients in whom incontinence interferes with monitoring of fluid and electrolyte balance (36). Chronic use of indwelling catheters also increases the risk of urinary tract infection and inflammatory bladder wall changes, which contribute further to incontinence and infection.

Deep Vein Thrombosis

There is wide variability in the reported incidence of deep vein thrombosis (DVT) following stroke. The overall incidence of clinically apparent and silent DVT may be as high as 45% in acute stroke patients. This rate falls to 10% or lower in patients in the subacute phase of stroke who are receiving rehabilitation (36,42,43). The incidence of pulmonary embolism (PE) varies between 9% and 15% in patients who have DVT and, like DVT, is lower in those undergoing rehabilitation. DVT and PE account for 1% to 2% of mortality in stroke patients in rehabilitation settings (36), but PE has been implicated as a cause of death in 12% to 20% of patients in acute settings and in up to 50% of stroke patients with sudden death (44,45). Most fatal PEs occur between the second and fourth weeks after a stroke, when patients are most likely to be undergoing rehabilitation. Clinical symptoms of DVT (pain, swelling, erythema) may often be absent in stroke patients, even when diagnostic tests are positive. The risk of DVT and PE is high in patients with advanced age, more severe strokes, lower-limb plegia, reduced consciousness, obesity, history of a previous DVT, and longer duration of hospital stay (46). Many reports show that the prevalence of DVT appears higher in patients with hemorrhagic compared with ischemic strokes, which has partially been attributed to the use of anticoagulant medications in ischemic stroke patients (47).

Prophylaxis with low-dose subcutaneous unfractionated heparin (UFH) or low molecular weight heparin (LMWH) can be effective in preventing DVT and PE, but can also increase the risk of major bleeding, intracranial hemorrhage (ICH) or hemorrhagic transformation, especially in patients with large infarcts (9). There is a difference of opinion on their management, and guidelines for thromboprophylaxis in stroke vary between countries. North American guidelines strongly recommend early use of anticoagulants, heparin, or other antithrombotic measures to prevent DVT in immobilized stroke patients (48). In contrast, UK guidelines warn against the routine use of heparin or anticoagulation and recommend the use of aspirin and elastic compression stockings in stroke patients (24).

There is very strong, good-quality evidence in literature that anticoagulation significantly reduces the incidence of DVT. A pooled analysis of 16 trials involving 23,043 patients showed that treatment doses of UHF decreased DVT and PE but increased ICH in stroke patients. UHF used in preventive doses decreased DVT but had no effect on PE or ICH. LMWH (>6000 IU) decreased DVT and PE but increased the risk of ICH, but low-dose LMWH (<6000 IU) reduced both

DVT and PE without increasing the risk of ICH (49). It was not possible to identify optimum candidates for DVT/PE prophylaxis therapy from these studies, and it has been suggested that prophylaxis is used for stroke patients identified as being at high risk (based on the factors described earlier) during rehabilitation. There is also no evidence or consensus on the duration of treatment required in these patients, so a pragmatic approach based on individual patient characteristics has been recommended. The use of anticoagulants to prevent DVT or PE in patients with hemorrhagic stroke presents a greater challenge and remains controversial. A small randomized study in ICH patients has shown that low-dose heparin prophylaxis initiated on the second day after stroke was safe and effective in preventing PE and that early treatment started within two days was more effective than treatment started at an average of one week after stroke onset. However, these results remain to be confirmed by larger, better-designed studies (50).

The alternate approach of using graded compression stockings has been recommended in some guidelines, but a very large randomized controlled trial has shown no benefit in reducing DVT, PE, or mortality in stroke patients (51). Compression stockings were associated with a four-fold increase in skin ulcers and a small increase in lower-limb ischemia, suggesting harm, and should be avoided in stroke patients undergoing rehabilitation.

Regardless of the robustness of evidence on these interventions, a major challenge in stroke management is the translation of good research evidence into good clinical practice. In the Post-Stroke Rehabilitation Outcomes Project, Zorowitz et al. (42) showed that despite the strength of evidence and support from clinical guidelines, nearly 33% of patients without DVT and 1% of patients with DVT had no documented orders for anticoagulant medications. The study concluded that although much is known about the prevention and treatment of poststroke DVT, clinicians need to learn to apply prevention protocols to prevent interruptions to the rehabilitation process.

Edematous Limbs

Swelling of the limbs on the affected side is common after stroke. A recent study in 88 stroke patients on a rehabilitation unit showed that some degree of hand swelling was present in 73% and edema in 33% of patients (52). These problems are more common in patients with hypertonic fingers and impaired sensation, and have been associated with worse outcomes for arm and hand function. Limb edema also causes considerable discomfort and concern to stroke survivors, especially because it may never resolve in some patients. Elderly patients and those with more severe strokes are likely to suffer from these problems and have an increased risk of venous thrombosis.

The precise etiology of edema of the hand of the paralyzed arm is not known, but various mechanisms such as complex regional pain syndrome (formerly called reflex sympathetic dystrophy), posture, and lack of muscle activity have been suggested in the past. Geurts et al. (53) undertook an extensive review of studies on the etiology and treatment of poststroke hand edema and shoulder–hand syndrome. This review included etiological studies on lymph scintigraphy in hand edema, bone scintigraphy, putative risk factors, and the existence of autonomic dysregulation or peripheral nerve lesions. Therapeutic studies included investigations of continuous passive motion and neuromuscular stimulation in hand edema as well as oral corticosteroids, intramuscular calcitonin, and trauma prevention. They concluded that hand edema is not lymphedema but is rather associated with increased arterial blood flow, possibly resulting from autonomic dysregulation, and is probably worsened by trauma-causing aseptic inflammation of the joints. Furthermore, no specific pharmacological treatment had any advantage over physical methods for reducing hand edema (54). Available treatment modalities include elevation of the hand, massage, application of elastic bandages, immersion of the hand in cooled water, and pneumatic compression, all of which remain debatable.

MEDICAL MANAGEMENT IN REHABILITATION

The medical management of patients with stroke requires the skills of a well-coordinated multidisciplinary team because of the number of problems associated with stroke (e.g., impaired sensation or cognition, paresis, dysphagia), the high risk of stroke-related complications (e.g., aspiration pneumonia, venous thrombosis), the specialized needs of stroke patients (e.g., communication problems, visuospatial impairment), and patients' dependence on others for basic activities of daily living.

Most of the medical treatment during stroke rehabilitation is supportive, allowing time for neurologic injury to settle with minimization of further risk from potential complications. This includes maintaining stable respiratory and cardiovascular function, with particular attention to oxygenation and appropriate blood pressure; correcting fluid electrolyte imbalances and optimizing blood glucose levels; ensuring adequate nutrition; and preventing complications such as aspiration pneumonitis, urinary retention or infection, venous thromboembolism, pressure sores, and falls. Of particular importance is the maintenance of nutrition and hydration, because stroke is often associated with disturbances of water, glucose, and salt mechanisms. These conditions may be a result of impaired consciousness, inability to perceive or respond to hunger and thirst, or hypothalamic disturbances causing salt-losing or salt-retaining syndromes. Although stroke patients also have high metabolic needs, factors such as metabolic impairments, renal function, and glycemic status must be taken into consideration while planning nutrition regimens. Poor nutrition, dehydration, and electrolyte imbalance are the precursors of many—and contribute to the severity and consequences of almost all—complications encountered in stroke (see also Chapter 29). Meticulous attention to managing these often "silent" derangements is often rewarded by fewer complications,

better participation in rehabilitation, and better functional and psychological outcomes.

The key message emerging from several research studies and years of clinical experience is that the best intervention to reduce stroke-related complications and optimize rehabilitation outcomes is to manage stroke patients on specialized dedicated units where staff, who are knowledgeable about stroke and stroke-related complications, monitor patients regularly and institute measures that can proactively prevent the occurrence of such complications or provide early aggressive interventions to mitigate consequences once complications occur.

RESEARCH FRONTIERS

Although considerable literature is available on outcomes, rehabilitation, and service organization in stroke rehabilitation, research into the prevalence, management, and consequences of medical complications has merited relatively little attention (54). Studies that can measure the independent impact of complications on recovery and the benefits of prevention of individual complications are difficult to design because of the interactions between different processes of care in determining stroke outcome. There is still no satisfactory longitudinal representative cohort study with a large enough number of patients for accurate estimation of the incidence and prevalence of stroke-related medical complications and their temporal profile during various stages of stroke management. Similarly, there are no robust intervention studies on the prevention or treatment of these complications that can guide clinical practice for the specific management of these problems. There are several small ongoing studies that investigate various aspects of medical management of stroke patents, but small sample sizes and design heterogeneity will limit the impact of their findings and their potential for inclusion in meta-analyses.

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29

Physiology and Management of Spasticity After Stroke

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Spasticity is commonly defined as "a motor disorder characterized by a velocity-dependent increase in tonic stretch reflexes with exaggerated tendon jerks, resulting from hyperexcitability of the stretch reflex, as one component of the upper motor neuron syndrome" (1). It magnifies weaknesses and other motor abnormalities and thus worsens the functional impairments commonly associated with stroke, such as difficulty with gait and upper-limb use. In more severe states, it causes pain and leads to contractures and permanent joint deformities. Unfortunately, this often-quoted definition does not describe commonly observed clinical findings such as the intermittent nature of spastic hypertonia. It also does not consider the other abnormalities associated with the upper motor neuron syndrome (UMNS), of which spastic hypertonia is but one component: dystonia, co-contraction of agonists and antagonists, clonus, weakness, and incoordination (2–8). Lastly, this definition does not acknowledge the role of the sensory system in causing motor abnormalities. A proposed alternate definition is spasticity as "a disordered sensorimotor control, resulting from an upper motor neuron lesion, presenting as intermittent or sustained involuntary contraction of muscles" (9).

Because spasticity presents with related motor and neurologic disorders, a thoughtful clinical assessment should tease out the underlying dysfunction for a particular component of the clinical presentation in order to design an appropriate treatment plan that will address all impairments that contribute to the functional problem. For instance, even as pharmacologic interventions can effectively reduce hypertonia, they may either uncover or cause motor weakness and incoordination, which will have to be addressed through strengthening exercises.

Current estimates of the prevalence of spasticity range from 4% to 42.6% (2,10–21). The wide range of these estimates can be attributed to various factors such as the interval between stroke onset and assessment, sample size, assessment method, duration of follow-up, and study setting. In fact, many studies involved stroke survivors recruited from institutions rather than the community, thereby limiting knowledge of the population-based incidence of spasticity. Although certain conditions have been implicated as risk factors for poststroke spasticity, such as degree of paresis, sensory deficits, pain, and lower Barthel index (BI) scores, many patients in epidemiological studies also had severe motor, language, and cognitive impairments that may be related to more severe spastic hypertonia, raising the possibility that these conditions are comorbidities rather than causative factors.

ASSESSMENT AND GOAL SETTING

When assessing poststroke hypertonia, it is important to understand that spasticity is only one component of the muscle overactivity seen as part of the upper motor syndrome (Table 29.1). Abnormal co-contraction of agonist and antagonist muscles, spastic dystonia, synergistic limb patterns (synkinesis), weakness, and soft tissue contractures are important considerations in the assessment of poststroke patients (3–6,13,14). Upper motor neuron lesions cause motor dysfunction that result in a "convoluted mixture of obligatory and compensatory motor behaviors that are difficult to interpret" (16). Simple bedside testing is usually an inadequate determinant of an overall treatment strategy; a description of the problem in different circumstances is of far more value than a single examination (11). Assessments from physical, occupational, and speech therapists, as well as input from the patient and their caregivers, are essential for establishing patient-specific goals and an optimal treatment plan (17).

Perhaps the most systematic method of setting treatment goals is goal attainment scaling (GAS), initially developed in the mental health domain. Over the years, it has been applied to rehabilitation, and recently, to spasticity management (22). Using GAS, individual goals are identified and mutually agreed upon by the patient and clinician, and are weighted based on importance. Over the course of the treatment, the degrees to which goals are reached are compared to expected likelihood of achievement set a priori. Unlike other measures, the GAS method allows a patient to identify meaningful goals rather than relying on a standardized set of items.

Clinical, electrophysiological, and biomechanical measures have been used to quantify poststroke spasticity (Table 29.2). The most commonly used clinical measures of poststroke spasticity are the Ashworth (AS) and Modified Ashworth (MAS) Scales. The AS grades muscle tone from

TABLE 29.1 Upper Motor Neuron Syndrome

Positive symptoms
Spasticity
Spastic co-contraction
Spastic dystonia
Synergistic muscle patterns
Reflex release phenomena
Negative symptoms
Weakness, fatigue
Loss of dexterity, balance
Loss of selective muscle control
Rheologic changes
Contracture, fibrosis, atrophy

TABLE 29.3 Ashworth Scale and Modified Ashworth Scales

0. No increased tone
1. Slight increase in muscle tone, manifested by a catch and release or by minimal resistance at the end of the range of motion when the affected part is moved in flexion or extension (the modified Ashworth scale includes: 1+)
2. More marked increase in muscle tone through most of the range of motion, but affected part(s) easily moved
3. Considerable increase in muscle tone, passive movement difficult
4. Affected part(s) rigid in flexion or extension

0 (normal) to 4 (severe) and is shown in Table 29.3 (10). The MAS adds an additional intermediate grade (1+) but has less interrater reliability than the AS (12,23,24). Despite their widespread use, the AS and MAS have marginal intrarater and interrater reliability (23–26). The reliability of the AS for upper-limb spasticity can be improved if the examiner completes a standardized training program and testing is done in a similar format (25). Another limitation of the AS is its "clustering" effect of the patients in the middle grades; also, the measure does not differentiate contracture from hyperexcitable stretch reflexes (26). Caveats in the clinical use of these scales include the nonstandardized speed with which passive stretching is performed and scoring of joints with very limited range (i.e., less than 50% of expected range) due to muscle contracture. The Tardieu scale has advantages over the AS because it not only quantifies muscle reaction to stretch, but also accounts for the velocity of the stretch and measures the angle at which the catch, or clonus, occurs (Table 29.4) (27–29). The quality of muscle reaction to passive stretch at certain velocities is scored between 0 (no resistance with passive movement) and 4 (clonus greater than 10 seconds). The spasticity angle is the difference between the angle at the end of passive range of motion (PROM) at slow speed (V1) and the angle of catch at fast speed (V2 or V3). The spasticity angle provides an estimation of the relative contribution of neural mechanisms (spasticity) and the mechanical restraint of the soft tissues. Grading is performed at the same time of day and in a constant position of the body for a given limb (27). The Tardieu scale is a valid clinical measure of spasticity after stroke (30). To increase the internal consistency, validity, and reliability of clinical assessment of muscle tone using the AS or MAS, Platz et al. developed REPAS (REsistance to PASsive movement), a 32-point summary scale that provides detailed guidelines for the performance of different passive joint motions and scoring (31).

Electrophysiologic tests such as the H-reflex, H/M ratio, F-wave, and tonic vibration reflex (TVR) have been used to quantify spasticity in stroke patients (32,33). Historically, these measures tend to correlate poorly with the degree of spasticity (34). Recently, Pizzi and colleagues demonstrated a positive correlation between the flexor carpi radialis H/M ratio and the MAS scores at the wrist in 65 poststroke spastic, hemiparetic patients (35). The correlation was strongest with the higher AS scores (3 and 4). The soleus H/M ratio can be used to confirm the effects of intrathecal baclofen (ITB) during an ITB trial and potentially for troubleshooting (33,36). In a prospective case series involving 9 stroke, 17 traumatic brain injury, and 4 anoxic brain-injured subjects treated with 50 mcg intrathecal bolus of baclofen, there was a reduction of the H/M ratio from 62% ± 28% to 14% ± 19% and Ashworth scores from 2.4 ± 0.7 to 1.5 ± 0.6 on the more involved side 5 hours after bolus (36). This study suggests that the soleus H/M ratio may be more sensitive than the AS score in detecting a physiologic response to ITB bolus.

TABLE 29.2 Examples of Measures of Spasticity, Motor Control, or Function

	MEASURES OF SPASTICITY	MEASURES OF MOTOR CONTROL OR FUNCTION
Clinical	Ashworth Scale Modified Ashworth Scale Tardieu Scale REPAS Spasm frequency scale Tone Assessment Scale	Fugl-Meyer Wolf Motor Function Test Timed walk Timed Up & Go Box and Block Test Action Research Arm Test
Electrophysiological	H/M ratio	Dynamic EMG
Biomechanical	Servo-control device	Motion Analysis Systems

TABLE 29.4 Tardieu Scale

Quality of muscle reaction
0. No resistance
1. Slight resistance
2. Catch followed by a release
3. Fatigable clonus (less than 10 seconds)
4. Sustained clonus (greater than 10 seconds)
Angle of muscle reaction
Velocity of stretch
V1. As slow as possible
V2. Speed of limb falling under gravity
V3. As fast as possible

Biomechanical measurements of spasticity using a servo-controlled, motor-driven device can provide a more reliable measure of spasticity, but use of these devices is limited to the research laboratory. The device can provide a controlled stretch of a limb while measuring torque, joint angle, and reflex EMG activity (37,38). Large-amplitude perturbations have been used to quantify spastic stretch reflexes at a joint (37–39). These reflex measures were shown to be reliable measures of elbow spasticity in 16 chronic stroke patients with upper-limb spasticity (40). In this study, elbow stretch reflexes were assessed using a custom-made device attached to a Biodex System™. Movements into elbow flexion and extension were imposed at four speeds: 6, 30, 60, and 90 degrees per second. Ninety percent reliability in the measurement of peak torque, peak stiffness, and reflex threshold angle was obtained when at least two days of testing were performed. The biomechanical measures correlated well with the AS (Spearman rho = 0.84, $P < .005$) (40).

The assessment of patients with poststroke hypertonia should also include measures of motor control (Table 29.2). The Fugl-Meyer Scale (FMS) is a reliable and validated measure of the upper- and lower-extremity motor impairment based on the natural progression of functional return after a stroke (41). The FMS has been demonstrated to have high intrarater and interrater reliability and can be completed in 10 to 20 minutes. Decline of the function on the FMS has been shown to correlate closely with the severity of spasticity (42).

Given the complex relationship of spasticity, impairment, and disability, it is not always easy to ascertain the functional impairment of spasticity. Yet, it is worth assessing the functional changes after intervention because patients and caregivers set goals that favor functional improvement over reduction in impairment. The functional test for the hemiparetic upper extremity was developed at Rancho Los Amigos Hospital and consists of 17 graded tasks with 7 levels of difficulty. The test is based on the Brunnstrom scale, and each task is timed and graded pass/fail (13,37–39,43). The patient has three opportunities to try each task and can work no longer than three minutes on each item. The test is functionally based and has good interrater reliability, and the timing of each task allows detection of more subtle changes (44). Other tests of motor skills, such as the Action Research Arm, Jebsen-Taylor, Frenchay, and Box-and-Block, can be utilized as part of the overall assessment.

The BI is an ordinal scale of global function and mobility that may not be sensitive to the functional implications of spasticity (18,45). Francis and colleagues proposed a "Composite Functional Index" (CFI) that was shown to correlate well with reduction of arm spasticity (46). The index (range 0–17) uses the dressing, grooming, and feeding sections of the BI, and adds three subjective measures: putting arm through sleeve, cleaning palm, and cutting fingernails. In a meta-analysis of two randomized controlled trials, 26 of 47 had improved arm function (CFI) and reduced spasticity (MAS) after injections of abobotulinumtoxinA (Dysport™) (46). The disability assessment scale (DAS) (range 0–12) was developed to assess functional impairment in patients with poststroke upper-limb spasticity (i.e., dressing, hygiene, limb position, pain) and has shown good intra and interrater reliability (25).

Dynamic polyelectromyographic (PEMG) recordings can be used to identify the timing and duration of muscle overactivity in poststroke spastic hypertonia. These EMG recordings can be helpful in understanding muscle involvement when assessing for treatment with chemodenervation, chemical neurolysis, or surgical release of individual muscles (47). For example, in the patient with a spastic flexed elbow, PEMG can be used to identify spastic co-contraction of the elbow flexors and extensors (47). By combining PEMG with kinematic data from a motion analysis lab, the primary upper- or lower-extremity motor dysfunction can be localized (48,49). Quantitative gait analysis can differentiate quadriceps overactivity from hip flexor weakness or poor ankle mechanics as the cause of stiff-legged gait (50).

IMPACT ON REHABILITATION AND RECOVERY

Health care costs are four times higher for stroke survivors with spasticity compared to those without spasticity (21). Other investigators have suggested that the importance of spasticity may be overstated (18,51). Despite a lack of good epidemiological data, most clinicians would agree that treating spasticity "just because it's there," as suggested by Landau, is not the best practice (51). There are potential benefits of increased muscle tone. Increased extensor tone of the legs can assist with standing and transfers (52). Reflex muscle activity may preserve muscle bulk and slow osteoporosis (53).

When spasticity interferes with active or passive function or becomes painful, then appropriate interventions must be considered (54). Even though limb weakness may be the more important factor when considering active function, spasticity or spastic co-contraction can impede limb movement (6,54). Upper-limb spasticity, such as the adducted, internally rotated shoulder or flexed elbow, can make activities such as reaching overhead more difficult. Spastic co-contraction of elbow flexors and extensors can limit active elbow extension and flexion (54). Increased tone of the wrist and finger flexors can interfere with releasing objects after grasping them. Lower-extremity spasticity such as the adducted hip, flexed or extended knee can interfere

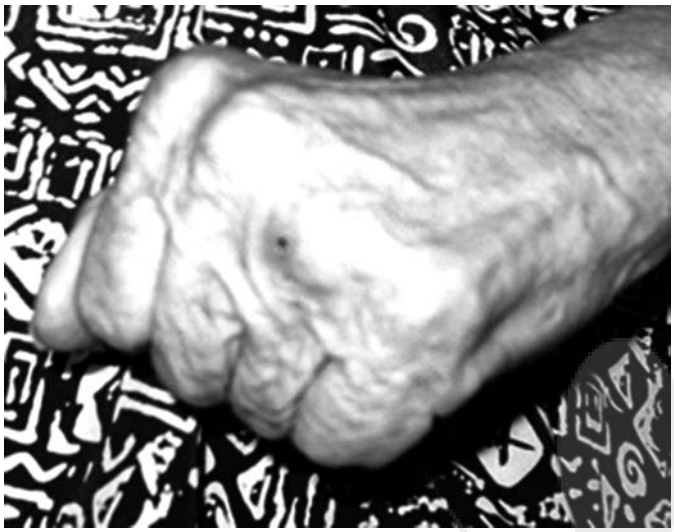

FIGURE 29.1 Finger flexor spasticity as shown in the "clenched fist" condition.

with standing, transferring, or walking. The inability to obtain a flat foot position during the stance phase of gait, as in the equinovarus foot, can lead to gait instability and make stair climbing more difficult.

Spasticity may play a more important role by interfering with passive functions such as hygiene in the axilla, elbow, and palm of the hand. Finger flexor spasticity, as in the "clenched fist" condition, can lead to skin breakdown and nailbed infections (47) (Figure 29.1).

Lower-extremity passive function such as perennial care, bladder catheterization, toileting, and bathing can be more difficult with spasticity of the hip adductors. Overactivity of the hip flexors or extensors can interfere with wheelchair positioning.

The pathophysiology of pain in spasticity is not well understood, but it has been proposed that it may involve an interaction between dysfunction of nociceptive pathways and thalamocortical projections, tonic muscle overactivity, structural changes in muscles and tendons, and biomechanical problems including joint malalignment. For instance, the poststroke shoulder pain that is associated with spasticity in 31% to 57% of cases (5,36,55–61) may result from the interplay between central poststroke pain, adhesive capsulitis, rotator cuff tendinitis, and muscle shortening and spasm (62). Pain associated with spasticity is characterized as nonradiating and sharp as in the case of spasms, present at rest and worsening during passive or active movement of the involved body part (63).

In an uncontrolled observational study of 13 patients with spastic hemiplegia, subjects had reduced shoulder pain and improved ROM after phenol injection of the nerve to the subscapularis muscle (64). In a randomized double-blind, placebo-controlled study, 10 spastic poststroke patients had reduced spasticity, improved ROM, and decreased shoulder pain after onabotulinumtoxinA injections to the subscapularis muscle (65).

Early treatment of spasticity may lead to improved outcomes in motor recovery. Windows of opportunity may exist in the early management of spasticity (66). If one takes "a wait and see" approach, optimal treatment benefits may be lost. Twitchell noted that severe proximal spasticity at one month after stroke was a predictor of poor motor recovery (67). In some stroke survivors, spasticity may be a constraint on motor recovery, and early treatment may improve their motor recovery. Although not all stroke survivors will have improved motor recovery, early spasticity treatment may affect the clinical course of the increased tone. A double-blind, placebo-controlled trial of three treatments for lower-extremity spasticity in 28 patients with acute TBI demonstrated improved ROM and reduced MAS in the patients treated with serial casting and saline or onabotulinumtoxinA (Botox™), when compared to physical therapy alone (68). Despite the limited number of subjects, this study suggests that early intervention may have a beneficial effect on the long-term consequences of spastic hypertonia. A recent controlled study reported significant reduction of finger flex or stiffness six months after early treatment with botulinum toxin, possibly due to prevention of contractures. Wrist and finger flexors were injected with 150 units of incobotulinumtoxinA versus placebo at 6 weeks after stroke. Each group had nine subjects who received four weeks of therapy. The treated group had reduced Ashworth scores, pain, and passive nail trimming at one and six months after injection (69). Further investigation is needed to identify which patients may benefit most from early spasticity treatment.

ORAL MEDICATIONS

Stroke survivors generally have a poor tolerance for oral medications because of the central nervous system (CNS) side effects. Of the oral antispasticity medications currently available in the United States, only baclofen, tizanidine, Valium, dantrolene sodium, and clonazepam have been evaluated in persons with stroke (70–73). In 2004, Montané et al. completed a systematic review of double-blind randomized controlled trials of antispastic oral medications for stroke and reviewed six trials (71,72,74–78). Because of the small numbers, lack of quality of life measures, and high incidence of adverse drug effects (drowsiness, sedation, and muscle weakness), they concluded that the evidence supporting use of oral antispastic medications in stroke is weak (72) (Table 29.5).

Baclofen is a structural analog of gamma-aminobutyric acid (GABA), which is one of the main inhibitory neurotransmitters in the CNS (79). The half-life of oral baclofen is 3.5 hours, and, although 15% is metabolized in the liver (70), it is excreted primarily by the kidney. In a double-blind, placebo-controlled crossover trial of 20 stroke patients, those treated with up to 30 mg/day of baclofen for 1 month had reduced Ashworth scores, no functional improvement, and higher adverse events (50% vs. 15%) versus those on a placebo (80). The most common adverse effects were sedation, dizziness, and weakness. In a retrospective review of 35 subjects with acquired brain injury that included

TABLE 29.5 Oral Spasticity Medications

AUTHOR (YEAR)	STUDY DESIGN	SUBJECTS AND INTERVENTION	RESULTS
Basmajian (1984) (202)	Randomized, double-blind, placebo-controlled, crossover	24 stroke survivors out of 50 subjects, but only 19 completed study 3 treatment conditions: Ketazolam 10 and 20 mg/day (1 week each) Diazepam 5 and 10 mg/day (1 week each) Placebo (2 weeks)	Ketazolam and diazepam conditions better than placebo on most outcomes ($P < .05$) but no significant difference between ketazolam and diazepam
Bes (1988) (74)	Randomized, double-blind, parallel group	N = 105 hemiplegics (89 stroke, 16 cranial trauma) 2 groups well-matched for sex, age, height, and body weight: Tizanidine (46 stroke) started at 6 mg/day and titrated up to maximum of 24 mg/day within 2 weeks (mean dosage at week 8: 17.08 mg/day) Diazepam (43 stroke) started at 7.5 mg/day and titrated up to maximum of 30 mg/day (mean dosage at week 8: 19.52 mg/day)	15 subjects on tizanidine and 6 on diazepam dropped out due to side effects Tizanidine group improved walking distance on flat ground; 3 of 11 bedridden subjects on tizanidine, and 2 of 4 bedridden subjects on diazepam became ambulatory
Cocchiarella (1967) (203)	Randomized, double-blind, placebo-controlled, multiple crossover	Mixed diagnoses; 16 stroke survivors out of 19, but were not identified in data analysis 5 treatment conditions: Placebo Diazepam 6 mg/day Diazepam 15 mg/day Phenobarbital 45 mg/day Phenobarbital 90 mg/day	No significant difference in leg drop and straight leg raise tests, and total steps taken Slower ambulation while on diazepam 15 mg/day compared to placebo
Glass (1974) (204)	Double-blind, placebo-controlled, crossover	24 stroke survivors out of 62; 16/62 participated in crossover phase, but only 11/16 completed (unknown number of stroke survivors in crossover phase or among dropouts) 4 treatment conditions: Dantrolene (100 mg qid) Diazepam (5 mg qid) Dantrolene (100 mg qid) and diazepam (5 mg qid) Placebo	Combined dantrolene and diazepam was superior to diazepam or dantrolene alone or placebo in clinical measures
Meythaler (2001) (71)	Randomized, double-blind, placebo-controlled, crossover	9 stroke survivors among 17 subjects 2 treatment conditions: Placebo Tizanidine 4 mg qHS titrated to goal of 12–36 mg/day	Only 6 tolerated up to 9 pills of tizanidine (36 mg/day), even as 11 tolerated all 9 placebo pills Somnolence in 41% on tizanidine and none in placebo
Meythaler (2004) (81)	Retrospective	35 acquired brain injuries (7 stroke) Average oral baclofen dose 57 mg/day	Decreased lower, but not upper limb spasticity 17% complained of sleepiness

Source: Adapted from Francisco GE. Pharmacologic management of lower-limb spastic hypertonia in stroke: what is the evidence? In: Condie E, ed. *Report of a Consensus Conference on the Orthotic Management of Stroke Patients*. Copenhagen: ISPO; 2004:137–147.

7 stroke patients, those treated with an average dose of 57 mg/day of baclofen had reduced lower-extremity spasticity and no change in the upper extremity (81). No functional measures were reported, and 17% of the patients had sleepiness, which limited dose increases (81).

Dantrolene sodium is a hydantoin derivative that acts primarily on the muscle fiber. It exerts its effect by blocking the release of calcium from the sarcoplasmic reticulum, which reduces the force of the muscle contraction (70). Recent studies suggest that this phenomenon results from an alteration in the relationship between calcium channels and ryanodine receptors within the sarcoplasmic reticulum (82). The half-life of dantrolene sodium is 4 to 15 hours after oral dose and 12 hours after intravenous dose; it is metabolized primarily by the liver (70). The most common side effects are drowsiness, nausea, paresthesias, and weakness. Even though the risk of hepatic toxicity is rare (1%–2%), it is recommended to monitor liver function tests before and during treatment (70). In a double-blind, placebo-controlled crossover study of 31 stroke patients treated with 50 to 200 mg per day of dantrolene, subjects showed no change in AS or Barthel scores while reducing strength in the unaffected

limb, but not the paretic limb, based on isokinetic testing (11). In a double-blind parallel study, 14 stroke patients who achieved reduced spasticity with dantrolene for 6 weeks were randomized to either a placebo or continued dose of dantrolene for 6 more weeks (83). The placebo group noted increased deficits, and 13 of the 14 chose to continue dantrolene (average dose 165 mg/day) after the 6-week trial had ended. Side effects were mild and transient (83).

Tizanidine is an alpha-2 adrenergic agonist that binds to spinal and supraspinal imidazoline receptors and prevents the release of excitatory neurotransmitters (70). The half-life of tizanidine is 2.5 hours, and it is metabolized by the liver. The most common side effects are drowsiness, dry mouth, weakness, hypotension, and elevated liver function tests (5%) (70). Because of this, liver function tests should be monitored before treatment, and at one, three, and six months and then annually after initiating treatment. In a small double-blind placebo-controlled crossover study that included 9 stroke patients treated with 12 to 36 mg/day of tizanidine, subjects demonstrated dose-dependent reduced upper- and lower-extremity AS scores. No functional measures were reported. The most common adverse events were somnolence (41%), increased liver function tests (18%), and dry mouth (12%) (71). In a double-blind comparative study of 30 stroke patients treated with tizanidine (8–20 mg/day) or baclofen (20–50 mg/day), both groups had similar improvements in AS scores. The side effects in the tizanidine group were mild and transient, and no patients discontinued the study. For the baclofen, three patients discontinued the study due to severe side effects (78). In an open-label dose titration study of 47 chronic stroke patients treated with tizanidine (2–36 mg/day), total upper-extremity AS score improved with no decline in strength. Pain intensity, quality of life, and physician assessment also improved. The maximum average daily dose was 20 mg/day, and 10 out of 47 patients were able to tolerate the maximum dose of 36 mg/day. The most frequent side effects were somnolence (62%), dizziness (32%), asthenia (30%), dry mouth (21%), hypotension (13%), and elevated liver function tests (4%) (84).

Cyproheptadine, a serotonin receptor antagonist, has been demonstrated as effective in reducing delay in the relaxation of finger flexors immediately after grip in a small group of stroke patients, suggesting a role of monoaminergic brainstem pathways in poststroke spasticity (85).

Despite limited evidence in the literature to support the use of oral antispasticity medications in stroke patients, and frequent adverse effects, there is a role for them. Because somnolence is a common side effect of oral medications, low doses at night may be useful in select patients who have difficulty sleeping because of muscle spasms. As with most medications in stroke survivors, it is suggested to "start low and go slow." Rather than higher doses of one medication, a combination of lower doses of two medications may be better tolerated (86). Also, these medications should be tapered off slowly, especially baclofen, because abrupt withdrawal can result in seizures and other life-threatening situations.

NERVE BLOCKS

Injection of a local anesthetic near a motor nerve or diagnostic nerve block (DNB) is a useful tool in the management of poststroke spasticity. DNB can determine the potential benefits of longer-lasting interventions such as botulinum toxin chemodenervation, neurolysis, or surgery; assist in the diagnosis of contractures; facilitate serial casting; and reduce painful spasms to allow participation in therapy (87). Neurolytic procedures using phenol or alcohol are effective in treating focal spastic hypertonia from various etiologies, including cerebral palsy, traumatic brain injuries, and stroke (64,88–96) (Table 29.6).

In sufficiently high concentrations, phenol (5%–6%) and alcohol (35%–60%) work by denaturing proteins, leading to neurolysis, while at lower concentrations (i.e., 3% and lower), phenol acts as an anesthetic (97). Phenol appears to control muscle hypertonia as a result of denervation and degeneration of muscle spindles (98). Phenol injures afferent and efferent nerve fibers, and the damage to the axons and membranes can be extensive (99,100).

Following injection of either agent, muscle relaxation is almost immediate due to the anesthetic effects. The neurolytic effect sets in about an hour after injection and lasts for a few months. The effect may last for as long as a year or longer, depending on the degree of nerve blockade. Hypertonia usually recurs due to muscle reinnervation, but this recovery is incomplete (98). Common side effects include pain at the injection site, postinjection dysesthesia, localized swelling, and excessive weakness (97,101). If inadvertently injected into vessels, or if systemic absorption occurs, CNS effects, such as tremors, convulsions, and CNS depression may result.

There is a paucity of well-designed studies on the use of phenol or alcohol in the treatment of spastic hypertonia. For one, these drugs are rarely used in the upper limb because of concerns with complications, most especially dysesthesia. Most published studies reported treatment of spasticity of the finger flexors, elbow flexors, and other muscle groups in the traumatic brain injury population (88,91,92,102). Hecht treated 11 patients with painful shoulder attributed to hypertonia of the subscapularis muscle (64). Three to 6 mL of aqueous phenol 6.7% was percutaneously injected into the subscapular nerve branches. This resulted in improvement in shoulder flexion, abduction, and external rotation, presumably because of a decrease in pain and hypertonia.

One investigation reported effective treatment of hip flexor spasticity by injecting up to 3.5 mL of phenol 5% into the belly of the psoas major and minor muscles under ultrasonic monitoring (94). Nine of the twelve patients had spasticity from stroke. In addition to increased range of motion, improvement in sitting position, standing and walking posture, and pain relief were noted. No complications occurred. Another study reported the beneficial effects of phenol in reducing spasticity of tibial-innervated muscles (103).

An investigation demonstrated significant reduction of quadriceps muscle tone with use of etidocaine 1%, 2 cm^3 after a femoral nerve block (104). The primary intent of this study was

TABLE 29.6 Phenol, Alcohol, and Anesthetic Nerve Blocks

AUTHOR (YEAR)	STUDY DESIGN	SUBJECTS AND INTERVENTION	RESULTS
Albert (2000) (104)	Case series	7 stroke survivors out of 12 subjects with hemiplegia disabled by quadriceps overactivity Etidocaine 1%, 2 cm^3 was injected to block the branch of the femoral nerve to either the vastus intermedius or lateralis	Decrease in quadriceps spasticity, but results were difficult to interpret, based on the data reported
Chua (2000) (90)	Case series	5 stroke survivors out of 8 subjects with hemiplegia and severe knee flexor spasticity Ethyl alcohol 50%–100% (with 1% lidocaine) injected to sciatic nerve using repetitive monopolar electric stimulation	MAS scores of knee flexors improved significantly at 1 ($P < .005$), 3 ($P < .01$), and 6 ($P < .02$) months after injection
Kirazli (1998) (105)	Randomized, double-blind (?), parallel group	N = 20; onabotulinumtoxinA 400 units injected to lower-limb muscles using electromyographic guidance versus phenol 5% tibial nerve block	Significant improvement in AS in both groups ($P < .05$) for ankle plantar flexor; toxin group had more improvement in AS of ankle invertors than phenol ($P > .05$); AS and clonus duration more improved in toxin group than phenol at weeks 2 and 4, but not at weeks 8 and 12

Source: From Francisco GE. Pharmacologic management of lower-limb spastic hypertonia in stroke: what is the evidence? In: Condie E, ed. *Report of a Consensus Conference on the Orthotic Management of Stroke Patients*. Copenhagen: ISPO; 2004:137–147.

to demonstrate an anatomical injection technique, and thus it used an anesthetic, the effect of which on muscle tone was transient. Chua and Kong used ethyl alcohol of varying concentrations (50%–100%) to block the sciatic nerve and found that the decrease in hamstring muscle tone lasted up to 6 months after intervention and, in some subjects, improved the quality of ambulation and facilitated wheelchair positioning (90).

The popularity of phenol and alcohol has been eclipsed by botulinum toxin chemodenervation. The latter is easier to administer and appears to have a better side-effect profile, but phenol and alcohol are much less expensive and may last longer. Although both treatments are effective, there has been no convincing evidence as to the superiority of one over the other in treating spastic hypertonia. Only one attempt has been made to compare the effects of phenol 5% and botulinum toxin type-A (BTX type A) in controlling clonus and hypertonia. In the investigation, both phenol and BTX-type A improved muscle tone (as measured by AS scores) of ankle plantar flexors and invertors, but it appeared that the BTX group had superior efficacy over phenol ($P < .05$), both in decreasing muscle tone and ankle clonus at 2 and 4 weeks, but not at 8 and 12 weeks, after treatment (105). The study result may have been affected by the relatively low dose of phenol used, because the amount injected was not adjusted based on clinical response after the first few injections, as is commonly done in clinical practice. Table 29.7 presents further comparison of the clinical characteristics of these two medications.

TABLE 29.7 Comparison of Phenol and Botulinum Toxin Treatment for Spasticity

	PHENOL	BTX
Effectiveness	✓✓✓	✓✓✓
Evidence of efficacy	Lower limb No RCT	Upper limb ✓ RCT
Ease of administration		✓✓✓
Onset	✓✓✓	
Duration	✓✓	
Pain and occurrence of other adverse events		✓✓✓
Cost	✓✓✓	

BOTULINUM TOXINS

BTXs are arguably the most commonly used intervention for spastic hypertonia. Derived from the bacterium *Clostridium botulinum*, it has seven types, designated A through G, which are antigenically and serologically distinct but structurally similar (106). The toxin molecule is formed by heavy and light polypeptide chains that are linked by a disulfide bond. BTXs act by binding on presynaptic cholinergic nerve terminals. Once in the nerve terminal, it blocks the release, but not the synthesis, of acetylcholine into the neuromuscular junction, thereby disallowing muscular contraction. In addition to its reduction of alpha motor neuron activity on extrafusal muscle fibers, BTXs exert their effects on reduction of Ia afferent signal from muscle spindles at the gamma motor neuron level. The decreased signal from Ia afferents will then result in a reduction of feedback to alpha motor neurons, resulting in decreased muscle activity. The duration of clinical effect is three to four months, and is most likely due to axonal sprouting and muscle reinnervation when new neuromuscular junctions are established.

DePaiva et al. suggested that previously blocked junctions undergo functional repair (107).

In the past decade, two BTX serotypes, A and B, have emerged as an important treatment for focal poststroke spastic hypertonia. A recent consensus paper supported the use of BTX for focal spastic conditions in adults (108). Its popularity is due to the impressive clinical outcomes experienced by stroke survivors and clinicians, despite the relative lack of convincing scientific evidence of its effects on function. For a variety of reasons, such as study design limitations, sensitivity of outcome measures, and appropriateness of patient selection criteria, published literature has yet to demonstrate that BTXs lead to functional enhancement, although significant improvement in muscle tone has been shown.

BTXs also have the advantage of target treatment specificity (i.e., exerting significant changes only in injected muscles), as opposed to the systemic effects of oral medications, and have a better adverse event profile. For instance, the incidence of drowsiness and sedation, which are commonly associated with oral spasmolytics, are practically nonexistent with toxins. BTXs also appear to be favored by many clinicians over phenol and alcohol, which are more technically challenging and have a higher incidence of complications, such as dysesthesia.

Evidence of Efficacy of Botulinum Toxin Type A (BTX-A)

Upper Limb

Various studies have demonstrated significant improvement of upper-limb poststroke spastic hypertonia (Table 29.8). Simpson investigated the effect of three total doses of onabotulinumtoxinA as compared to placebo in 39 subjects (109). Saline or one of three doses of onabotulinumtoxinA (75 units, 150 units, or 300 units) were injected to the biceps, flexor carpi radialis (FCR), and flexor carpi ulnaris (FCU). At two, four, and six weeks after injection, all treatment groups had better outcomes than placebo, but the group that received the highest dose had the most robust improvement in hypertonia reduction in the elbow and wrist flexors. The effects lasted for about 16 weeks. This dose-dependent effect of BTX was also demonstrated in a later study (110). Ninety-one stroke survivors received either onabotulinumtoxinA or placebo to spastic finger, wrist, and elbow flexors. Participants were randomized to one of the following groups: placebo, 90, 120, and 360 units of onabotulinumtoxinA. All treatment groups demonstrated improvement in MAS scores ($P < .05$), but the group that received the highest dose also had the most improvement.

Brashear et al. compared onabotulinumtoxinA 200 to 240 units to placebo injected into the wrist, finger, and thumb flexors. At 4, 6, 8, and 12 weeks, the onabotulinumtoxinA group had superior improvement in muscle tone over the placebo group (25). Additionally, this study also measured changes in various impairment and functional domains, including pain, deformity, hygiene, and orthotic fit, using the DAS. At week 6, the treatment group had more significant improvement on the DAS in the principal target of treatment ($P < .001$). As in the Simpson study, no major adverse event was reported (110).

A large-scale Japanese study demonstrated efficacy of onabotulinumtoxinA in treating upper-limb spasticity. In a multicenter study involving 109 subjects, higher-dose onabotulinumtoxinA (200–240 units) injected to wrist and finger flexor muscles was superior to lower dose (120–150 units) when compared to placebo. Higher-dose onabotulinumtoxinA also resulted in significant improvement in limb position as measured by the DAS at 6, 8, and 12 weeks after injection (111).

Experience with the use of abobotulinumtoxinA has been similar. In one study, 59 subjects were randomized to receive either placebo or 1000 units of abobotulinumtoxinA divided between the biceps, FCR, FCU, flexor digitorum superficialis (FDS), and flexor digitorum profundus (FDP). At 4 weeks after injection, the abobotulinumtoxinA group had a more significant improvement in muscle tone (as measured by MAS) when compared to the placebo ($P = .004$) group. The same investigators also conducted a dose-ranging investigation involving 83 stroke survivors, who were randomized to one of three abobotulinumtoxinA doses (500, 1000, or 1500 units) or placebo. Muscles injected included the biceps, FCR, FCU, FDS, and FDP (112,113). The treatment groups demonstrated more significant improvement in tone than the placebo group. Weakness was observed in the 1500-unit group.

Another investigation compared the efficacy of abobotulinumtoxinA 500, 1000, and 1500 units with placebo in treating spastic hypertonia of the biceps, wrist flexors, finger flexors, and thumb adductors/flexors (114). When compared to placebo at 6 weeks, improvement in muscle tone in the elbow and wrist flexors ($P < .05$) and passive elbow range of motion ($P < .02$) were noted in all treatment groups. Consistent with Bakheit et al.'s findings, the group that received higher doses had greater hypertonia reduction than the placebo group but did not have an advantage in terms of duration of effect (114).

Prior to its recent introduction in the United States, incobotulinumtoxinA (Xeomin™) was studied in upper-limb poststroke spasticity (115). One hundred forty-eight patients with wrist and finger flexors spasticity and at least moderate disability on the DAS were treated either with incobotulinumtoxinA (median, 320 units) or placebo for up to 20 weeks. The incobotulinumtoxinA group had better reduction in AS scores at week 4 and up to week 12. There was no significant difference in the incidence of adverse events in both groups. After completion of the double-blind, placebo-controlled phase, 145 subjects continued in an open-label extension for up to 69 weeks (116). During that time the subjects received up to five additional incobotulinumtoxinA injections. Throughout the duration of the open-label period, there was significant improvement in AS scores of elbow, wrist, finger and thumb flexors, and forearm pronators, and DAS. Neutralizing antibodies were not detected during the study period.

TABLE 29.8 Randomized, Controlled Botulinum Toxin Trials for Upper Limb Spasticity

AUTHOR (YEAR)	STUDY OBJECTIVE	SUBJECTS	INTERVENTION	OUTCOME MEASURES	FOLLOW-UP	RESULTS
Simpson (1996) (109)	To evaluate the safety and efficacy of local treatment of upper-extremity spasticity in chronic stroke patients	N = 39; At least 9 months post stroke; Mean 2.5 on AS at elbow and wrist with minimum 2 at either joint	OnabotulinumtoxinA (300 units; n = 9); OnabotulinumtoxinA (150 units; n = 9); OnabotulinumtoxinA (75 units; n = 9) or placebo (n = 10) to biceps, FCR, or FCU	MAS; FIM, Rand 36 Item Health Survey, Fugl Meyer Scale, caregiver dependency, function and pain assessment, motor task/function rating scale, grip strength, global assessment of spasticity scale	2, 4, 6, 10, 16 weeks	Decreased AS score of elbow and wrist flexors at weeks 2, 4, and 6 in high-dose group versus placebo Decreased AS score of wrist flexors at week 6 in low-dose group versus placebo
Hesse (1998) (132)	To investigate comparative efficacy of abobotulinumtoxinA plus electrical stimulation (ES) versus abobotulinumtoxinA alone in the treatment of chronic upper limb spasticity after stroke	N = 24; 6–12 months post stroke; MAS at least 3 at elbow, wrist and fingers	AbobotulinumtoxinA 1000 units + ES (n = 6); AbobotulinumtoxinA 1000 units only; placebo + ES (n = 6); placebo only (n = 6), to biceps, brachioradialis, FCU, FCR, FDP, FDS	MAS, limb position at rest, three functional activities, pain	2, 6, 12 weeks	MAS not significantly different, but cleaning the palm was better in abobotulinumtoxinA + ES group compared with abobotulinumtoxinA alone or placebo alone at all time points
Smith (2000) (114)	To assess dose response relationships to a single dose of BTX in upper limb spasticity associated with stroke or head injury	N = 21; At least 1 year post stroke	AbobotulinumtoxinA 1500 units (n = 6); AbobotulinumtoxinA 1000 units (n = 7); AbobotulinumtoxinA 750 units (n = 6); placebo (n = 6); Different muscles injected based on clinical pattern of spasticity	MAS, passive and active range of movement, time to dress upper body, FAT, finger curl, global clinical assessment score, gait (if mobile)	2, 6, 12 weeks	Decreased wrist and finger flexor MAS scores and greater number of patients improved on global clinical assessment at week 6 when all abobotulinumtoxinA groups were combined and compared with placebo Decreased MAS score in abobotulinumtoxinA 500 units group versus placebo at week 6; Improved passive range of movement in abobotulinumtoxinA 1500 units group versus placebo at weeks 6 and 12
Bakheit (2000) (113)	To define an effective and safe dose of abobotulinumtoxinA for the treatment of upper limb spasticity in stroke patients	N = 83; At least 3 months post stroke; MAS 2 or more at elbow, wrist and fingers	AbobotulinumtoxinA 1500 units (n = 19); AbobotulinumtoxinA 1000 units (n = 22); AbobotulinumtoxinA 500 units (n = 22); placebo (n = 20) to biceps, FDS, FDP, FCU, FCR	MAS, range of movement, pain, Rivermead Motor Assessment, Barthel ADL index, three functional activities	2, 4, 8, 12, 16 weeks	Decreased MAS score at any joint in all abobotulinumtoxinA groups versus placebo at week 4; Decreased MAS of elbow and wrist flexors in all abobotulinumtoxinA groups and of finger flexors in abobotulinumtoxinA 1000 units group versus placebo over 16 weeks

Bhakta (2000) (205)	To investigate whether reduction in spasticity after BTX treatment translates into reduction in disability and carer burden	N = 40; At least 6 months after stroke; Elbow or finger MAS > 2	AbobotulinumtoxinA 1000 units (n = 20); placebo (n = 20) Different muscles injected based on clinical pattern of spasticity	Patient disability scale, carer burden scale, MAS, range of movement, pain, grip strength	2, 6, 12 weeks	Improved patient disability scale score in abobotulinumtoxinA group at 2 and 6 weeks versus placebo. Improved carer burden at 12 weeks. Decreased MAS of finger flexors in abobotulinumtoxinA group versus placebo at all time points and of elbow flexors at week 2. Decreased grip strength in abobotulinumtoxinA group compared with placebo at week 6
Bakheit (2001) (112)	To study the efficacy and safety of BTX in the treatment of upper-limb spasticity caused by stroke	N = 59; At least 3 months after stroke; MAS 2 or more in at least two of elbow, wrist, fingers and 1+ in remaining area	AbobotulinumtoxinA 1000 units (n = 27); placebo (n = 32) to biceps, FDS, FDP, FCU, FCR	MAS, range of movement, pain, Barthel ADL index, Goal Attainment and subjective global assessment scales	4, 8, 12, 16 weeks	Decreased MAS score at all joints in abobotulinumtoxinA group versus placebo at week 4, and finger and wrist flexors over 16 weeks. Improved elbow passive range of motion in abobotulinumtoxinA group versus placebo over 16 weeks
Brashear (2002) (25)	Assess the effects of one set of injections of botulinum toxin on muscle tone and measures of disability with respect to self-care, limb position, and pain	N=126; At least 6 months after stroke; Wrist AS 3 or more, fingers AS 2 or more	OnabotulinumtoxinA 200–240 units (n = 64); placebo (n = 62) to FCU, FCR, FDP, FDS =/- FPL or AP	AS, DAS, global assessment scale	1, 4, 6, 8, 12 weeks	DAS principal target and AS scores improved in onabotulinumtoxinA group versus placebo at all time points. Greater number of patients in onabotulinumtoxinA group improved by at least one point on global assessment versus placebo at all time points
Childers (2004) (110)	To test the hypothesis that intramuscular BTX reduces excessive muscle tone in a dose-dependent manner in the elbow, wrist, and fingers after stroke	N = 91; At least 6 weeks after stroke; Wrist AS 3 or more, elbow AS 2 or more	OnabotulinumtoxinA 360 units (n = 21); OnabotulinumtoxinA 90 units (n = 21); OnabotulinumtoxinA 180 U (n = 23); placebo (n = 26) to biceps, FCU, FCR, FDP, FDS. A second injection with same dose was given at >12 weeks if AS 2 or higher at wrist and/or elbow flexors	MAS, pain score, and functional disability measure SF-36, FIM, physician and patient global assessments	1, 2, 3, 4, 5, 6, 9, 12, 18, 24 weeks	Decreased AS score of elbow and wrist flexors in all onabotulinumtoxinA groups versus placebo at most time points up to week 9. Global response scores higher in 360- and 180-units groups versus placebo at some time points

(*continued*)

TABLE 29.8 Randomized, Controlled Botulinum Toxin Trials for Upper Limb Spasticity (*continued*)

AUTHOR (YEAR)	STUDY OBJECTIVE	SUBJECTS	INTERVENTION	OUTCOME MEASURES	FOLLOW-UP	RESULTS
Suputtituda (2005) (206)	To define the lowest effective dose and safety of BTX in the treatment of adult patients with upper-limb spasticity	N = 50; Any cause spasticity (but only stroke included); "Upper limb spasticity"	AbobotulinumtoxinA 1000 units (n = 5); AbobotulinumtoxinA 500 units (n = 15); AbobotulinumtoxinA 350 units (n = 15); placebo (n = 15) to biceps, FCU, FCR, FDP, FDS	MAS, ARAT, Barthel ADL index, visual analogue pain scale	2, 4, 8, 16, 24 weeks	Decreased MAS scores in all abobotulinumtoxinA groups versus placebo at week 8. Improved ARAT score in abobotulinumtoxinA 500-units group versus placebo at weeks 8 and 24. Decreased ARAT scores in abobotulinumtoxinA 1000 units versus placebo at weeks 8 and 24
Jahangir (2007) (207)	To assess the effectiveness, safety, and impact of BTX on ADLs and quality of life in poststroke hand spasticity in Malaysian patients	N = 52; At least 1 year after stroke; MAS at least 2 at wrist and fingers	OnabotulinumtoxinA 80 units (n = 27); placebo (n = 25) to FCR, FCU, FDS, FDP	MAS, Barthel ADL Index, Euroqol EQ-5D	1, 12 weeks	Decreased MAS scores at wrist and fingers in onabotulinumtoxinA group versus placebo at weeks 1 and 12
McCrory (2009) (208)	To examine the effect of BTX type A on quality of life and person-centered outcomes in patients with upper-limb spasticity following stroke	N = 96; >6 months after stroke; MAS at least 2 in two out of three of elbow, wrist, fingers and 1+ remaining area	AbobotulinumtoxinA 750–1000 units (n = 54); placebo (n = 42); Different muscles injected based on clinical pattern of spasticity; a second injection was given at week 12, choice of muscles and dose based on response to first injection	Assessment of quality of life measure, 100-point pain VAS, anxiety and depression rating scale, goal attainment scale, MAS, Modified Motor Assessment Scale, Carer Burden scale	8, 12, 20, 24 weeks	Decreased MAS scores in abobotulinumtoxinA groups versus placebo in all joints at weeks 8 and 20. Goal attainment score higher in BTX group compared with placebo at week 20. Higher proportion of participants with global benefit at weeks 12 and 24 in abobotulinumtoxinA group versus placebo
Kanovsky (2009) (115)	To assess the impact of incobotulinumtoxinA on muscle tone, functional disability, and caregiver burden in patients with poststroke upper-limb spasticity	N = 148; >6 months after stroke; AS score 2 or higher in wrist and finger flexors and at least 2 (moderate disability) in a subject-selected domain of the DAS	IncobotulinumtoxinA group (dose not fixed; maximum 400 units; median 320 units) versus placebo to various upper-limb muscles causing any of five clinical patterns (flexed wrist, clenched fist, flexed elbow, pronated forearm, thumb-in-palm)	AS: DAS: Carer Burden Scale; Global Assessment Scale of Treatment Benefit	2,4,8,12 weeks	Significantly higher proportion of incobotulinumtoxinA group had at least 1-point drop in AS in the wrist flexors versus placebo at week 4

Kaji (2010) (117)	To evaluate the efficacy and safety of one-time injection of botulinum toxin in Japanese patients with poststroke upper-limb spasticity	N = 109; >6 months after stroke; MAS 2 or higher in finger flexors and 3 or higher in wrist flexors; Score of 2 or 3 in DAS for at least one domain (hygiene, pain, dressing, limb position)	High-dose onabotulinumtoxinA (200–240 units; n = 51); High-dose placebo (n = 26); Low-dose onabotulinumtoxinA (120–1550 units; n = 21); Low-dose placebo (n = 11) to FCR, FCU, FDS, FDP =/- FPL	AUC of the change from baseline in MAS wrist flexor in high-dose group; DAS	1, 4, 6, 8, 12 weeks	Decreased MAS scores in wrist flexors in high-dose onabotulinumtoxinA versus high-dose placebo. No difference between low-dose onabotulinumtoxinA versus low-dose placebo. DAS (limb positioning and dressing) more improved in onabotulinumtoxinA versus placebo groups
Shaw (2010) (209)	To compare the clinical effectiveness and cost-effectiveness of treating upper-limb spasticity due to stroke with botulinum toxin type A plus an upper-limb therapy program with the upper-limb therapy program alone	N = 333 adults; upper-limb spasticity at the shoulder, elbow, wrist, or hand; reduced upper-limb function due to stroke more than 1 month previously	OnabotulinumtoxinA plus a 4-week upper-limb therapy program; Control group enrolled in upper-limb therapy program only	ARAT; MAS; Motricity Index; grip strength; Nine-Hole Peg Test; upper-limb basic functional activity questions; Barthel Activities of Daily Living (ADL) Index; Stroke Impact Scale, European Quality of Life-5 Dimensions (EQ-5D), and the Oxford Handicap Scale. Numerical pain rating scales; Canadian Occupational Performance Measure. EQ-5D data were used to calculate the quality-adjusted life-years (QALYs) associated with intervention and control treatments, and the incremental cost per QALY gained of botulinum toxin type A plus therapy compared with therapy alone was estimated	3, 6, 9, 12 months	No significant difference between the groups for primary outcome (arm function) at 1 month. No significant differences in arm function at months 3 and 12. Decreased MAS scores in elbow flexors in onabotulinumtoxinA group versus controls at 1 month only; higher incidence of general malaise/flu-like/cold symptoms in onabotulinumtoxinA group versus controls

Lower Limb

Kaji et al. randomized 120 patients with lower-limb spasticity to receive either onabotulinumtoxinA 300 units or placebo to ankle plantar flexors and invertors (117). The drug group had significant decline in the MAS score of ankle plantar flexors at 12 weeks after injection. Although the treated group showed a trend towards improvement of gait speed, this was not significantly different from the placebo group. In both studies, there was no marked difference in the frequency of treatment-related adverse events between the onabotulinumtoxinA and placebo groups (111).

A study on the effect of abobotulinumtoxinA involving 23 stroke survivors showed that 1000 units to various lower-limb muscles was significantly superior to the placebo in improving AS scores in the ankle plantar flexors ($P < .0002$) and invertors ($P = .0002$) (118). Muscles injected included the gastrocnemius, soleus, tibialis posterior, and flexor digitorum longus. Another investigation of the impact of abobotulinumtoxinA injected to both heads of the gastrocnemius and soleus showed similar results (119). In this study, 234 subjects were randomized to one of four groups (placebo, abobotulinumtoxinA 500, 1000, and 1500 units) (119). Similar to previous findings, the most significant improvement in spasticity was in the group that received the highest dose (1500 units).

A randomized, double-blind, dose-ranging trial by Mancini et al. on 45 spastic feet due to stroke demonstrated the efficacy and safety of about 300 units of BTX-A injected in various lower-limb muscles (120). Subjects were randomized into three groups: Groups 1 (mean total BTX dose, 167 units), 2 (mean total BTX dose, 320 units), and 3 (mean total BTX dose, 540 units). Even as all three groups improved on various outcome measures, including the modified AS, Medical Research Clinical Scale, gait assessment, ankle clonus, and visual analog scales for gait and pain, groups 2 and 3 had more improvement at 4 months after injection. Group 3 reported the highest incidence of adverse events 4 weeks after treatment, suggesting a dose–response relationship.

Evidence of Efficacy of BTX Type B (BTX-B)

There is limited published research on the use of rimabotulinumtoxinB (marketed as Myobloc™ in the United States, and as Neurobloc™ in Europe and elsewhere), for spastic hypertonia. An open-label study reported that Myobloc™ effectively decreased upper-limb tone in 10 subjects with acquired brain injuries (9 of whom had a stroke) (121). A total dose of 10,000 units was injected into various muscles, including the biceps (3750 units), FCR (2500 units), FCU (2500 units), FDS (625 units), and FDP (625 units). AS scores improved significantly from baseline in the elbow ($P = .016$), wrist ($P = .004$), and finger flexors ($P = .02$) at week 4. The most commonly reported adverse event was dry mouth.

Clinical Issues in the Use of BTX

In the United States, BTX dosing for spastic hypertonia is neither standardized nor based on scientific data. Instead, dosing is based on recommendation by experts and unique experience of clinicians (122). The optimal dose of BTX is the most effective amount required to achieve a predetermined outcome such as reduced hypertonia, increased range of motion, and/or improved hygiene and function, without causing an adverse event (e.g., weakness). Several factors affect the outcome of BTX therapy and influence clinical decision regarding choice of dose. These are summarized in Tables 29.9, 29.10, and 29.11.

TABLE 29.9 Factors That Affect Dose Selection of BTX

Patient-related factors
Spastic hypertonia severity
Muscle and limb involvement
Spastic hypertonia duration
Age and body mass
Outcome of prior BTX treatment
Clinician-related factors
Experience, knowledge, and expertise
Other factors
Cost
Availability of adjunctive therapy

Source: Reprinted with permission from Francisco GE. Botulinum toxin for poststroke spasticity. *Ann Acad Med.* 2007;36:22–30.

BTX is usually not administered more frequently than every three months because of theoretical concern for antibody development (122). This cautionary measure is based on findings in earlier studies on the use of BTX in cervical dystonia, where frequent injection, administration of "booster" injections, and initial high doses appeared to contribute to the development of BTX antibodies (123,124). It is estimated that the incidence of antibody to BTX in the spastic hypertonia population is less than 1%, but there are as yet no published data based on a prospective investigation (125,126). Repeated injection of BTX appears to be effective and safe (127,128). Lagalla et al. studied the effects of repeated injections every 3 to 5 months over a 2-year period to various upper-limb muscles in 28 stroke survivors (127). Muscle tone, range of motion, and satisfaction and functional measures (e.g., putting on gloves, axillary hygiene) improved after each treatment, and this response was sustained over time. Additionally, there was no significant increase in treatment doses, and treatment intervals increased from a mean of 3.9 ± 1.2 months between the first two sessions to 6.4 ± 1.7 months between the fourth and fifth doses.

The preparation of onabotulinumtoxinA for injection has not been standardized, but a common practice is to dilute a 100-unit vial with 1 to 2 mL of preservative-free saline. A small prospective study comparing dilution of 100 units of onabotulinumtoxinA with 1 and 2 mL of saline did not show a difference in improving hypertonia of wrist and finger flexors (129). Another small trial suggested that dilution of onabotulinumtoxinA with 5 mL of preservative-free saline is superior to more concentrated solution for decreasing spastic hypertonia of elbow flexor muscles (130). This is not an issue with Myobloc™, which already comes in a solution. No published information is available regarding dilution of abobotulinumtoxinA.

TABLE 29.10 Recommended or Published OnabotulinumtoxinA Doses for Spastic Hypertonia Due to Various Etiologies

UPPER-LIMB MUSCLES	MUSCLES DOSE (UNITS)	REFERENCES
Subscapularis	50–100	(108)
Teres major	25–100	(108)
Latissimus dorsi	50–150	(108)
Pectoralis complex	75–150	(108)
Triceps	50–200	Author's experience
Biceps	50–200	(99,100,108,116,183,184)
Brachialis	40–100	(108)
Brachioradialis	25–75	(108)
Pronator teres	10–50	(108,185)
Pronator quadratus	25–100	(108)
Flexor carpi radialis	20–70	(22,99,100,108,115,186,187)
Flexor carpi ulnaris	20–60	(22,99,100,108,115,186,187)
Flexor digotorum superficialis	20–60	(22,99,100,108,115,186,187)
Flexor digitorum profundus	10–30	(22,99,100,108,115,186,187)
Flexor pollicis longus	5–25	(108,186,187)
Opponens pollicis	5–25	(186)
Adductor pollicis	5–15	(108)
Lumbricals	per lumbrical	(108,188)
LOWER-LIMB MUSCLES		
Quadriceps mechanism	50–200	(108)
Hamstrings	50–200	(108)
Hip adductor group	200–400	(108,189)
Gastrocnemius	50–250	(95,106,108,190)
Soleus	50–200	(95,106,108)
Tibialis posterior	50–150	(95,106,108)
Tibialis anterior	50–150	(108)
Extensor hallucis longus	50–100	(191,192)
Flexor hallucis longus	25–75	(108,192)
Flexor digitorum longus	25–100	(108,192)
Flexor digitorum brevis	20–40	(108)

Source: Reprinted with permission from Francisco GE. Botulinum toxin for poststroke spasticity. *Ann Acad Med.* 2007;36:22–30.

TABLE 29.11 Published AbobotulinumtoxinA Doses for Spastic Hypertonia

UPPER-LIMB MUSCLES	DOSE (UNITS)	REFERENCES
Subscapularis	250	(73)
Biceps	100–400	(57,58,61,62)
Brachialis	250	(62)
Brachioradialis	100	(58)
Flexor carpi radialis	150	(58,74)
Flexor carpi ulnaris	100–150	(57,58,74)
Flexor digitorum superficialis	150–300	(57,58,74)
Flexor digitorum profundus	150–200	(57,58,74)
LOWER-LIMB MUSCLES		
Hip adductor group	500–1000	(83)
Gastrocnemius	250–1000	(60,64,92)
Soleus	200–500	(60,64,92)
Tibialis posterior	200–500	(60,64,92)
Flexor digitorum longus	150–300	(64)

Source: Reprinted with permission from Francisco GE. Botulinum toxin for poststroke spasticity. *Ann Acad Med.* 2007;36:22–30.

Little has been published in the literature on the role of adjunctive therapy modalities with BTX. Small, uncontrolled trials claim that the combination of BTX and various therapy modalities enhances clinical outcome. These include electrical stimulation of muscles injected with onabotulinumtoxinA or abobotulinumtoxinA, ankle taping, and casting (131–133). A "low dose" of onabotulinumtoxinA plus casting resulted in improved ankle range of motion and foot positioning similar to that obtained with a "high dose" (190–320 units) but without subsequent taping. The combined effect of BTX and physiotherapy and other therapeutic modalities in the stroke population has yet to be systematically investigated.

The reviewed studies have demonstrated that BTX is an effective therapy for focal poststroke spastic hypertonia, but no persuasive evidence has been published on its impact on generalized spastic hypertonia and function. Only a few studies attempted to investigate the effect of BTX on the functionality of upper limb (e.g., changes in hygiene and use of orthosis; decrease in caregiver burden) (25,132,134). The same observation is true for lower-limb studies, which primarily addressed spastic hypertonia reduction. Only one

study investigated gait as a main outcome measure (119). The lack of a systematic substantiation of the influence of BTX on poststroke recovery may be due to study design, patient selection, and choice of study outcome measures.

INTRATHECAL BACLOFEN

ITB therapy differs from the oral form of the medication in that it provides direct infusion of baclofen into the intrathecal space, thereby bypassing the blood–brain barrier. In contrast to oral baclofen, ITB is delivered in close proximity to the drug's site of action in the dorsal horn of the spinal cord. Therefore, only a small concentration of the drug is required to exert therapeutic effects; this avoids increasing the risk of side effects commonly associated with oral baclofen, such as sedation, drowsiness, and weakness. A programmable pump that infuses baclofen includes a small titanium disk containing a refillable reservoir for the drug and houses a computer chip that regulates the battery. A flexible silicone catheter, connected to the pump, delivers the drug into the intrathecal space. Prior to ITB pump implantation, a screening trial consisting of a bolus injection of 50 to 150 micrograms of baclofen is customarily performed to determine responsiveness of hypertonia to the medication.

ITB was initially used in persons with stroke and severe multilimb spastic hypertonia (135,136). Typical goals were facilitation of hygiene, positioning, and comfort. Lately, more clinicians have been utilizing ITB therapy chiefly to enhance upper-limb function and gait (137,138). When applied in the appropriate clinical setting and combined with a rehabilitation program, ITB therapy is an effective means of managing poststroke spastic hypertonia in individuals at various functional levels.

The body of literature supporting the efficacy of ITB in poststroke spastic hypertonia is limited. Thus far, no randomized, controlled study has been published. Much of what is known is based on a handful of open-label trials and case series (Table 29.12) and a consensus statement of experts (135–137,139–142). Two small investigations were conducted using a randomized, double-blind, placebo-controlled, crossover design during the first part of the study (ITB bolus injection during the screening trial), which then assumed an open-label design during the continuous ITB infusion phase (135,136). These patients showed a significant improvement in spastic hypertonia. A much larger series involving 94 subjects suggested that ITB therapy can positively enhance function and quality of life based on significant changes in functional independence measure (FIM) and

TABLE 29.12 Intrathecal Baclofen in Poststroke Spastic Hypertonia

STUDY/AUTHOR	SUBJECTS	STUDY DESIGN	OUTCOME
Meythaler et al. (1996) (135)	Stroke = 3 TBI = 3	Randomized, double-blind, placebo-controlled, crossover (screening phase only); open label after ITB pump implantation 3 months follow-up	Improved AS, SFS, and reflex scores No effect on motor strength on the normal side
Meythaler et al. (2001) (71)	Stroke = 21	Randomized, double-blind, placebo-controlled, crossover (screening phase only); open label after ITB pump implantation 12 months follow-up	Improved AS, SFS, and reflex scores No effect on motor strength on the normal side Three subjects recovered ability to ambulate
Francisco and Boake (2003) (137)	Stroke = 10, all ambulatory	Open label Mean 8.9 months follow-up	Improved modified AS scores and gait speed. Preserved strength in unaffected limbs.
Remy-Neris et al. (2003) (142)	Stroke = 4 TBI = 3	Case series, open label; bolus intrathecal baclofen only	Improved AS scores and maximal walking speed, but preferred walking speed was unchanged Minimal knee extension and maximal ankle flexion were the only kinematic data that significantly improved
Horn et al. (2005) (140)	Stroke = 13 TBI = 12 HE = 3	Case series; open label 2, 4, and 6 hours post-ITB bolus injection	Improved AS scores and gait velocity Significant correlation between baseline gait velocity and peak change in velocity after ITB bolus No significant correlation between AS and change in temporospatial outcome gait measures
Ivanhoe et al. (2006) (141)	Stroke = 74	Open label Post-ITB follow-up at 3 and 12 months	Significant improvement in AS, FIM, and SIP scores at both follow-ups No effect on muscle strength on unaffected side Largest study in stroke

Abbreviations: AS, Ashworth Scale; FIM, functional independence measure; HE, hypoxic encephalopathy; ITB, intrathecal baclofen therapy; SFS, spasm frequency scale; SIP, sickness impact profile; TBI, traumatic brain injury.

Source: From Ref. (139). Francisco GE, Yablon SA, Schiess MC, Wiggs L, Cavalier S, Grissom S. Consensus panel guidelines for the use of intrathecal baclofen therapy in poststroke spastic hypertonia. *Top Stroke Rehabil*. 2006;13(4):74–85. Thomas Land Publishers.

sickness impact profile (SIP) scales, respectively (141). The limitation of study design and choice of outcome measures, however, prevent interpretation of the results and correlation with clinically significant functional changes. Thus far, only three investigations have suggested actual functional improvement. Two small case series demonstrated significant improvement in gait speed, whereas one demonstrated increased upper-limb use following ITB and physical or occupational therapy (137,140).

A consensus statement suggested that ITB therapy be considered in stroke survivors whose spastic hypertonia did not respond adequately to other pharmacologic and nonpharmacologic management interventions (139). ITB should also be considered regardless of the severity of hypertonia, as long as the spastic condition is significant enough to cause other problems, such as pain, joint deformities, postural abnormalities, and functional deficits like impairment in gait and inability to adequately perform activities of daily living. It should also be considered in persons whose progress in a rehabilitation program is hindered by spastic hypertonia that failed to respond to other treatment strategies. Table 29.13 summarizes typical goals for the application of ITB in stroke.

In spite of the potential benefits of ITB, less than 1% of stroke patients with severe disabling spasticity are treated with ITB (143). Possible reasons for ITB underutilization include surgical risks, excessive weakness, less effect on upper limbs, and limited functional improvement.

Concerns regarding the early use of ITB therapy after a stroke are based on animal studies, where early use of baclofen and other medications that mimic or enhance the effects of GABA after experimentally induced cerebral lesions slowed neurologic recovery (144,145). Reports also suggest that certain drugs, including baclofen and other GABA agonists, may have a negative impact on cognitive and motor recovery after a stroke (146). However, it is widely acknowledged that delayed or inadequate treatment of spastic hypertonia may result in costly complications such as contractures, persistent pain, and failure to benefit from rehabilitation efforts. Thus, the same consensus statement recommended that ITB therapy should be considered as early as three to six months after stroke, whenever it causes significant functional impact or hinders progress in rehabilitation (139).

Although not unique to persons with stroke, certain clinical issues warrant thoughtful consideration before institution of ITB therapy, such as concomitant use of antiplatelet agents and anticoagulants. There is insufficient evidence regarding the risk of withdrawing these medications prior to ITB screening or implantation to guide treatment. Thus, the decision whether to withdraw antiplatelet and anticoagulation treatment, its timing, and reinstitution, will have to be made in consultation with the implanting surgeon and other specialists (cardiologists, hematologists, neurologists) involved in the patient's care. Seizures are also known to occur during ITB therapy in other patient populations, but their occurrence among stroke survivors with ITB is not known (147,148). Changes in gastrointestinal motility associated with ITB therapy have also been described (149). This may aggravate constipation, which commonly occurs during the acute and subacute phases of recovery from a stroke, when individuals are relatively immobile. Sexual dysfunction associated with ITB has been reported in the spinal cord injury population but has yet to be reported in stroke survivors (150).

TABLE 29.13 Goals for ITB Therapy in Poststroke Hypertonia

High-level patient
Mobility
Increased speed of gait
Increased safety of gait
Improved quality of gait
Prevent long-term injury due to alteration in joint biomechanics
Activities of daily living (ADLs)
Dressing
Independence in hygiene
Decreased time to accomplish ADLs
Others
Discontinuation of oral spasmolytic drugs (and avoidance of drug side effects)
Decreased time spent on stretching as part of an exercise program
Low-level patient
Improved positioning
Facilitation of hygiene
Decreased caregiver burden and time
Prevention of complications (i.e., contractures and nonuse of paretic limb)
Increased orthotic fit and compliance
Decreased pain due to nighttime spasms
Improved quality and duration of sleep

Source: From Ref. (139). Francisco GE, Yablon SA, Schiess MC, Wiggs L, Cavalier S, Grissom S. Consensus panel guidelines for the use of intrathecal baclofen therapy in poststroke spastic hypertonia. *Top Stroke Rehabil*. 2006;13(4):74–85. Thomas Land Publishers.

The Impact of BTX and ITB on Functional Recovery

BTX and ITB therapies are effective treatments for poststroke spastic hypertonia, but their influence on function has not been fully demonstrated by well-designed studies. Even though it is tempting to dismiss their therapeutic impact on functional recovery due to the dearth of published evidence, common clinical experiences dictate otherwise. Perhaps the lack of scientific evidence does not accurately reflect the effect of BTX and ITB on function, but rather results from limitations in study design and methods. Likewise, it is also possible that it is incorrectly assumed that spastic hypertonia is the chief cause of a functional deficit, whereas other abnormalities associated with the UMNS, such as incoordination and co-contraction of agonist and antagonist muscles, are the primary reason for impaired function. Often, an erroneous assumption is made that a decrease in spastic hypertonia alone will automatically translate to enhanced function. Doing so oversimplifies function, which is a complex and multifaceted phenomenon that depends not only on muscle tone but also on muscle strength, coordination, and endurance, as well as the influence of behavior and cognition. Some have suggested

that tonic stretch reflex activity does not meaningfully contribute to active motor function after stroke (2).

Inappropriate patient selection may also explain poor functional outcomes in BTX and ITB studies. Patients with no or poor potential for motor and functional recovery could not be expected to demonstrate further functional improvement despite significant reduction of spastic hypertonia. Moreover, BTX injections and ITB therapy may worsen residual function by transiently inducing or uncovering latent weakness if too high a dose is used. Sheehan and Francis et al. have discussed this issue in greater detail in their excellent reviews (46,151).

ROLE OF SURGICAL INTERVENTION

Surgical procedures are typically reserved for those stroke patients with muscle or tendon shortening who have not responded to the less invasive procedures, or as a "last resort." Tendon transfer, release, or lengthening are the most common orthopedic procedures (152). The split anterior tibial tendon transfer (SPLATT) and tendon Achilles lengthening (TAL) have been used to manage the spastic equinovarus foot (153–157). In a retrospective review of 73 operated feet in patients with stroke, cerebral palsy, and brain injury, there was improved ability to ambulate, decreased need to wear orthosis, and increased ability to wear normal shoes with minimal complications (158). In a study of 21 stroke patients 1 year after a SPLATT, 83% reported good or excellent results. All ambulatory patients had improved gait, and 35% were able to discontinue their orthosis. Poor surgical outcomes were associated with nonambulatory status (159). The additional transfer of the flexor hallucis longus and flexor digitorum longus to the os calcis with the SPLATT and TAL improved calf strength, and patients had less reliance on orthotics (70% vs. 40%) (160). Pinzur et al. reported improved prehension after brachioradialis to finger extensor tendon transfer in four patients with spastic hemiplegia (161). Eighteen patients with spastic hand deformities had improved prehension after release of the flexor-pronator origin and step-cut lengthening of flexor pollicis longus (162). Polyelectromyography may be useful in identifying which patients would benefit most from orthopedic procedures (163). Other procedures, such as neurotomy, have also been shown to benefit spastic conditions (75,93,164).

NONPHARMACOLOGIC MODALITIES

Collaboration with physical and occupational therapists is critical to the effective management of poststroke spasticity (66). The therapist can help with patient evaluations, education, and establishment of patient-specific goals (17). A number of conventional therapies have been used to manage spasticity and improve function (17,165) (Table 29.14). These therapies are aimed primarily at providing prolonged stretch to shortened muscles and tendons, reducing muscle overactivity, strengthening weak muscles, potentiating medications, restoring biomechanics, improving endurance, integrating into functional tasks, and improving motor control (166,167).

TABLE 29.14 Rehabilitation Interventions for Spasticity

Inhibitory/serial casting
Weight bearing
Cryotherapy
Neurofacilatory techniques
Electrical stimulation
Aquatic therapy
EMG biofeedback
Constraint-induced movement therapy
Robotic training
Partial weight support treadmill training

Unfortunately, there is a significant variation in the use of these therapies, and lack of controlled trials (168). The reader is referred to three reviews on the benefits of stretch and physical modalities in the management of spasticity (168–170). In a randomized, controlled study of 44 stroke patients, those treated with 20 sessions of Bobath treatment for 4 weeks had improved motor function and reduced spasticity, compared with the orthopedic treatment group (171,172).

Surface electrical stimulation in stroke survivors has been shown to reduce atrophy, enhance strength, and possibly reduce spasticity (7,173–180). The antispastic effect has been suggested to involve facilitation of Renshaw cell recurrent inhibition, antagonist reciprocal inhibition, cutaneous sensory habituation, and augmentation of Ib fiber activation (181). Unfortunately, these studies have shown limited functional improvement, and many patients are unable to tolerate the electrical stimulation (175,182). Initial work with an upper-limb neuroprosthesis used to improve function was limited to the laboratory, and stimulation was limited to hand opening (57,178).

A new approach is a device that combines a wrist-hand orthosis with neuromuscular electrical stimulation (NMES) of wrist and finger flexors and extensors during a repeated prehension exercise paradigm. The NESS H200™ is a neuroprosthesis that is well tolerated and has been shown to reduce impairments and improve function (180,183–185). The major advantage of this system is that the device is custom-fitted to the patient's forearm, assuring that the electrodes always stay in the correct place and provide consistent activation of the targeted muscles. The device is easy to don and doff and can be activate with one hand. The integrated NMES system provides reproducible stimulation of both wrist and finger flexors and extensors. The NESS 200 is intended to be self-administered and allows NMES-assisted exercises involving prehension. The simplicity of using the system improves compliance with the treatment program (74). Improved function can be obtained when NMES is combined with a home exercise program. In a multicenter, multicountry nonrandomized study, 77 stroke survivors completed a 5-week daily home training program with the NESS H200. Subjects trained two to three times each day for seven days a week, and all enrolled subjects completed the study. The Jebsen-Taylor simulated feeding time improved

35%, the light object lift improved 45%, and the nine-hole peg test improved 59%. Mean spasticity reduction was 0.87 at the elbow and 0.78 at the wrist as measured by the AS. Thirty-three of the 77 patients had persistent upper-limb pain with mean reduction 3.5 to 1.9 (74). Although this study is promising, it did not include a control group, so it is difficult to determine whether the benefits resulted from the NMES or from the regular exercise program.

Whole-body vibration in chronic stroke patients appears to decrease spasticity, but studies with larger sample size and long-term follow-up are needed to better understand its role in managing poststroke spasticity (186,187).

LOOKING AHEAD: THE FUTURE OF SPASTIC HYPERTONIA MANAGEMENT

Spastic hypertonia and the UMNS, being complex and multifaceted conditions, create opportunities for innovative therapies for the future. Drugs that have been used for indications other than stroke have the potential to alleviate spastic hypertonia and other abnormalities. 4-amino-pyridine, an orally administered medication touted to alleviate symptoms in multiple sclerosis by improving impulse conduction along damaged nerve fibers, has been reported to have antispasticity properties (188). Clonidine, already used as an adjunctive oral therapy for spastic hypertonia, can also be delivered intrathecally (189,190). Its use is more common in Europe than in the United States. The use of intrathecal tizanidine has also been described in painful conditions, although its effect on spasticity, similar to that of the oral preparation, is yet to be shown (191). Another intrathecally administered drug, ziconotide, a neurotoxin that is an emerging treatment for severe pain, has been shown to have spasmolytic properties in the spinal cord injury population (192). An ancient therapy, acupuncture, has been used to treat spastic hypertonia, but its efficacy has yet to be established (see Chapter 37) (193–196). Earlier studies have suggested that spinal cord stimulation decreases spasticity, but clinical application of this modality has become more common for pain (197,198). Interest in the use of direct motor nerve stimulation appears to have been revived, judging by the recent publication of the results of animal investigations (199,200). Neuromodulation, through brain and spinal cord stimulation, is also a promising avenue for the future treatment of spastic hypertonia, as is gene therapy (201). Being able to control muscular overactivity through genes capable of specifically inducing synaptic inhibition and suppressing neuromuscular transmission offers the advantage of addressing the root of the neuromuscular dysfunction (201).

Decisions on the treatment of spasticity after stroke depend on the severity of spastic hypertonia and its impact on function and well-being. Other factors to consider include disease etiology and duration, previous response to therapies, topographical involvement, response to medication side effects, and cost. Therapeutic efforts have focused on peripheral (e.g., altering muscle properties through physical techniques) and central (e.g., influencing neurotransmission through GABA-mediated medications and modifying reciprocal inhibition through chemodenervation) strategies. Spastic hypertonia and the other UMNS signs and symptoms result in physical deformities and performance deficiencies. Thus, it is logical for interventions to target not only the underlying CNS pathology but also the ensuing physical abnormalities. Consequently, it is a widely held belief that concurrent use of various pharmacologic and nonpharmacologic treatment modalities results in a more optimal management outcome.

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30

Musculoskeletal Complications After Stroke

Richard D. Wilson, David T. Yu, and John Chae

Musculoskeletal complications are common after stroke, with a quarter or more of stroke survivors experiencing them (1–4). The consequences of musculoskeletal complications can range from an annoyance to a major hindrance during and after stroke rehabilitation. Most of the musculoskeletal complaints are related to pain, yet some are not painful but interfere with function. It is not surprising that musculoskeletal complications are prevalent among hemiparetic stroke survivors. Biomechanics in these patients can be altered by weakness, sensory loss, spasticity, neglect, impaired motor control, and maladaptive compensatory strategies. This chapter addresses musculoskeletal complications that are commonly reported in the literature. Hemiplegic shoulder pain is one of the most common musculoskeletal complaints after stroke, and is a major focus of this chapter. Other complications include arthralgias, joint contractures, complex regional pain syndrome (CRPS), and heterotopic ossification (HO). It is important to note that musculoskeletal pathologies that are common in the general population, such as low back pain, are also common in those with stroke. This chapter focuses on musculoskeletal complications of stroke.

PAIN

Pain is one of the top complications after stroke. In fact, after the first week, pain has been found to be the most common cumulative complication in stroke survivors (1). Studies in stroke survivors have shown that pain is associated with lower health-related quality of life (5–7), lower function (8,9), and higher mortality (10). Guidelines highlight the importance of prevention, assessment, and treatment of pain throughout rehabilitation (11) to provide the greatest chance of recovery and to obtain the highest level of independence possible.

Pain is prevalent, affecting more than 25% of stroke survivors in the first week after stroke (12) and more than 33% of stroke survivors during hospitalization and acute rehabilitation (1,13,14). The prevalence of pain in the first 2 years after a stroke is estimated to be between 15% and 50% (15), which is similar to the estimated prevalence of chronic pain in community-dwelling adults (15%–51%) (16–19). It appears that the development of new pain complaints is higher in stroke survivors than community samples. The only population-based study that included a matched reference group found that the proportion of pain related to the stroke is 10% (20), which is similar to the estimates of 10% to 21% in other studies (15,21). The most common musculoskeletal stroke-related pain complaints are related to the shoulder, other arthralgias, and muscle stiffness and spasms (15,20,22–24).

That the prevalence of pain is so high in stroke survivors likely is the result of multiple factors. First, pain is undertreated in older adults, many of whom tend to have other illnesses that may be prioritized more highly for treatment by providers (25). Second, pain is undertreated in those who have communication or cognitive impairments because of their inability to express their needs (26,27). Finally, there are many chronic pain syndromes without adequate treatments that result in prolonged suffering and frustration for patients and providers (28–30). It is important for providers who care for stroke survivors to inquire about the presence of pain and to adequately address complaints. This chapter provides information germane to providers caring for stroke survivors and primarily focuses on musculoskeletal conditions that are directly related to the stroke.

Shoulder Pain

Shoulder pain is a common complication after stroke that can inhibit functional recovery and reduce quality of life (31,32). Many types of shoulder pathology after stroke have been reported in the literature, including shoulder subluxation, impingement syndrome, rotator cuff injury, tendonitis, bursitis, capsulitis, peripheral nerve injuries, CRPS, spasticity, central hypersensitivity, and contractures. No single type of pathology accounts for all shoulder pain after stroke. Conversely, it is important to recognize that more than one type of shoulder pathology may cause pain in an individual.

Among hemiplegic stroke survivors, the reported prevalence of shoulder pain ranges from 5% to 84%, reflecting differences in study methods and samples (33,34). Population-based studies estimate the prevalence of shoulder pain to be 17% at 1 week and 20% to 24% at 1 to 16 months after stroke (35,36). The estimates of prevalence in rehabilitation settings are 37% to 55% (37–40), likely because of the greater number of associated risk factors in this population compared to the general population of stroke survivors.

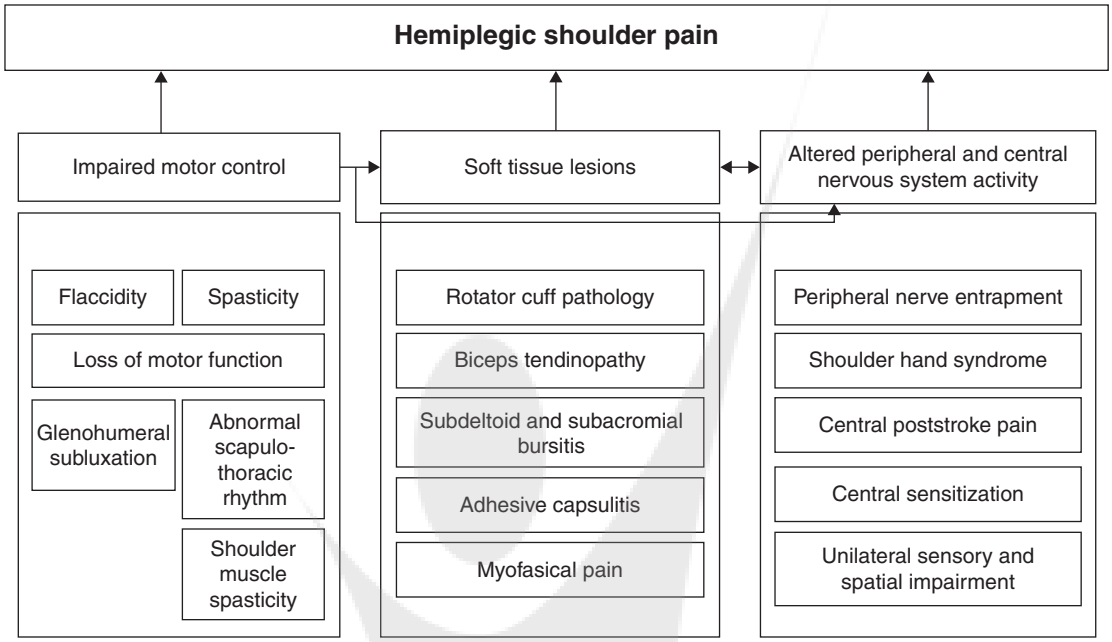

FIGURE 30.1 Systematic organization of pathologies underlying hemiplegic shoulder pain.

Source: Adapted from Ref. (52). Kalichman L, Ratmansky M. Underlying pathology and associated factors of hemiplegic shoulder pain. *Am J Phys Med Rehabil*. 2011;90(9):768–780.

Gamble et al. reported resolution of pain in 80% of cases when management included prompt diagnosis and early, appropriate intervention (41). However, studies consistently report a significant number of cases that do not resolve, with 20% of moderate to severely impaired stroke survivors reporting pain 4 years after stroke (42). The data suggest that poststroke shoulder pain can improve in many cases with prompt diagnosis and appropriate intervention, but that a significant number of cases become chronic and refractory to available treatments.

Many potential risk factors for shoulder pain after stroke have been cited in the literature and have been most consistently correlated with severity of motor impairment (35,36,41–43). Other commonly reported risk factors include duration of motor impairment (44), sensory impairment (36,43,45), reduced range of motion (43,44), spasticity (46), central sensitization (47,48), soft tissue injuries (49–51), and comorbidities such as diabetes mellitus (36,43). A systematic approach to integrating potential underlying pathologies has proposed three categories of pathology: (a) impaired motor control, (b) soft tissue lesions, and (c) altered peripheral and central nervous activity (see Figure 30.1) (52).

Shoulder Subluxation

Subluxation is defined as partial dissociation or increased translation between two articulating surfaces of a joint (53). Subluxation may be contrasted to dislocation, defined as complete dissociation between two articulating surfaces of a joint. By convention, shoulder subluxation resulting from hemiparesis after stroke refers to increased translation of the humeral head relative to the glenoid fossa. Generally, in clinical practice and in research, shoulder subluxation after stroke is measured in the inferior direction with the upper limb in a dependent position, allowing the weight of the limb to distract the humeral head from the glenoid fossa (38,44,46,54–65). Though these methods have become the standard by convention, the content validity of measuring only inferior subluxation is questionable and may contribute to the inconsistent correlation between subluxation and pain reported in the literature.

Shoulder subluxation is common in hemiplegia. Though subluxation has been reported to occur in up to 81% of cases (61), one of the largest cohorts of hemiplegic subjects followed over months reported an incidence of approximately 50%(46). However, even in this case, an overestimation resulting from selection bias toward more impaired hemiplegic subjects cannot be ruled out. Though shoulder subluxation is one of the most commonly cited causes of shoulder pain in the literature, the relationship between subluxation and pain remains controversial. Although a number of studies suggest a correlation between subluxation and pain (33,46,66–68), others have demonstrated absence of correlation (38,42,69–72). Many differences in study methods may underlie the disparity in the literature, although the lack of correlation between subluxation and pain in several studies suggests that subluxation may not be a direct cause of pain in many cases. It is also possible that subluxation predisposes the shoulder to other types of painful pathology. Several studies have corroborated this notion by demonstrating a correlation between

shoulder subluxation after stroke and the development of other causes of shoulder pain, including CRPS, peripheral neuropathies, and rotator cuff injury (33,73–75).

Shoulder subluxation in hemiplegia occurs because of the paralysis of active restraints that play a critical role in maintaining glenohumeral stability (76–79). Shoulder subluxation tends to occur early after stroke, with most cases occurring within the first three weeks, particularly in patients with flaccid hemiplegia (55). Spasticity develops in most hemiplegic patients and may have an effect on reducing shoulder subluxation. An inverse correlation between shoulder subluxation and spasticity has been reported in two studies in which the authors attribute the reduction of subluxation to return of muscle tone or volitional activation (55,58). In another study, subluxation was reduced only when shoulder muscles became spastic within the first week after stroke, but was not reduced when spasticity occurred at three weeks or later. This suggests that there may be a critical, brief time window for spasticity to have an effect on reducing subluxation (55). The results of this study also suggest that the passive restraints of the shoulder may only be sufficient for maintaining joint stability for a short period of time. Stretching of the joint capsule and ligaments may not be reversible after a point. In only one study, a higher incidence of shoulder subluxation was found when spastic and flaccid hemiplegic subjects were compared (46). Studies of electric stimulation (ES) of shoulder muscles to reduce subluxation after stroke also suggest that changes in muscle properties can reduce subluxation. However, it is not clear if relevant changes in muscle properties are a result of the improvement in muscle tone, improvement in purely passive mechanical properties, or (less likely) improvement in voluntary muscle contraction. The majority of ES studies have shown that stimulation-induced muscle contraction can reduce subluxation. Several of these studies have shown that the reduction of subluxation is maintained for months after muscle stimulation has been discontinued, suggesting an effect of passive muscle properties (54,57,65,80). Though a few studies have shown that subluxation can be reduced in chronic stroke patients, a 2002 meta-analysis of the data suggests that ES for reducing poststroke shoulder subluxation is most effective when applied early after stroke (81).

The clinical diagnosis of shoulder subluxation can be made without imaging studies. The most commonly used clinical measure of shoulder subluxation in hemiplegia quantifies inferior subluxation by determining the number of fingerbreadths that can be inserted between the inferior border of the acromion and the superior border of the humeral head while the patient is seated with the upper limbs hanging passively. The patient is seated because muscle tone may increase in the standing position, reducing the subluxation. Comparison to the unaffected shoulder is recommended, but care should be taken to palpate only the bony landmarks to avoid misinterpreting a unilateral flaccid or atrophied deltoid muscle as the difference between shoulders. The clinical fingerbreadth measure detects abnormal translation in the inferior direction only. This clinical measure has a resolution of a half fingerbreadth and does not detect small changes in glenohumeral displacement that may be significant. Despite anatomical variability in finger widths, the reliability of the fingerbreadth measure has been established (82). The reliability of this technique may be in part a function of its limited resolution. Imaging studies such as plain radiographs, computed tomography, ultrasound, and magnetic resonance imaging also show subluxation, often with greater resolution and the ability to detect abnormal translation in other dimensions. Because the clinical significance of subluxation in multiple dimensions is not known, the significance of small amounts of subluxation is not known. Because the role of subluxation as a cause of pain is controversial, these additional studies are not currently standards for diagnosing shoulder subluxation.

Despite the controversial relationship between shoulder subluxation and pain, treatment of subluxation continues to be the standard of care in rehabilitation facilities, for several reasons. First, shoulder subluxation may be painful in some cases, particularly when manual reduction of the subluxed joint diminishes pain. Second, shoulder subluxation may predispose hemiplegic patients to the development of other painful conditions. If chronic shoulder pain develops, it is often refractory to available treatment, warranting prevention for at-risk patients and prompt treatment in patients with subluxation. Third, subluxation may inhibit functional recovery by limiting the range of motion. Support of the hemiplegic upper limb in the seated and standing positions remains the standard of care for stroke survivors with shoulder subluxation and those with flaccid paralysis of shoulder muscles who are at risk for developing shoulder subluxation.

Upper-limb support includes the use of wheelchair adaptations and judicious use of selected supports. When seated in the wheelchair, hemi-trays are appropriate for patients with sufficient motor function to maintain the upper limb in a resting position on the tray. A trough, in some cases with Velcro enclosures, attached to the wheelchair is suited to patients who lack sufficient motor control to prevent the upper limb from sliding from a tray. It should be mentioned, however, that wheelchair arm troughs and trays have not been shown to reduce subluxation or pain, and occasionally have been thought to predispose the affected shoulder to impingement syndromes (83,84). Selected supports may be used to support the affected upper limb during transfers and ambulation, though findings have been mixed and there is little evidence to recommend their use (83,85,86). If a sling-type support is used, a neoprene cuff-type hemisling is recommended. Slings that place bulky material, such as a roll, under the axilla may cause lateral subluxation. Swathe-type slings that hold the shoulder in adduction and internal rotation and the elbow in flexion should be avoided because they can rapidly lead to capsulitis, cause contractures over time, and promote undesirable synergistic patterns of muscle activation (84).

The use of tape to support the subluxed glenohumeral joint, known as *strapping*, has been evaluated in randomized, controlled trials with mixed results (87–89). A Cochrane

review of external supports suggests that strapping may delay the onset of shoulder pain but does not reduce pain severity or associated disability (86).

The limitations of orthotic applications such as strapping, slings, and wheelchair adaptations have prompted investigators to evaluate the efficacy of ES for reducing poststroke shoulder subluxation and pain. The stimulation is most commonly delivered through electrodes placed on the skin surface (i.e., transcutaneous ES). Electrodes are typically placed over the posterior deltoid and supraspinatus muscles. Baker et al. proposed that placing the cathode over the deltoid and the anode over the supraspinatus would reduce undesirable stimulation to the upper trapezius and resultant shoulder shrugging (54). Stimulation is typically delivered for six hours daily for six weeks. Transcutaneous ES reduces shoulder subluxation when applied within weeks of stroke onset (56,57,80,81,90), though one trial did not find improvement (91).

Clinical trials evaluating the efficacy of transcutaneous ES for reducing subluxation in chronic hemiplegia (54) and for reducing shoulder pain have yielded mixed results (56,57). Clinical application of transcutaneous ES has been limited for several reasons. First, stimulation of cutaneous nociceptors results in stimulation-induced pain. Pain with transcutaneous ES is a well-recognized entity, and methods to improve tolerance by gradually increasing stimulation time or intensity until tolerance for therapeutic stimulation develops has been described (54,92). However, this strategy does not promote tolerance in all cases. Furthermore, it is time-consuming for the therapist and patient; the previously reported clinical trials were conducted in the context of inpatient rehabilitation and may not be practical under the economic pressures of the present health care environment. Approximately 30% of hemiplegic patients do not tolerate transcutaneous ES even when methods to enhance tolerance are employed (59). Second, activation of deep muscles cannot be achieved without stimulation of more superficial muscles. Third, clinical skill is required to place the electrodes and adjust stimulation parameters to provide optimal treatment. Treatment is typically administered daily by a skilled therapist. Few patients are able to administer treatments at home by themselves or with the assistance of a caregiver. Fourth, transcutaneous ES may interfere with the user's daily activities. Surface electrodes can be displaced from the skin during movement and connecting leads can be accidentally pulled during activity. The significance of this limitation is obvious when considering that most treatment regimens require stimulation over hours, daily, for weeks.

Newer technologies permit direct stimulation of target peripheral nerve or motor points through percutaneously placed electrodes. Electrical stimulation delivered through electrodes implanted near the target nerve has several potential advantages over transcutaneous ES. First, percutaneous ES is less painful than transcutaneous ES for reducing shoulder subluxation after stroke (93). The stimulating surface of the electrode is placed near the peripheral nerve or muscle motor point so that stimulation of cutaneous nociceptors can be avoided. This method permits the use of lower stimulus intensities than when the current has to cross the skin, which is a poor conductor. Stimulation frequencies as low as 12 Hz, which minimize muscle fatigue and facilitate muscle conditioning, can be used. These lower frequencies are associated with significant pain when using surface ES. Undesirable stimulation of adjacent muscles not intended for stimulation also can be avoided. Second, implanted electrodes are placed optimally at the beginning of treatment and remain in place for the treatment duration. Thus, the system is more reliable, can be administered by the user or caregiver at home, and obviates the need for daily application by a therapist. This percutaneous intramuscular system also permitted users to perform typical daily activities while receiving treatment. The efficacy of six weeks of ES delivered directly to peripheral nerves of four shoulder muscles using this partially implanted system for treating shoulder pain in chronic stroke patients with hemiparesis and subluxation was demonstrated in a multicenter randomized clinical trial (94,95). In this trial, pain reduction remained significant for at least one year after completing treatment. However, the reduction of subluxation between treatment and controls was not significant, calling into question the mechanism of pain reduction (94–96). This approach was simplified to a single-lead percutaneous intramuscular electrode that stimulates the axillary nerve at the middle and posterior deltoid muscles of the painful shoulder for three weeks (97). In a case series of subjects with shoulder pain with or without subluxation, a reduction in pain occurred after a three-week stimulation period and remained throughout the three-month follow-up period (98).

An alternative to the percutaneous intramuscular system is a fully implanted ES system comprised of a percutaneously injected microstimulator, battery, and electrode housed within a titanium and ceramic cylinder. The device has been investigated in small case studies and has shown success in reduction of subluxation and shoulder pain (99–101). The potential advantages of this fully implanted system are numerous. It obviates the need for users to wear external components, making it easier to use; in addition, reliability is improved, infection risk posed by percutaneous hardware is avoided, and the risk of accidental electrode displacement is reduced. The system is designed to remain in the body for the life of the user. Thus, chronic or repetitive treatment is facilitated.

In summary, shoulder subluxation tends to occur early after stroke in patients with flaccid hemiplegia and may be reversible through facilitation of muscle tone, motor recovery, or stimulated muscle contraction. There may be a brief, critical time window for reducing subluxation during the acute phase after stroke. The use of external upper-limb support, including judicious use of slings and wheelchair adaptations, is indicated for patients with subluxation or those with flaccid hemiparesis who are at risk. Electrical stimulation reduces subluxation in acute stroke, but the effect on subluxation in chronic stroke is less clear. The effect of ES in treating shoulder pain after stroke appears to be a reduction of pain regardless of improvement in subluxation.

Capsulitis and Related Conditions

Capsulitis, also known as *adhesive capsulitis* or *frozen shoulder*, is a common complication after stroke and refers to shortening and thickening of the glenohumeral joint capsule. Several studies have found a high prevalence of joint capsule thickening and synovial membrane contrast enhancement on magnetic resonance imaging for those with shoulder pain after stroke compared to controls (102,103), indicative of capsulitis (104,105). The inflammatory response seen in this condition probably results from irritation and injury to shortened capsular fibers. The term *adhesive* refers to adhesions of the capsule during surgery found by Neviaser et al. (106). Other authors report fibrosis of the capsule but no adhesions at the time of surgery (107). Fibrosis most likely occurs in the chronic phase of this condition if inadequately treated. There is an association of the development of capsulitis after stroke with immobility (108,109), impingement (110), and subluxation (111), which raises the question of whether capsulitis has a causative role or is a result of shoulder-related sequelae of stroke (52). Ultimately, the cause of capsulitis remains unknown.

On physical examination, decreased shoulder external rotation and abduction associated with pain is the hallmark of capsulitis. Because many patients with spastic hemiparesis have tonic adduction and internal rotation of the shoulder, shortening of shoulder internal rotators is common. Thus, palpation of these muscles during the exam is useful to determine whether musculotendinous shortening contributes to decreased range of motion and pain. It is also useful to measure passive shoulder rotation with the shoulder in adduction, because shoulder internal rotators have more slack than in abduction. In practice, shortening of capsular fibers often coexists with spasticity and shortening of the internal rotators of the shoulder (i.e., subscapularis, pectoralis, anterior deltoid, teres major, and latissimus dorsi muscles). In such cases, treatment of all contributing entities affords better and longer-lasting outcomes than treatment of only one. In the stroke literature, decreased shoulder abduction and external rotation resulting from end range of motion or pain often is considered diagnostic of capsulitis, making it difficult to assess the relative contribution of spastic or shortened shoulder muscles in many published studies.

Keeping in mind the potential contribution of spastic shoulder muscles, the diagnosis of capsulitis can, in most cases, be made by physical exam alone. Contrast-enhanced magnetic resonance imaging is a noninvasive method for diagnosis of capsulitis, with findings of increased thickness and enhancement of the joint capsule and synovial membrane in the axillary recess and rotator interval (104,108). Occasionally, intra-articular injection of an anesthetic agent can corroborate the diagnosis or help to evaluate the relative contribution to shoulder pain when multiple diagnoses are suspected. Usually, there is already a high index of suspicion, and the diagnostic injection is combined with therapeutic steroids. Arthrography can also be diagnostic but usually is not warranted. Typical findings on arthrography include a scalloped appearance of the joint space border or a capsule that accommodates significantly less than the expected 12 mL of contrast. Contrast seen in the subacromial bursa after intra-articular injection typically indicates a rotator cuff tear.

Generally, idiopathic capsulitis tends to resolve over 15 to 20 months and treatments do not offer different long-term endpoints compared to no treatment. However, treatments may offer relief sooner than watchful waiting, thus decreasing the time patients spend in pain and with limitations in shoulder range (112). Treatment of capsulitis is comprised of restoration of range of motion and reduction of inflammation. If spasticity or shortening of shoulder muscles contributes to pain, limits function, or predisposes to recurrent capsulitis, additional measures may be indicated. When possible, management of inflammation, spasticity, and pain should be performed concurrently with restoration of motion. Range-of-motion restoration often is done under the supervision of a therapist with close communication between therapist and physician, although the results of physical therapeutic interventions are mixed (113,114). If range of motion does not improve as expected, underlying biomechanical barriers, such as spasticity, or medical barriers, such as pain, may have to be addressed. Care should be taken to avoid impingement problems caused by excessive shoulder abduction without concomitant shoulder external rotation and scapular rotation. As mentioned previously, swathe-type slings that hold the shoulder in adduction and internal rotation should be avoided. Caregiver training and home supervision are important in most cases because stroke survivors with hemiplegia often have some degree of neglect that may require cues for performing the appropriate range-of-motion exercises; there is also a need to promote attention to upper-limb positioning in bed. Caregivers often are able to assist with range-of-motion exercises that patients have difficulty performing independently. Caregiver involvement becomes more critical in the setting of more pronounced unilateral neglect or cognitive impairment.

More aggressive interventions should be considered in patients for whom pain or range of motion is limiting recovery or ability to function, though the evidence is mixed. One study of a series of three intra-articular corticosteroid injections over three weeks in subjects with shoulder pain and restricted range of motion after stroke found a reduction in pain without a significant change in range of motion (115), whereas a randomized controlled trial of three intra-articular injections did not find a significant difference compared to placebo in pain, range of motion, or function (116). In a randomized trial in nonstroke subjects, a single injection of intra-articular corticosteroid provided faster relief of pain and an improvement in range of motion as compared to placebo (117). Another randomized trial in nonstroke subjects found equal improvement among different locations of the corticosteroid injection (subacromial, glenohumeral, or combined), and faster pain relief and improvement in range of motion compared to oral medications, although there was no difference in range of motion or function at 24 weeks (118). Although arthroscopic release

and manipulation under anesthesia have been described in adhesive capsulitis in the nonstroke population, it is not clear that these treatments offer any better long-term outcomes than corticosteroid injection; in fact, they possibly offer a slower recovery (119). Additionally, manipulation under anesthesia is less appealing because of the small risk of humeral fracture, dislocation, rotator cuff injury, labral tears, and brachial plexus injury (120).

Impingement Syndrome and Rotator Cuff Injury

Impingement syndrome refers to injury to the supraspinatus muscle or tendon resulting from repetitive compression between the inferior border of the acromion and the greater tuberosity of the humerus. The greater tuberosity of the humerus rotates under the acromion with internal shoulder rotation, diminishing space for the supraspinatus muscle and tendon during shoulder abduction. Repetitive compression of the supraspinatus muscle occurs when the shoulder is abducted more than 90 degrees without concomitant shoulder external rotation. Though not adequately studied, biomechanical changes after stroke such as laxity of passive restraints because of subluxation, weakness of muscles that stabilize the joint, abnormal muscle tone, and motor recovery in a proximal-to-distal gradient may place stroke survivors at greater risk for impingement syndrome. Inflammation of the supraspinatus muscle and tendon, and the surrounding subacromial bursa, are common sequelae. Though rotator cuff injury can occur because of trauma and may include any of the four rotator cuff muscles, after stroke, rotator cuff injury is more common from injury to the supraspinatus muscle or tendon that occurs as a result of impingement that has not been adequately addressed (33,72).

The roles of impingement syndrome and rotator cuff injury have not been studied rigorously as a cause of shoulder pain after stroke. In some circles their contribution to poststroke shoulder pain is well accepted, though in others it remains controversial. In one cross-sectional study, half of 28 subjects with chronic hemiplegia and functionally limiting shoulder pain experienced pain reduction after injecting lidocaine near the subacromial region of the affected shoulder (72). A similar proportion also was shown to have signs of supraspinatus tendinopathy and impingement syndrome in a different cross-sectional study of patients in acute rehabilitation with shoulder pain (37). Although the prevalence rates of rotator cuff tears and tendinopathies have been found to be high in those with shoulder pain after stroke, it also has been noted that the presence of tears and tendiopathies is not related to the severity of pain (121). These results indirectly suggest that impingement syndrome, supraspinatus tendonitis, or subacromial bursitis are common causes of pain in hemiplegic stroke survivors. However, recent magnetic resonance imaging studies comparing those with shoulder pain to a pain-free group found no differences in the prevalence of rotator cuff pathology or subacromial bursitis (102,103). Studies in which the painful hemiplegic shoulder is compared to the contralateral shoulder by arthrography have produced mixed results on the prevalence of rotator cuff tears (33,109). It is likely that impingement syndrome and rotator cuff injuries are common in those with stroke because they are common in the general population and have a higher incidence with increasing age (122,123). Unfortunately, the high prevalence of rotator cuff pathology in patients without shoulder pain increases the risk of misdiagnosis in those with shoulder pain after stroke (123).

Prevention is the critical component of impingement syndrome management, and includes measures to prevent the syndrome from occurring as well as preventing further injury once it exists. Shoulder flexion or abduction, whether during passive or active exercise, always should be accompanied by external rotation. Altered biomechanics of the shoulder in hemiplegia resulting in displacement of the arc of the humeral head and tubercle may predispose the shoulder to impingement (124). Overhead passive range-of-motion exercises with shoulder internal rotation and the use of overhead pulleys that promote similar movement have been implicated as causes of impingement syndrome (33). Wheelchair arm supports also have been implicated (84). Care also should be taken to ensure that inadequate trunk control does not result in weight bearing through the elbow to the glenohumeral joint, particularly when it causes shoulder pain or occurs in the presence of hemisensory loss, unilateral neglect, or severe cognitive impairment. Ultimately, as in able-bodied patients, treatment should attempt to enhance shoulder posture, particularly in retraction and elevation, and restore active restraints by strengthening the external and internal rotators of the shoulder. However, an adequate strengthening regimen may not be possible because of severity of hemiparesis. A subacromial steroid injection also can be considered, particularly if shoulder pain is interfering with therapy or recovery, as it has been shown to improve pain, disability, and active range of motion for those with a painful shoulder after stroke and rotator cuff disorder (125).

Complex Regional Pain Syndrome

Much of the literature discussing CRPS after stroke predates the introduction of more accurate nomenclature, and thus refers to reflex sympathetic dystrophy (RSD) or shoulder hand syndrome. Generally, CRPS after stroke refers to type I (CRPS I) because it follows central nervous system injury rather than damage to a peripheral nerve (126). However, as discussed later in this section, root-level injury or peripheral nerve injury may result from traction to neural tissue from persistent shoulder subluxation or possibly compression of nerve between bones. Thus, it is possible that type II (CRPS II), which occurs after a peripheral nerve injury, may also occur, although there are no reports in the literature.

The reported prevalence of CRPS I in hemiplegia ranges from 12.5% (127) to 70% (128). The variability in reported prevalence of CRPS I may result from differences in the diagnostic criteria used. It also has been suggested that the incidence likely is lower than previous estimates that were made prior to

the routine treatment in rehabilitation facilities (129). Tepperman documented increased radionuclide uptake in the wrist, metacarpophalangeal (MCP), or interphalangeal joints of the hemiplegic upper limb on delayed images using scintigraphy in 25% of 85 hemiplegic subjects. The incidence of shoulder pain in these subjects was not reported. In their study group, the authors reported 100% sensitivity and specificity for MCP tenderness relative to their scintigraphic diagnostic criteria for CRPS I (130). VanOuwenaller found that 50 (23%) of 157 hemiplegic subjects with shoulder pain had clinical findings of CRPS I. The majority of these subjects had radiographic evidence of shoulder subluxation (92%) or spasticity (94%), suggesting that these may have played a role in the pathogenesis of CRPS I (46). Other studies of stroke cohorts over time also correlate early subluxation with the development of CRPS, suggesting traction injury to vaso nervorum as a possible etiology (46,75). It also is possible that shoulder subluxation and CRPS I are related coincidentally rather than causally. One prospective study evaluating the prognostic factors associated with CRPS I found that motor impairment, rather than subluxation, was clinically predictive, which also would explain the association between subluxation and CRPS I (131). Two reviews found that trauma related to altered shoulder biomechanics likely was the causative etiological factor (132,133). The pathophysiology of CRPS I remains a mystery, although multiple theories exist (134).

The diagnosis of CRPS I after stroke is made clinically. There have been attempts to standardize the diagnostic criteria for CRPS I to improve clinical care for patients and to improve comparability of scientific studies. The most recent iteration of diagnostic criteria from the 2004 Budapest International Association for the Study of Pain (IASP) consensus group set forth both clinical and research diagnostic criteria (see Tables 30.1 and 30.2) (135). Triple-phase bone scan has been recommended as a diagnostic tool (129,136–138). However, the sensitivity and specificity of triple-phase bone scanning has caused its utility as a diagnostic tool to be doubted (139). The typical presentation includes pain and limited range of motion at the shoulder, wrist, and hand, but not at the elbow. These findings often are accompanied by edema, warmth, and redness primarily involving the wrist and hand. Three subtypes have been identified within CRPS I: (a) a relatively limited syndrome predominated by vasomotor signs, (b) a relatively limited syndrome predominated by neuropathic pain or sensory abnormalities, and (c) a florid CRPS syndrome of high levels of motor or trophic signs and possible disuse-related changes (140). Interventions specific to each subgroup have not yet been identified.

Although no definitive treatments for CRPS I exist, goals of treatment include edema reduction, pain control, maintenance of range of motion, maintenance or increase in muscle strength, and restoration of function (139,141). Approaches to treatments often are empirical and based on presenting symptoms. Oral steroids appear to have the highest level of evidence. Other treatment options include sympathetic blocks; membrane stabilizers; edema control, mobilization, strengthening, and physical modalities; motor imagery and mirror therapy; and psychological and behavioral interventions (134). The specifics of these studies are beyond the scope of this chapter, and additional literature review is recommended if these treatments are pursued.

Brachial Plexopathy and Axillary Nerve Injury

Brachial plexus injury and other peripheral nerve injuries as causes of shoulder pain after stroke are controversial primarily because of the lack of a diagnostic gold standard. Although electromyography (EMG) is considered the diagnostic gold standard for brachial plexus injuries, electrodiagnosis of brachial plexopathy in hemiplegia is confounded

TABLE 30.1 Clinical Diagnostic Criteria for Complex Regional Pain Syndrome

1. Continuing pain that is disproportionate to any inciting event
2. Must report at least one symptom in *three of the four* following categories
   Sensory: Reports of hyperalgesia and/or allodynia
   Vasomotor: Reports of temperature asymmetry and/or skin color changes and/or skin color asymmetry
   Sudomotor or edema: Reports of edema and/or sweating changes and/or sweating asymmetry
   Motor or trophic: Reports of decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair, nail, skin)
3. Must display at least one sign[a] at time of evaluation in *two or more* of the following categories
   Sensory: Evidence of hyperalgesia (to pinprick) and/or allodynia (to light touch and/or deep somatic pressure and/or joint movement)
   Vasomotor: Evidence of temperature asymmetry and/or skin color changes and/or asymmetry
   Sudomotor or edema: Evidence of edema and/or sweating changes and/or sweating asymmetry
   Motor or trophic: Evidence of decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair, nail, skin)
4. There is no other diagnosis that better explains the signs and symptoms

[a]A sign is counted only if it is observed at the time of diagnosis.

Source: Reprinted with permission from Ref. (135). Harden RN, Oaklander AL, Burton AW, et al. Complex regional pain syndrome: practical diagnostic and treatment guidelines, 4th ed. *Pain Med.* 2013;14(2):180–229.

TABLE 30.2 Research Diagnostic Criteria for Complex Regional Pain Syndrome

1. Continuing pain that is disproportionate to any inciting event
2. Must report at least one symptom in *each of the four* following categories
   Sensory: Reports of hyperalgesia and/or allodynia
   Vasomotor: Reports of temperature asymmetry and/or skin color changes and/or skin color asymmetry
   Sudomotor or edema: Reports of edema and/or sweating changes and/or sweating asymmetry
   Motor or trophic: Reports of decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair, nail, skin)
3. Must display at least one sign[a] at time of evaluation in *two or more* of the following categories
   Sensory: Evidence of hyperalgesia (to pinprick) and/or allodynia (to light touch and/or deep somatic pressure and/or joint movement)
   Vasomotor: Evidence of temperature asymmetry and/or skin color changes and/or asymmetry
   Sudomotor or edema: Evidence of edema and/or sweating changes and/or sweating asymmetry
   Motor or trophic: Evidence of decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair, nail, skin)
4. There is no other diagnosis that better explains the signs and symptoms

[a]A sign is counted only if it is observed at the time of diagnosis.

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by loss of motor units that result from loss of descending input from upper motor neurons after central nervous system injury (142). Further, proximal nerve conduction studies lack reliability because volume-conducted potentials from nontarget muscles affect recorded potentials from target muscles. The studies using advanced imaging techniques to evaluate nerve injury have yet to be reported.

Prolonged nerve conduction latencies in the proximal upper limb of hemiplegic subjects have been reported by several investigators (73,74,143). Interpretations of these findings differ based on the diagnostic criteria used. Chino et al. documented significantly delayed latencies of the suprascapular, axillary, musculocutaneous, and radial nerves compared with published normative values and evidence of denervation on needle EMG in 21 hemiplegic subjects with shoulder subluxation. They postulated that shoulder subluxation may lead to traction injury to the brachial plexus (73). Kingery et al. documented delayed mean central latencies across the brachial plexus and spontaneous activity during needle EMG in hemiplegic subjects when compared with the unaffected limb. Subjects also had to meet strict physical examination criteria for brachial plexus injury. Although the findings in both studies were similar, in contrast to Chino, Kingery interpreted his results to reflect loss of motor units secondary to cortical injury rather than injury to the brachial plexus (143).

Based on available data, brachial plexopathy or peripheral nerve injury should be considered in the diagnosis of hemiplegic shoulder pain when (a) a mechanism for brachial plexus injury exists or (b) muscle tone, reflex changes, weakness, or sensory loss are not consistent with a CNS lesion, especially in the setting of pronounced shoulder subluxation. Because shoulder subluxation has been postulated as the cause of nerve injury, measures to prevent and reduce shoulder subluxation are warranted.

Bicipital Tendonitis

Bicipital tendonitis has not been well described in the stroke literature. However, it bears inclusion in the differential diagnosis of hemiplegic shoulder pain. The prevalence in those with shoulder pain after stroke has been estimated at 54% (37). Bicipital tendonitis should be suspected particularly in hemiplegic patients with spasticity or movement synergies that result in overactivation of the biceps as elbow flexors or forearm supinators.

The diagnosis is suggested when there is greater tenderness to palpation of the long head of the biceps as it originates from the anterior glenoid labrum on the affected side compared to the unaffected side (144). Provocative maneuvers such as Yergason's test, which provokes pain at the biceps origin with resisted forearm supination, are useful when cognition and motor abilities are adequate. An examination under ultrasound may improve diagnostic ability, though sensitivity is only 49% (145). Injection of an anesthetic agent at the point that is most painful over the bicipital groove, often combined with a therapeutic steroid, can corroborate the diagnosis and provide treatment (146). As with all paratendon injections, care must be taken to avoid injecting steroid directly into the tendon because of the risk of rupture. Long-term benefit usually requires alleviation of the underlying biomechanical stresses through use of spasmolytic medications, botulinum toxin, chemical neurolysis, or (rarely) tendon release, depending on the clinical scenario.

Central Hypersensitivity

A more recent theory as to why there may be persistent pain in the shoulder of some stroke survivors is based on evidence implicating alteration in pain perception because of peripheral and central hypersensitivity (43,48,147). It is possible

that an injury at the paretic shoulder, whether from a fall, poor handling by caregivers, or repetitive microtrauma, results in an initial injury and acute pain, but maladaptive changes from central hypersensitivity may allow the pain to persist or worsen beyond the initial injury, even after the initial injury has healed (43,48,147). Central hypersensitivity is a change in the central nervous system that results in an enhancement in the function of neurons and circuits in nociceptive pathways. The manifestation of this plasticity of the somatosensory nervous system in response to inflammation and neural injury can lead to pain from innocuous stimulation or exaggerated perception of pain from low-level painful stimuli (148). One of the primary methods of demonstrating central hypersensitivity is through generalized hyperalgesia or a higher sensitivity to pain at unaffected tissues remote to the site of injury (149). In one study of stroke survivors with chronic shoulder pain compared to pain-free stroke survivors, a higher sensitivity to pain was found not only at the hemiparetic shoulder but also at the nonhemiparetic shoulder and leg, suggesting that a central process may affect the perception of pain over the whole body of those with chronic shoulder pain (47). Further evidence of a central hypersensitivity was shown in a comparison of somatosensory functioning between those with chronic shoulder pain after stroke, pain-free stroke survivors, and a healthy population in which greater allodynia to cold and sharpness were found when comparing ratios of affected to unaffected arms of those with hypersensitivity and pain-free stroke survivors (43,48).

Evidence of central hypersensitivity in those with shoulder pain after stroke suggests that new targets for treatment should be explored. Rather than attempting to design treatments addressing a painful response to a noxious stimulus, greater success might be achieved through addressing changes within the nervous system that result from central hypersensitivity. Electrical stimulation has been suggested as a neuromodulatory treatment for chronic shoulder pain after stroke, but no trials have confirmed the efficacy of this (95,100).

Spasticity

The principles of assessment and management of spasticity following stroke are presented in Chapter 29. The association between spasticity and hemiplegic shoulder pain has been recognized for some time (46). However, whether spasticity actually causes shoulder pain is uncertain. As noted earlier, spasticity can coexist with adhesive capsulitis, impingement syndrome, rotator cuff disease, bicipital tendonitis, and CRPS. Associated deleterious biomechanical effects on the glenohumeral joint may contribute to the pathogenesis of these conditions. Some also have postulated that spasticity, especially of the subscapularis and other internal rotators of the shoulder, directly causes pain by traction on the periosteum of the muscle insertion (150). Examination typically demonstrates hypertonia of the shoulder adductors, flexors, and internal rotators. Treatment intervention may include stretching, strengthening of antagonist muscles, and oral spasmolytics (151). However, there are no controlled trials to demonstrate the efficacy of these interventions in reducing hemiplegic shoulder pain.

Given the prominence of hypertonia of the shoulder internal rotators, adductors, and flexors, botulinum toxin injections to these muscles have received considerable attention. Yelnik and associates demonstrated the initial feasibility of botulinum toxin injection to the subscapularis in reducing hemiplegic shoulder pain (152). However, subsequent randomized clinical trials of botulinum toxin injections to subscapularis, pectoralis, and biceps muscles have yielded inconsistent results. Although some showed significant benefit (153–155), others did not (156–158). Quantitative reviews have also yielded inconsistent conclusions (159,160). Botulinum toxin injections may be beneficial for a select group of stroke patients with shoulder pain and hypertonia. However, because of the inconsistency in the literature, specific recommendations must await additional data from larger, well-defined clinical trials.

Contractures

As with all upper motor neuron syndromes, contractures are common complications after stroke. Spasticity, paralysis, and muscle imbalance can result in joint immobilization and fixed positioning of limbs. Prolonged joint immobilization results in collagen deposition and organization of fibrous structures in surrounding soft tissues, affecting muscle belly rather than tendon (161,162). Stiffness and loss of elasticity occur with associated shortening of soft tissues. Changes in the joint also take place. Animal and human studies have shown proliferation of intra-articular fibrofatty connective tissue, and adhesion formation between the fibrofatty connective tissue and cartilaginous surfaces also takes place after immobilization (163). The fibrous connective tissue capsule surrounding synovial joints undergoes compositional change that further affects biomechanics (163). The primary effect of these changes is an increase in resistance to stretch that is independent of muscle activity (164). A number of deleterious effects can result, including loss of functional movement, pain, interference with hygiene, and development of pressure sores (165). In general, the clinical goal is prevention of permanent muscle shortening or contracture, and is typically approached with passive and active range-of-motion work and treatment of spasticity. In some cases, reversal of contracture can be accomplished with surgical or nonsurgical interventions, but restoration of movement and function often is challenging and incomplete. As with all rehabilitation interventions, management must be considered within the context of functional restoration for the individual patient. It has been estimated that about half of stroke survivors will develop a contracture within six months, with the most commonly affected joints being the shoulder and hip (166). However, after stroke, contractures can involve any joint affected by spastic paralysis.

Prevention of contractures requires prompt initiation of daily management beginning 24 to 48 hours after stroke

onset. Spasticity evolves in the majority of hemiplegic patients within one week of stroke onset (55). Assessment of joint range also should be performed daily so that more aggressive treatment can be initiated if range of motion declines. Passive range-of-motion exercises, splinting, and positioning are the mainstays of contracture prevention. After stroke, voluntary and involuntary muscle activations generally are split into extensor or flexor synergy patterns. Preventative measures must consider these muscle synergies in assessing contracture risk for a given joint, and efforts should be apportioned according to risk. Joints should be moved through their complete range at least daily, and ideally several times daily. Adherence to a consistent regimen of aggressive stretching is thought to prevent contractures after stroke (167,168), although this is not supported in the literature (169,170). If pain occurs during passive range-of-motion exercise, analgesic medications should be given to minimize pain during exercise.

When impairment in range of motion occurs in the setting of associated spasticity, spasmolytic medications should be considered. The use of oral spasmolytics is common, but their effectiveness is limited by several factors. First, titration to the optimal dose can take time. Second, sedative side effects can limit use, particularly in the acute phase after stroke and in elderly patients. Temporary chemodenervation with short-acting local anesthetic agents has been advocated to facilitate passive range-of-motion exercises (171), but the need for repeated injections or multiple injections when several muscle groups require reduction of tone can be impractical. Focal chemodenervation using injected botulinum toxin may be a more practical approach. However, the potential effects of weakening voluntary muscle on motor recovery should be considered carefully. The major advantages of botulinum toxin are that individual muscles can be targeted, the effect lasts for about three months, and sensory innervation is not affected. The use of botulinum toxin has a significant role in promoting functional movement in the upper limb (see Chapter 29) and in preventing contractures and their sequelae in the upper limb. However, permanent neurolysis using phenol should be considered only after motor recovery has reached a plateau, when there is a very high level of confidence that paralyzing the muscle(s) will not have any negative consequences on functional movement at that time or in the future and that effects on sensation will not reduce function or increase the risk of pressure sores. That said, permanent neurolysis can be effective in improving hygiene, reducing the risk of pressure sores, and improving functional movement. Muscle groups innervated by a single nerve, such as the hip adductor group innervated by the obturator nerve, are particularly amenable to neurolysis. Obturator neurolysis most often is performed to improve perineal hygiene or to reduce pressure sores at the medial knee, but have also been used to improve gait by reducing scissoring. When innervation of target muscles cannot be isolated to a single nerve, or when the sensory component of the nerve should not be sacrificed, motor point blocks can be considered.

Splinting is commonly considered in joints that are at high risk for contracture or when passive range-of-motion exercises are insufficient to maintain range (172). Contractures of wrist and finger flexion and ankle plantar flexion are common. Thus, preventative splinting of these joints in neutral position has been recommended when abnormal muscle tone or movement synergies put them at risk. In spite of frequent use, a systematic review of upper-limb splinting after stroke and other brain injuries found that the use of splinting does not affect upper-limb disability, range of motion of the wrist or thumb, or pain (173). A randomized controlled trial of nighttime ankle splinting compared to the use of standing at a tilt-table for 30 minutes per day early in stroke rehabilitation also failed to show a difference in the splinted group and tilt-table group in contracture prevention (174). These findings call into question the current practice of splinting, yet technological advances and the shift in focus to considering function and activities in the design, prescription, and evaluation of splints in the context of rehabilitation programs may offer benefits in the future (175). One randomized pilot trial found that the combination of botulinum toxin injection and splinting might reduce contracture formation and facilitate maintenance of range of motion (176).

Surgery, in general, should be considered only when no further motor recovery is anticipated and after other less-invasive management options have failed. The preoperative objectives should be clear to the clinicians, caregivers, and patients and are broadly directed at improving function or reducing the risk of medical complications. The physiologic objective typically is restoration of muscle balance. Successful outcomes require close attention to rehabilitation management following surgery. Clinical benefits have been reported in nonrandomized clinical trials in stroke survivors for a number of procedures, including release or lengthening of tight adductor tendons for hip adduction contractures (177), selective release or fractional tendon lengthening for knee flexion contractures (167), Achilles tendon lengthening for ankle equinus deformities, split tibialis anterior tendon transfer combined with Achilles tendon lengthening for ankle equinovarus deformities (178), and capsular release plus resection of subscapularis and pectoralis tendons for shoulder capsulitis (179).

Arthralgia

Arthralgia is common in the general population and is the number one comorbidity for stroke survivors (180,181). The association of arthralgia related to stroke is complex. One prospective study identified the acute poststroke phase as a period of increased risk for acute arthritis, primarily associated with the paretic limbs (182). There is evidence for a higher prevalence of joint pain in community-dwelling adults with stroke than those without stroke (183). However, the relationship between arthralgia and pain resulting from the stroke is less clear. An increasing prevalence of new-onset joint pain was described at 3 months (7.4%) and at 6 months after stroke (11.7%) in one cohort study (23). Yet, a matched population

study found no difference in the poststroke development of pain from joints, other than shoulder pain, in stroke patients in 2 years following stroke and reference subjects (22.0% vs. 18.5%, $P = .14$) (20). One possible explanation for the lack of agreement is a variable expression of arthralgia that is influenced by severity of paralysis and age. Ascribing new joint symptoms to a stroke is difficult given the varying nature of joint pains relative to the paretic side. In stroke survivors who have paresis on one side, there is a greater likelihood of having joint pain on the affected side, yet estimates of having joint pain solely on that side limit it to 1.8% (23,183). A radiographic study of hands of paretic subjects and controls found that the severity of paralysis was correlated with the extent of osteoarthritic asymmetry between the paretic and unaffected sides. Interestingly, hemiparalysis reduced ipsilateral expression of osteoarthritis and increased expression of osteoarthritis in the unaffected hand (184). One reason for these findings may be the additional stresses put on the unaffected side by prolonged use of walking aids or the use of upper limbs during transfers (183). Similarly, the unaffected leg may experience more stress because of difficulty in normal foot placement in hemiparetic gait.

It is clear that the comorbid arthralgia has a detrimental effect on stroke survivors, regardless of whether it arises before or after the stroke. Stroke survivors with osteoarthritis have longer lengths of stay and lower functional gains in acute rehabilitation settings than those without osteoarthritis (185). Stroke survivors with comorbid osteoarthritis experience daily pain, frustration, and activity limitations that interfere with participation in prescribed therapies, thereby reducing the potential for recovery (28). Even after the acute period of recovery, arthralgia interferes with daily function, and the cumulative effect of having disability related both to stroke and arthralgias is greater than the sum of either one alone (183). It also appears that the pattern of arthralgia relative to hemiparesis is important. Having arthralgia opposite to a hemiparetic upper limb is much more disabling than having arthralgia in the hemiparetic upper limb. In contrast, having arthralgia in the hemiparetic lower limb is much more disabling than having it in the opposite limb (183). Such findings may be important in consideration of therapeutic plans, although this has not been studied. Providers should evaluate stroke survivors routinely for arthralgias, and provide treatment so that recovery and function can be maximized.

Heterotopic Ossification

HO is a pathological process by which lamellar bone is formed in soft tissues that do not typically ossify. It is often observed after surgery, neurological injury, burns, and trauma (186). The prevalence of HO in stroke is lower than that in spinal cord injury or traumatic brain injury, estimated to be 0.5% to 1.2% (187), and is not as well studied. Although uncommon in stroke, HO is a complication that can interfere with mobility and recovery in addition to the damage caused by the stroke, and should be considered in stroke survivors with unexplained joint immobility and pain (188,189). Early symptoms of HO may be mistaken for deep venous thrombosis, arthritis, cellulitis, or central pain (190–194). Awareness among providers who treat stroke survivors is necessary to allow early identification and the timely initiation of appropriate treatment.

Typical presenting signs and symptoms of HO include pain, skin erythema, fever, swelling around the affected joint, and gradual joint ankylosis (195). The primary complications are loss of function because of loss of joint mobility. Potentially, HO can occur in any soft tissue and around any joint. However, the joints most commonly involved are the hip, knee, and elbow, and the ossification tends to occur 4 to 12 weeks after the injury (186,195).

The etiopathogenesis of HO after neurologic injury is not known. The bone formation does not occur within the muscle, but rather in the para-articular connective tissue between muscle planes (194). It is thought that local inflammation may induce the formation of ectopic bone in those with spinal cord injury (196). The local inflammation causes release of prostaglandins that transform soft tissue mesenchyma into osteoblasts (197). The osteoblasts produce tropocollagen and alkaline phosphatase that are responsible for the formation of the bone matrix, calcium deposition, and mineralization of the bone matrix (197). The mineralized bone matrix has a histological appearance similar to that of the callus formation of healing bone (186). Although the exact mechanism is unclear, other important factors appear to be hypercalcemia, tissue hypoxia, changes in sympathetic nerve activity, immobilization, remobilization, and disequilibrium of parathyroid hormone and calcitonin (195).

Diagnosis of HO begins with identification of the clinical symptoms and signs. Often, because of the overlapping presentation with other complications such as deep venous thrombosis, multiple studies must be obtained to rule out other causes. Laboratory studies are limited in their ability to diagnose HO in the early stages. Alkaline phosphatase may show abnormally high levels in the presence of ectopic bone formation, but is not useful initially, as levels may not become elevated in the first two weeks of active ossification and may not peak until months after (198). If the ossification is limited in scope, alkaline phosphatase levels may not change at all. Nevertheless, the test is inexpensive and easily obtained and often used as a screening tool for HO. The association of prostaglandin production and HO has raised interest in the use of 24-h PGE_2 urinary excretion as a diagnostic tool, as a sudden increase may signify active ossification even before clinical symptoms arise (199). Unfortunately, serial testing is required to detect elevations, and the presence of seminal fluid or urinary tract infection may make interpretation unreliable. The 24-h PGE_2 urinary excretion also may be used to monitor treatment effectiveness, as there is a positive association between the magnitude of PGE_2 elevation and extent of active disease.

The triple-phase bone scintigraphy study is the most sensitive diagnostic imaging study for HO and also can be used to assess maturity of ossification and to monitor therapeutic effectiveness (186,195). The first two phases are indicative of

blood flow and pooling that are consistent with HO in about the second week. The third phase shows abnormality about a week later. Other imaging modalities, such as plain radiography, computed tomography, and magnetic resonance imaging are not as sensitive in detecting the early stages of HO and thus are not used as often for these purposes (186,195). Plain radiographs may not show abnormality until four to six weeks after ossification has been demonstrated on triple-phase bone scintigraphy. There is evidence that ultrasound may be useful for identifying HO earlier than radiographic appearance and with higher specificity than triple-phase bone scintigraphy (200,201). Ultrasound may be the test of choice, given its sensitivity and specificity for the early diagnosis of HO, and its concomitant use for evaluation of deep venous thrombosis.

In subjects with spinal cord injury, early prophylactic treatment with indomethacin 75 mg/day for 3 weeks resulted in a lower incidence of clinical, scintigraphic, or radiographic evidence of HO (25.0%) compared to those on placebo (64.7%) (202). Those receiving indomethacin also had later onset and lower severity of symptoms. Another study of rofecoxib compared to placebo also resulted in lower incidence of HO, but rofecoxib has been withdrawn from the market because of safety risks (203). Because of their deleterious side effects, nonsteroidal anti-inflammatory drugs are not recommended as prophylactic treatment for HO.

The use of bisphosphonates generally has been found to be effective in the treatment of HO in spinal cord injury (204–207). Successful treatment of HO with pharmaceuticals is dependent on the timing of initiation, although no randomized controlled trials have been completed. In a case series, subjects who had scintigraphically diagnosed HO received intravenous etidronate for three days, followed by six months of oral etidronate. In this case series, 78% of subjects who did not develop radiographic evidence of HO at baseline did not progress to radiographic HO. Of those who had both scintigraphically and radiographically evident HO at baseline, only 46% experienced a halting of progression (208). There also is evidence that oral etidronate is as effective as intravenous followed by oral etidronate (206), although the use of intravenous etidronate was associated with a lower severity of swelling.

Surgical excision is indicated in patients who have severe restriction in range of motion, intractable pain, or a risk of nerve or vessel involvement from HO (186,209). Studies in spinal cord and traumatic brain injuries have shown an improvement in range of motion and function following surgery, with those who had greater motor control having better outcomes (210,211). Recent studies have not shown a relationship between the extent and duration of HO, or severity of neurologic injury with recurrence rates (209,212,213). In those with established HO that causes severe functional loss or pain, surgical excision should now be considered sooner rather than later to allow greater chance for recovery.

SUMMARY

Musculoskeletal conditions are common complications in poststroke hemiplegia that have significant impact on functional recovery and quality of life. Mechanical abnormalities that underlie musculoskeletal complications always should be considered and corrected or mitigated when possible. Long-term outcomes often depend upon the degree to which biomechanical abnormalities can be addressed. Treatments that address acute as well as biomechanical issues potentially are most effective. The most common conditions include shoulder pain and contractures that can affect any joint affected by spastic paralysis. Of musculoskeletal complications after stroke, shoulder pain has been by far the most studied. Many types of shoulder pathology have been suggested as causes of shoulder pain in hemiplegia, including shoulder subluxation, capsulitis, tendinitis, rotator cuff injury, bursitis, impingement syndrome, spasticity, CRPS, and central hypersensitivity. Electrical stimulation for treating shoulder pain serves as an example of treatment in which sensory neuromodulation, reduction of subluxation, and promotion of motor recovery are potential benefits.

To allow stroke survivors to reach their full potential of recovery, providers need to be aware of the musculoskeletal complications and provide appropriate and timely treatment. Experienced clinicians recognize that numerous musculoskeletal complications can arise that are not discussed in this chapter or reported in the literature. In these cases, treatment should address acute issues as well as underlying causes.

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31

Depression and Other Neuropsychiatric Complications

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Stroke ushers in the potential for not only physical and cognitive impairments but also neuropsychiatric syndromes. They may arise immediately after stroke or develop later; they may dissipate, fully remit, or continue for many years. Depending on their nature and severity, stroke-related neuropsychiatric symptoms or syndromes increase suffering, promote disability, interfere with rehabilitation efforts, and cause family disruption. This chapter provides an overview of common and some rare neuropsychiatric syndromes after stroke and summarizes options for their treatment.

POSTSTROKE DEPRESSION

Epidemiology

Depression is the most common psychiatric syndrome after a stroke (1,2). Poststroke depression has been described by medical writers since the fifth century BC and likely even earlier. Poststroke depression received attention approximately 30 years ago with the work of investigators at Johns Hopkins University (3,4). Combined studies of 2178 patients hospitalized for acute stroke documented that 22% had major depression and 17% developed minor depression (5–7). In a sample of 80 patients admitted to an acute hospital unit (i.e., within a week of stroke), major depression occurred in 25% during the acute phase, 31% at 3 months, 16% at 1 year, 19% at 2 years, and 29% at 3 years after stroke (5). Kouwenhoven and colleagues' (8) review of hospitalized and community subjects found that the prevalence of depressive disorders ranges from 11% to 55% and that of depressive symptoms from 5% to 54%. However, precise prevalence rates are difficult to estimate because of a variety of factors, including what setting is used for patient recruitment, how depression is assessed, and who conducts the assessment. The poststroke depression literature often conflates depressive disorder and depressive symptoms (9). Only a few of the studies that used diagnostic criteria reported on the qualifications and training of the individuals making the assessment. Some studies made the diagnosis of major depression in the acute phase of stroke, disregarding the requirement of a two-week syndrome duration of the *Diagnostic and Statistical Manual of Mental Disorders*, fifth edition (*DSM-5*) (10) and the *International Statistical Classification of Diseases and Related Health Problems*, tenth revision (ICD-10) (8,11). Many studies have focused exclusively on depression after ischemic stroke samples (12). However, the overall prevalence rates of depression are similar in ischemic and hemorrhagic stroke patients (8). Likewise, prevalence rates were similar among patient settings (i.e., hospital, rehabilitation, and outpatient). Other issues that complicate the estimation of prevalence are the exclusion of individuals with severe aphasia, in whom assessment of depression is difficult, as well as the inconsistency in cut-off scores used on depression scales (1).

Diagnosis

The syndrome of depression consists of various physical, cognitive, emotional, and behavioral signs and symptoms. The *DSM-5* syndrome of depression is based on experience derived from psychiatric patients. The *DSM-5* criteria for an episode of major depression consist of nine symptoms: depressed mood, anhedonia, significant weight change, changes in sleep, psychomotor changes, fatigue, feelings of worthlessness or guilt, poor concentration or indecisiveness, and recurrent thoughts of death or suicide (10). At least five of these symptoms must be present for a two-week period, with at least one of the symptoms being depressed mood or anhedonia. Symptoms that do not meet full criteria for major depression are often considered minor depressive disorder (at least two, but less than five symptoms lasting more than two weeks). Robinson and Spalletta (1) advocated for major depressive disorder and minor depression as the two most appropriate ways to classify depressive symptoms following stroke. Beyond categorization of depression, assessment of an individual who has suffered a stroke is further complicated by the physical and cognitive sequelae of the brain lesion. Cohen-Cole and Stoudemire (13) outlined four approaches to the assessment of poststroke depression: inclusive (ruling in depressive symptoms regardless of whether they are related to medical illness), etiologic (ruling in those depressive symptoms that do not stem from

TABLE 31.1 Common Depression Screening Tools

Patient Health Questionnaire-2 items (PHQ-2) (20)
Patient Health Questionnaire-9 items (PHQ-9) (21)
Hospital Anxiety and Depression Scale (HADS) (22)
Beck Depression Inventory-II (BDI-II) (23)
Kessler Psychological Distress Scale-10 (24)

medical illness), substitutive (ruling in only psychological symptoms of depression), and exclusive (ruling in only the symptoms that are seen more in depressed patients than in those who are not depressed). Despite the concerns of stroke-related physical symptoms masquerading as depressive symptoms, the results of studies investigating the various types of depressive symptoms (e.g., somatic, cognitive, psychological) supported use of the inclusive approach for the assessment of poststroke depression and the use of *DSM* criteria without modification (14–17). Finally, a recent study found that some of the most common depression screening tools used (Table 31.1) performed favorably in identifying depression when compared to the structured clinical interview for *DSM-5* in stroke patients without severe aphasia (18). The Stroke Aphasic Depression Questionnaire (Hospital version) is an observational instrument with satisfactory psychometric properties and performance in identifying depression within the aphasic subgroup of stroke survivors (19).

Course of Depressive Disorders After Stroke

The timing of depression onset after stroke varies. It has been suggested that the risk of depression is similar during the early, middle, and late phases of recovery after stroke (2). However, several studies documented greatest risk for developing a depressive syndrome in the first month after stroke, with lower, but persistent, risk during the ensuing year (25–28). Robinson et al. (29) reported that approximately 34% of those who did not develop depression acutely after stroke went on to develop depression within a two-year period.

A high percentage of patients who develop depression soon after stroke improve during the next two years. Improvement of symptoms or remission from depressive disorder has been observed in 50% to 100% of samples (5,29–31), and spontaneous remission is more common in those with depression arising immediately after stroke (32). However, chronicity of depressive symptoms remains high in stroke survivors, especially in those whose symptoms emerged late in the acute phase or had minor depression early on (6,33–35). Findings from longitudinal studies paint a dual picture. Stroke survivors with early and more severe depressive symptoms may fare better as time goes on, whereas survivors with less severe early symptoms or who develop depression later on appear to have worse recovery (1).

RISK FACTORS

Several demographic and clinical characteristics increase the risk for depression after stroke. These include female gender (35–38), younger age (4,37), previous psychiatric illness (35–40), neuroticism (25), family history of psychiatric illness (41), greater disability (42,43), medical comorbidity (36), fatigue (44), and lower education and socioeconomic status (35,37,38). Asian stroke survivors may be at lower risk for poststroke depression than Caucasians (30,45).

There is debate as to whether the location of lesion increases the risk for poststroke depression. One analysis found no difference in the risk for depression for lesions in either hemisphere (9). However, another analysis found increased risk for those with left anterior lesions (7). Shorter distance of the left-hemispheric lesion's anterior perimeter from the frontal pole (46–48) as well as shorter time (i.e., first few months) from stroke are influential factors in the association between lesion location and depression (49,50). Other biological risk factors for depression after stroke include a history of previous stroke (35) and elevated serum leptin levels (51).

Relationship to Functional and Cognitive Impairment

A complex relationship exists between depression, functioning, and cognitive impairment after stroke. Impairment in activities of daily living (ADLs) is the single strongest correlate of depression after stroke (1,7). Specific physical problems are associated with depression after stroke, such as incontinence (42), ambulation (42,52), sleep apnea (53), stomach pain and physical discomfort (54). Depression can negatively impact the neurological recovery process (40,55,56). Depressed patients have greater impairment in ADLs at one-month follow-up than those who are not depressed (57) and less improvement in functional impairment at two-year follow-up, despite equivalent ADL impairment at baseline (58). Depression and functional dependence are associated with poor quality of life, social support, physical functioning, self-esteem, perceived control, and pessimism in stroke patients (59,60). History of depression prior to stroke is associated with increased risk of new stroke (61,62).

In studies including 17,934 stroke patients, depression was consistently associated with cognitive impairment, disability, and stroke severity (55). Patients with poststroke depression are more likely than nondepressed stroke patients to have impairments in executive functioning, problem solving, psychomotor speed, attention, and memory (63). Depression is also correlated with neglect and deficits in visual perception, abstract reasoning, and language (64). Severity of depression is associated with severity of cognitive impairment (65), especially in women who had psychiatric disorders prior to stroke (37). Depression was found to be a predictor of cognitive impairment after stroke (66) mainly in those with left-sided lesions (65,67–69). Aphasia has been linked to depression after stroke, but the evidence is mixed, as many studies on poststroke depression exclude aphasic patients (12). In those

studies that do include patients with aphasia, the prevalence of depression was not significantly influenced by aphasia (8).

Poststroke depression increases mortality. Patients who were depressed during the first month after stroke had greater risk of mortality at one-year follow-up than patients who did not become depressed after stroke (31,42). The mortality risk of patients with poststroke depression remained greater at follow-up assessments of 2 years (42), 8 years (70), and 10 years (71).

Mechanisms

Both biological and psychological explanations for the development and persistence of poststroke depression have been proposed (72). One biological mechanism implicates disruption of ascending norepinephrine fibers and was based on the early observation that stroke of the left frontal pole or left basal ganglia posed the highest risk for depression (48,63,68,73–77). However, the original findings have not been consistently replicated (6,9,49,64). A related biological mechanism postulates decreased production of norepinephrine and serotonin as a result of lesions involving the transmission of biogenic amines in axons projecting through the basal ganglia (78). This view has been supported by studies documenting a reduction of the cerebrospinal fluid serotonin metabolite 5-hydroxy-indoloacetic acid (5-HIAA) in poststroke depression (79,80).

Inflammatory responses may also contribute to poststroke depression. Increased levels of cytokines, including interleukins IL-1, IL-6 (81–85), IL-18 (86), and tumor necrosis factor-alpha (TNF-alpha) (87,88) have been reported after stroke. Heightened inflammatory response activates the enzyme indoleamine 2,3-dioxygenase, leading to decreased serotonin. High levels of leptin may contribute to poststroke depression, either independently or as part of the poststroke inflammatory response (51). Stroke patients homozygous for the short allele of the serotonin transporter 5-HTTLPR are more likely to develop poststroke depression than those with at least one long allele (89). Individuals with short 5-HTTLPR alleles may thus have decreased 5-HT uptake and be more vulnerable to poststroke stress.

Conflicting results related to these biological hypotheses have led others to propose a psychosocial mechanism for poststroke depression (90,91). This hypothesis postulates a link between severity of disability (55,92,93), psychosocial risk factors (35,37,38,94), and poststroke depression. More research is needed to better understand the specific mechanisms of poststroke depression and their potential interplay.

We proposed a conceptual model that integrates biological and psychosocial contributors to poststroke depression (95,96). According to this model, stroke increases vulnerability to depression by compromising frontolimbic circuitry (1) and by initiating inflammatory (72,97) and resculpting (98) brain responses. The "psychosocial storm" to which the stroke patient is exposed magnifies these events by increasing inflammatory responses, producing reactive oxygen species, interfering with dendrite remodeling and neurogenesis, and disrupting functional connectivity (99–113). The "psychosocial storm" originates both from the patient's sudden disability and the resulting change in the patient's needs and family life. The "storm" can be conceptualized as a result of the interaction between the severity of the patient's clinical state and the strengths of the environment in which the patient lives. The patient becomes deskilled by the abrupt loss of strength, coordination, language, executive functions, behavioral disorganization, lack of motivation, fear for his or her life, and hopelessness caused by stroke and poststroke depression, as well as by the tasks of a demanding rehabilitation. These factors, combined with lack of readiness, often lead to a feeling of incompetence and helplessness, which fuel the experience of stress and promote depression (114–116). The family of the stroke survivor experiences a similar upheaval. The usual family goals and tasks are now anachronistic. The family needs to reengineer itself and learn how to meet new demands of the disabled stroke victim. Family members need to assist the patient both with daily routine and by coordinating and facilitating (e.g., driving, waiting) physical, occupational, and speech therapies. Family plays a role even when they do not live with the depressed stroke patient (e.g., coordination of caregivers, finances, relocation). The pessimism and resignation of the poststroke depressed patient often contaminates those expected to help and in turn can immobilize them. Without guidance, even the most committed family members may not be able to be of effective help, and may even become a hindrance. Finally, physical, occupational, and speech therapists need to understand the psychosocial context of the poststroke depressed patient and his or her "ecosystem" and coordinate their interventions (e.g., dose, timing, barriers) so that they are not excessively demanding and disorienting to patients and families. These problems must be addressed early after the onset of stroke because there is a time window in which neural repair is most active and in which interventions can be highly effective (117–120).

Treatment

A recent review by Robinson and Spalletta (1) suggested that antidepressant medications are effective in poststroke depression. In addition to reducing depressive symptoms, antidepressants may reduce mortality (121), motor impairment (122), and disability (123). The effect on disability was independent of the effect of antidepressants on depressive symptoms (124). Use of antidepressants early after stroke was associated with gradual improvement of disability over 2 years, whereas late treatment did not prevent gradual deterioration revealed by 12- and 24-month follow-up (125). However, a Cochrane meta-analysis showed an unclear benefit of antidepressants in poststroke depression (126). Likewise, whereas a study showed that escitalopram may even prevent development of poststroke depression (127), a Cochrane review of 10 medication trials showed unclear benefit for prevention of poststroke depression (128). Moreover,

use of antidepressants may itself increase the risk of ischemic and hemorrhagic stroke (129).

Electroconvulsive therapy has been used clinically to treat poststroke depression, although there are no randomized controlled trials (130,131). Transcranial magnetic stimulation (TMS) decreased depression in stroke survivors with treatment-refractory poststroke depression in a preliminary study with sham control (132). Another preliminary study found improved depression scores in stroke survivors given high-frequency TMS compared to those given low-frequency TMS or sham control (133).

Psychosocial interventions for poststroke depression have received much less attention than pharmacotherapy. A 2008 Cochrane review identified only four randomized controlled trials of psychotherapy (126). One employed pragmatic counseling by a social worker (134), another used cognitive behavioral therapy (135), the third used motivational interviewing (136), and the fourth used supportive psychoeducation (137). In three of these studies, the control group was usual care and one (135) used both usual care and attention-control comparison groups.

Although the interventions showed some advantage over the comparison conditions, the effect size was small (126). More recently, a study of a combination of antidepressant (recommendations of sertraline were made, but the patient's own physician chose what to administer) plus a psychosocial/behavioral intervention resulted in higher remission rates than usual care at the end of the intervention and at 12-month follow-up (138). Problem-solving therapy may be more effective than placebo in preventing the development of depression in nondepressed stroke patients, but this effect was not significant in intention-to-treat analysis (127). However, the Cochrane review concluded that there was a significant but small treatment effect for preventing depression based on four psychotherapy interventions (128). Two of the four psychotherapy studies included used problem solving (139,140), one used motivational interviewing (136), and the other involved active management by interventionists of patient psychosocial stressors (141).

A meta-analysis of rehabilitation interventions showed that exercise-based interventions significantly decreased poststroke depression (142). Studies involving cognitive behavioral therapy (143) and family involvement (144) in the treatment of poststroke depression are underway. Other approaches include motivational interviewing, grief resolution, selective optimization with compensation, cognitive deficits adaptations, and executive skills training to augment traditional cognitive behavioral therapy (145).

Alexopoulos and colleagues (95) recently developed an "ecosystem focused therapy" that targets the psychosocial storm originating from the patient's disability, the resulting changes in the patient's needs and family life, and the biological burden involved in this cascade of depressogenic events (Figure 31.1). This individually tailored,

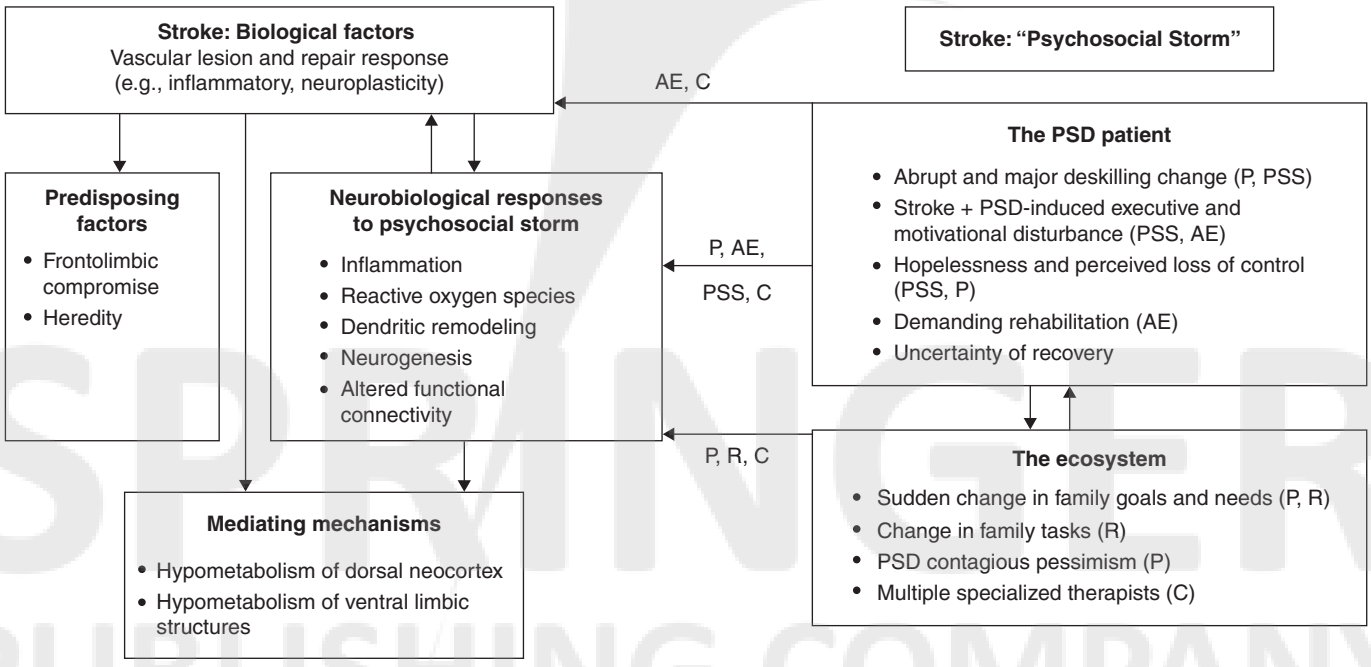

FIGURE 31.1 Integrative model of poststroke depression.

Abbreviations: EFT components targeting contributors to PSD: AE, adherence enhancement structure; C, coordination of care with specialized therapists; P, new perspective; PSS, problem-solving structure; R, reengineering family goals, involvement, and plans.

comprehensive psychotherapeutic approach focuses on development of a new and adaptive perspective of functioning; rehabilitation adherence enhancement; problem solving for behavioral activation; adjustment of family goals, involvement, and plans; and coordination of care with specialized therapists (95). A preliminary study of ecosystem-focused therapy yielded encouraging results (95), and a randomized controlled trial is under way.

POSTSTROKE APATHY

Definition and Epidemiology

Apathy has been defined in varied ways over the centuries, beginning with the Greek philosophic understanding of being free from passions or excessive emotions. In modern times, current diagnostic systems do not include apathy as a separate syndrome, nor is it defined (ICD; *DSM*). The major feature of apathy is "loss of motivation not attributable to emotional distress, intellectual impairment, or diminished level of consciousness" (146), which in turn affects emotional, cognitive, and behavioral functions. Accordingly, there is reduction in goal-directed cognition (e.g., reduced interest in learning and experiencing new things, unconcern with personal problems), goal-directed behavior (e.g., reduced effort, energy, and independence in performing daily activities), and related emotion (e.g., reduced responsiveness to desirable or undesirable events) (147). A European task force elaborated upon these criteria and formally proposed their use (148) (Table 31.2). Although apathy is often part of a depressive illness, apathy can be a stand-alone syndrome and, after stroke, may occur either together with depression or independently (149,150). Apathy is also differentiated from abulia, akinesia, akinetic mutism, dementia, delirium, despair, and demoralization (151). Assessment tools used to measure apathy are the Apathy Evaluation Scale (152), six subset items from the Williams Brain Impairment Behavior Scale (153,154), and the apathy subscale of the Neuropsychiatric Inventory (155). The prevalence of poststroke apathy has been estimated to range between 19% and 55% (156) and, when narrow definitions are used, between 20% and 25% (157).

Clinical Outcome and Correlates

Poststroke apathy is associated with advanced age (158–160), medical comorbidity (156), functional dependency (156,158, 161), and cognitive impairment (156,158–160). Poorer performance in attention and speed of information processing tasks is often accompanied by apathy (158). Lesions located in the posterior limb of the internal capsule (160) and bilateral basal ganglia have been associated with apathy (162), but disagreement exists (158,163). One study indicated a trend for right-sided and right fronto-subcortical circuit hyperintensity scores to be elevated (158).

The onset and course of apathy after stroke vary. Stroke patients were 3 times as likely to develop apathy 6 months and 12 months after stroke as they were at 2 months after stroke (163). Apathy and depression, initially independent at 3 months after stroke, became increasingly comorbid at 15-month follow-up (164). This same study found that dementia at initial assessment after stroke was often followed by development of apathy and depression. Poststroke apathy is a predictor of poor recovery from stroke. Patients with higher apathy had less functional improvement after three months of rehabilitation (159). Mayo and colleagues (156) identified five distinct trajectories of apathy in stroke survivors measured at four time points over the course of a

TABLE 31.2 Proposed Diagnostic Criteria for Apathy in Neuropsychiatric Disorders

For a diagnosis of apathy, the patient should meet criteria A, B, C, and D

A: Loss of or diminished motivation in comparison to the patient's previous level of functioning, not consistent with age or culture. These changes in motivation may be reported by the patient or observed by others.

B: Presence of at least one symptom in at least two of the three following domains for a period of at least four weeks and present most of the time:
- **Domain B1:** Loss of, or diminished, goal-directed behavior as evidenced by at least one of the following:
  - –Loss of self-initiated behavior
  - –Loss of environment-stimulated behavior
- **Domain B2:** Loss of, or diminished, goal-directed cognitive activity as evidenced by at least one of the following:
  - –Loss of spontaneous ideas and curiosity for routine and new events
  - –Loss of environment-stimulated ideas and curiosity for routine and new events
- **Domain B3:** Loss of, or diminished, emotion as evidenced by at least one of the following:
  - –Loss of spontaneous emotion, observed or self-reported
  - –Loss of emotional responsiveness to positive or negative stimuli or events

C: These symptoms (A–B) cause clinically significant impairment in personal, social, occupational, or other important areas of functioning.

D: The symptoms (A–B) are not exclusively explained by or the result of physical disabilities, motor disabilities, diminished level of consciousness, or direct physiological effects of a substance.

Source: Adapted from Ref. (148). Robert P, Onyike CU, Leentjens AFG, et al. Proposed diagnostic criteria for apathy in Alzheimer's disease and other neuropsychiatric disorders. *Eur Psychiatry*. 2009;24:98–104.

year. Whereas half of the sample experienced consistently low apathy and 33% experienced consistent minor levels of apathy, 3% suffered from high apathy throughout the study whereas 7% had worsening apathy and an additional 7% had an improving apathy trajectory. Greater apathy, regardless of trajectory, was associated with poorer physical function, physical health, participation in treatment, and health perception (156).

Mechanisms and Treatment

Lesion location influences the comorbidity of apathy and depression after stroke. Patients with right hemisphere stroke had similar levels of apathy and depression, but apathy and depression scores were not correlated. Low apathy and high depression scores were reported in left hemisphere stroke (165). No correlation was found between apathy and depression in a study of patients with five neurodegenerative disorders using the Neuropsychiatric Inventory, whose depression subscale does not include apathy items (166). In stroke and traumatic brain injury, right-sided lesions led to greater apathy than left-sided lesions (167). Overall, an average of 61% of patients with focal frontal lobe lesions had apathy, whereas apathy was identified in 40% of patients with basal ganglia lesions (168–170). Among those with subcortical lesions, damage of the caudate nucleus, globus pallidus, and mediodorsal thalamic nuclei were most frequently associated with apathy. Taken together, these studies suggest that the anterior cingulate cortex, frontal cortex, and ventral striatum are the locations most likely to lead to poststroke apathy.

Few studies have been conducted on the treatment of poststroke apathy unrelated to depression. Anecdotal evidence, primarily case reports, suggests that stimulants (171), amantadine (172), selegiline (173), and methylphenidate (174) may be beneficial. A preliminary study suggested that some cholinesterase inhibitors may help behavioral disability and apathy of stroke patients (175). Nefiracetam, an agent acting on GABAergic, cholinergic, and monoaminergic systems, improved apathy in patients with poststroke depression when used at the high dose of 900 mg/day (157,176).

ANOSOGNOSIA FOR HEMIPLEGIA

Definition

Anosognosia was originally defined by Babinski (177) as lack of awareness of a motoric impairment after stroke. Since then, the definition of anosognosia has expanded, and its current definition encompasses lack of awareness of a variety of functions or dysfunctions. Clinical presentations of anosognosia include inability to recognize one's limb as one's own (asomatognosia), thinking that one's limb belongs to another person (somatoparaphrenia), feeling that the affected limb moves on its own (kinesthetic hallucination), feeling that there is a strange, functional limb (phantom supernumerary limb), giving the limb a name (personification), feeling that the limb is odd (strange feelings), indifference toward the limb (anosoadiaphoria), and negative feelings toward the limb (misoplegia) (178). Anosognosia can be implicit or explicit. For example, patients with implicit anosognosia may be able to verbally acknowledge a deficit but act in a way that does not consider the deficit, such as trying to use an affected arm. In explicit anosognosia, patients may insist that nothing is wrong with their affected side but act in accordance with the paralysis, for example, using a one-handed strategy for tasks typically requiring two hands. The severity of anosognosia ranges from mild to severe and may consist of unawareness of all or part of one's deficits (179). There is some overlap between neglect and anosognosia. *Neglect* refers to inattention to contralesional space, whereas *anosognosia* is unawareness of contralesional paralysis (179). Berti and colleagues (180) suggested that the frequent co-occurrence of neglect and anosognosia is due to involvement of common cortical areas.

Epidemiology and Course

The incidence of anosognosia after stroke varies. A meta-analysis documented that anosognosia occurs in 32.3% of stroke patients (181), whereas other reviews found ranges of 8% to 27% (182) and 7% to 77% (183). The wide range in the incidence of anosognosia has been attributed to differences in the definition of anosognosia across studies. Other causes of the wide range of estimates are differences in patient samples, including difference in time of assessment after stroke, severity of stroke, location of stroke, catchment area, and so on (183). Inclusion of mild anosognosia may lead to inflated estimates. Approximately 60% of patients who did not spontaneously report their hemiparesis readily acknowledged it when asked directly about limb strength (184). Moderate and severe anosognosia had an incidence of 10% (184).

Anosognosia declines over time. One study of right hemisphere stroke patients showed that 32% of patients presented anosognosia during the first 3 days after stroke, 18% after 1 week, and 5% after 6 months (185). However, the decline in anosognosia may have been due in part to practice effects resulting from repeated assessments (186). Other studies also showed that remission of anosognosia occurs in the majority of cases within three months after stroke (178).

Patients with proprioceptive loss, visuospatial neglect, disorientation, and hemianopia during the acute phase of stroke are likely to have anosognosia (187). Chronic anosognosia is usually part of a behavioral syndrome including visuospatial neglect, as well as memory and temporospatial orientation deficits.

It remains unclear whether anosognosia is a predictor of functional outcomes after stroke. One study found no association of anosognosia with rehabilitation outcomes (188), whereas others showed that neglect, rather than anosognosia, contributes to worse outcomes (189,190). Nevertheless, anosognosia for left hemiplegia was correlated with worse motor function (189,191). Early, reversible anosognosia (i.e., within three months after stroke) predicted low functional recovery at one-year follow-up (192).

TABLE 31.3 Common Clinical Interview Measures Used in Diagnosing Anosognosia

Anosognosia Questionnaire (178)	General questions assessing anosognosia itself and 8 anosognosic phenomena
Bisiach Scale (196)	4-point response scale; similar questions to the Anosognosia Questionnaire
Anosognosia for Hemiplegia Questionnaire (197)	10 items; 3-point response scale
Structured Awareness Interview (198)	8 items
Berti et al. assessment (199)	Incorporates both implicit and explicit awareness items (rated on 3-point and 10-point response scale, respectively)
Experimental Bimanual Task (200)	Distinguishes implicit awareness; 8 tasks; patient allowed 3 attempts each; 4-point rating scale of each task

Diagnosis

Traditionally, anosognosia is identified through clinical examination. Various instruments have been developed to capture the heterogeneous nature of anosognosia (Table 31.3). There are other assessments, such as the Visual-Analogue Test for Anosognosia for motor deficit (193) and the Patient Competency Rating Scale (194), that use discrepancy scores between patient self-ratings and caregiver ratings. The Awareness Interview (195) incorporates the discrepancy between patient's self-ratings of abilities with neurological and neuropsychological performance measures.

Mechanisms

Various stroke-induced lesions may result in anosognosia. Right-sided lesions have been implicated, including lesions in the somatosensory cortex, motor and premotor cortices (180), insula (180,201), and frontotemporal cortex (202). A meta-analysis showed that the most common regions associated with anosognosia are in the frontoparietal cortex, basal ganglia, and thalamus of the right hemisphere (181). Chronicity of anosognosia has been correlated with severity of damage to right-sided frontoparietal cortical or subcortical areas (203). Nonetheless, bilateral lesions and left-sided cortical and subcortical lesions also can produce anosognosia (202). However, aphasia resulting from left-sided lesions may interfere with the detection of anosognosia. Damage to the insula (particularly its anterior part) and adjacent subcortical structures was associated with anosognosia for hemiplegia immediately after stroke. Additional lesions in the premotor cortex, cingulate gyrus, parietotemporal junction, hippocampus, and amygdala were associated with the persistence of anosognosia for hemiplegia into the subacute phase (185).

Anosognosia may be caused by disturbances in a variety of complex emotional and cognitive processes (183,187,204). Anosognosia may stem from avoidance of emotional focus toward the physical impairment (205) resulting from damage to brain areas governing affective drive or emotional arousal. This breakdown in arousal prevents the identification of and adjustment to a new impairment (206). Impairment in monitoring systems has been proposed as a mechanism for anosognosia, including disruption of sensory feedback systems involving the motor impairment (207), or inactivation of the monitoring system that coordinates intention to move with actual movement (208). However, not all studies have supported these hypotheses (196,209,210). Others argued that anosognosia results from inability of the right hemisphere to monitor and check confabulations and denial emanating from the left hemisphere (211).

However, this explanation cannot account for anosognosia in those with left-sided lesions. Another theory implicates a disturbance in space-for-action representations that limits the spatial input to the motor monitoring system in stroke patients with damage to the parietal lobe (181). The association of anosognosia with advanced age, greater severity of stroke, and presence of dementia prior to stroke suggests that anosognosia is facilitated by impairment in multiple brain systems (190).

Treatment

There is no definitive treatment for anosognosia (179). Guidelines for the clinical assessment and management of anosognosia have been developed and consist of: (a) assessment of the extent of unawareness, type of coping methods, chronicity, and associated neurological and neuropsychological disturbances; (b) establishment of therapeutic alliance with patient and family; (c) development of an individualized rehabilitation plan; (d) assistance with patient development of interest in their own rehabilitation; and (e) continuation of a training program for as long as improvement is possible (212). Techniques for working with anosognosia patients can include video feedback, mirror therapy, and mental rehearsal, in addition to traditional physical and occupational therapies (179,213). A secondary data analysis showed that antidepressants prevented worsening of anosognosia more effectively than placebo (214).

OTHER NEUROPSYCHIATRIC COMPLICATIONS

Anxiety

Anxiety has been studied considerably less than depression in stroke survivors. Often anxiety and depression are comorbid in the immediate months after stroke, with generalized anxiety disorder (GAD) and depression joint prevalence rates of

TABLE 31.4 Results of Aström Study of Generalized Anxiety Disorder (GAD) Comorbidity in Stroke Survivors

		GAD	
	GAD PRESENT (% OF TOTAL SAMPLE)	COMORBID WITH DEPRESSION (% OF TOTAL SAMPLE)	GAD ALONE (% OF TOTAL SAMPLE)
3 months	31%	21%	10%
1 year	24%	14%	11%
2 years	25%	14%	11%
3 years	19%	15%	4%

15% to 27% (215–218), whereas GAD without depression had a prevalence of 6% to 13% (215,217,218). One study found that 5% of men and 19% of women had an anxiety disorder at four months after stroke, with agoraphobia being most common (4% men, 17% women) and the rest developing GAD (219). Anxiety, once developed, tends to persist long after stroke. Using the Hospital Anxiety and Depression Scale in stroke patients 2 to 5 years after stroke, 19% had anxiety symptoms, 11% had depressive symptoms, and 17% had both (220). Aström (215) followed patients for five years using *DSM* criteria and found significant comorbidity of GAD and depression in stroke survivors (Table 31.4). The presence of anxiety disorder can negatively impact the outcome of co-occurring depression and recovery of function after stroke (215,221). Mortality was significantly greater for those with comorbid anxiety and depression at four months than for those with anxiety alone at one year after stroke (219).

In addition to depression, other correlates of anxiety after stroke are poor psychosocial functioning, anterior circulation lesions, history of migraine, and history of insomnia (216). At multiple follow-up times over three years, stroke survivors with GAD had decreased social networks and increased dependence in ADLs compared to those without GAD (215). In the acute phase, anxiety by itself was related to right hemisphere lesions, whereas anxiety comorbid with depression was associated with left cortical lesions (215,218). GAD in particular was associated with posterior lesions, whereas subthreshhold worry was associated with anterior lesions (218). Three years after stroke, comorbid depression and GAD were correlated with cerebral atrophy, as was GAD with subcortical atrophy, compared to those without GAD (215).

A recent Cochrane review identified only two treatment trials for poststroke anxiety and both targeted anxiety comorbid with depression (222). Both trials involved psychopharmacological treatments and neither used a placebo control. One study measured anxiety with the Hamilton Anxiety Scale (HAS) (223) at baseline and at six-week follow-up among three treatment groups: paroxetine alone, paroxetine plus psychotherapy, and "usual care" (224). Both the paroxetine and paroxetine plus psychotherapy groups had significantly reduced mean HAS scores at follow-up compared with the "usual care" group. The second study compared buspirone hydrochloride with "usual care" and showed a significant reduction in HAS scores for the buspirone group at one month follow-up (225). Clearly, there is need for placebo controlled studies of treatment of poststroke anxiety, with or without depression. Psychotherapy studies are also needed regarding poststroke anxiety. Cognitive behavioral interventions theoretically would be well suited to treat anxiety in the poststroke context, and at least one such study is underway (143).

Involuntary Emotional Expression Disorder

Involuntary emotional expression disorder (IEED) occurs in populations with structural brain damage such as stroke, traumatic brain injury, and dementia. Previously known as pseudobulbar affect, IEED involves uncontrollable and excessive laughing and/or crying (226) that may be inappropriate and incongruent with mood (227). Episodes of emotional expression can be quite brief (a few seconds) or last a few minutes (228). Prevalence estimates in stroke survivors range widely between 4.3% (229) and 52% (230). Scales used to assess IEED include the Affective Lability Scale (231), the Pathological Laughing and Crying Scale (232), and the Center for Neurologic Study—Lability Scale (233); differing scales and cut-off scores have contributed to the variability in prevalence estimates (229). The mechanism of IEED is unclear, although one long-standing hypothesis involves the disinhibition of a fasciorespiratory control center in the brainstem, leading to expression of affect that is desynchronized from emotion (234). Another hypothesis implicates the cerebellum in a disconnection of perceived emotion and displayed emotion (235). Patients with frontal or temporal lesions, regardless of hemisphere, more often had IEED than patients with lesions located elsewhere (236). Bilateral lesions of the pons were also associated with IEED (237).

Tricyclic antidepressants and selective serotonin reuptake inhibitors are commonly used to treat IEED (228). In stroke survivors, citalopram (237), nortriptyline (232), fluoxetine (238), and sertraline (238) were more effective than placebo at treating symptoms of IEED. A treatment for IEED recently approved by the FDA is a combination of dextromethorphan 20 mg and quinidine 10 mg, based on studies of individuals with multiple sclerosis and amyotrophic lateral sclerosis (239–241). Dextromethorphan is the pharmacologically active ingredient that acts on the central nervous system, whereas quinidine sulfate is an inhibitor of CYP2D6-dependent oxidative

metabolism of dextromethorphan used to increase the systemic bioavailability of dextromethorphan. Dextromethorphan inhibits glutamate at the NMDA receptor site by acting as a weak, noncompetitive NMDA receptor antagonist and blocking glutamate-mediated calcium influx through the channel. In addition, dextromethorphan is an agonist of the sigma-1 receptor and may indirectly modulate NMDA-induced neuronal activation and inhibit presynaptic release of glutamate.

Mania

Poststroke mania is uncommon. In a recent review of 50 years of literature on poststroke sequelae, mania was noted in only 74 adult stroke survivors (242). Manic symptoms secondary to stroke were described by Krauthammer and Klerman (243) and are similar to those of primary mania; they include euphoric or elevated mood, pressured speech, racing thoughts, grandiosity, and decreased need for sleep (244–248). The emergence of manic symptoms ranged from immediately after stroke to two years after stroke (249). Poststroke mania was more likely to be found in patients with right hemisphere lesion, in male patients, and in those with at least one vascular risk factor (242). Neither personal nor family history of psychiatric disorder was associated with mania after stroke (242). Genetic vulnerability and subcortical atrophy have also been proposed to contribute to poststroke mania (250,251), but disagreement exists (242). Right hemispheric lesions affecting the ventral limbic circuit, especially the orbitofrontal and basotemporal cortices, dorsomedial thalamic nucleus, and head of the caudate nucleus have also been implicated (245,250,252–254).

There are no randomized controlled treatment studies of poststroke mania. Clinical reports suggest that lithium (245,255), clonidine (256), olanzapine (252), and valproic acid (257) can be helpful. Lithium treatment in secondary mania may be limited by adverse effects, and anticonvulsant medications, such as divalproex sodium, may be better tolerated in this population (258).

Psychosis

Poststroke psychosis with hallucinations and delusions is rare. In a study of 1191 stroke survivors followed for 9 years, only 5 patients had psychotic symptoms (259). Patients with psychotic symptoms were more likely to have right frontoparietal lesions and greater subcortical atrophy compared to patients without psychotic symptoms. Delusions after stroke were most common in nursing home residents with right hemisphere strokes (260). Another study reported on 8 patients with right temporo-parieto-occipital stroke who developed new psychotic symptoms up to 11 years following their strokes (261). The majority of these patients experienced seizures around the time of psychotic symptoms and anticonvulsants ameliorated these symptoms. Epilepsy should be ruled out as a cause of poststroke psychotic symptoms (262). Treatment of psychosis after stroke includes both typical and atypical antipsychotic drugs. The latter may be preferred for their tolerability and better side-effect profile, although they themselves potentially increase risk for stroke (263). As noted earlier, anticonvulsants may also be useful (261).

Aggression

Anger and aggressive behavior are seen frequently in stroke survivors. Milder forms of aggression occur in 17% to 35% of stroke patients (264–267); more intense anger and aggression are less common, with prevalence estimates between 5% and 13% (267,268). Anger and aggressive behavior have been associated with greater cognitive impairment in stroke patients (69,260,265,268) and with left hemisphere lesions (260,268). Aggression has been associated with frontal lesions (265,268), specifically in the fronto-lenticulocapsular-pontine base areas (266). Santos and colleagues proposed four potential contributing factors to poststroke anger and aggression: lesion location, reaction to having to cope with stroke, premorbid personality aggressive traits, and reaction to a perceived hostile environment (267). Comorbidity of aggression with depression and anxiety has been noted (265). Implicated in both aggression and depression is a decreased cerebrospinal fluid (CSF) level of the serotonin metabolite 5-HIAA (269,270). This view has led to the use of antidepressants in the treatment of aggression co-occurring with depression. Aggressive patients who were depressed and were randomized to treatment with either nortriptyline or fluoxetine, and whose depression responded to medication, showed improvement in aggression compared to those on placebo or whose depression did not respond to antidepressants (265). Another study of fluoxetine versus placebo found that poststroke anger was significantly improved in those treated with fluoxetine for three months and that improvement was maintained for an additional three months (271). Effective treatments for aggression are crucial for the stroke survivor's rehabilitation (272,273).

CONCLUSION

Neuropsychiatric syndromes are common after stroke. They complicate behavioral management, impair the quality of life for stroke victims and their families, and interfere with rehabilitation. For this reason, the clinical examination of stroke patients should focus on behavioral abnormalities as well as neurological deficits. Although no definitive syndrome-lesion relationships have been identified, characterizing the presentation of poststroke neuropsychiatric syndromes can guide pharmacotherapy and behavioral interventions. In depression, the most common neuropsychiatric syndrome occurring after stroke, antidepressants may reduce depressive symptoms, motor impairment, disability, and even mortality. Similarly, use of serotonin antidepressants may ameliorate poststroke anxiety syndrome. Behavioral interventions offering support, guidance, and coping mechanisms to stroke patients and their families can be of great value both in alleviating depression and anxiety and in increasing participation in rehabilitation.

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32

Fatigue After Stroke

Kathleen Michael

Though implicated as a major disabling symptom in several chronic neurological conditions (1,2), fatigue remains poorly understood in individuals with stroke (3–6). We know little about the characteristics and mechanisms underlying poststroke fatigue, and even less about the effects of fatigue on activity behaviors, social engagement, and function in everyday life (4). For many individuals with stroke, fatigue ranks among their most distressing and function-limiting symptoms (3,6), yet we have seldom evaluated it, nor have we developed effective evidence-based treatments. The frequency, severity, and significance of poststroke fatigue are strongly evident in current scientific literature, signaling a call to action to develop effective medical and rehabilitation interventions to reduce the impact of fatigue on the function, independence, and quality of life of individuals living with stroke.

In this chapter, we describe what is currently known about fatigue after stroke. We develop a working definition and discuss some theories and identify some potential mechanisms that may account for poststroke fatigue. We characterize physiologic and biochemical dimensions, work performance and behavioral components, and symptom–sensory elements. We identify predisposing factors and outline the assessment of fatigue in individuals with stroke, along with proposed management strategies to reduce symptom distress and promote function and well-being. Finally, we suggest research directions to further develop knowledge about the mechanisms and features of poststroke fatigue that may lead to effective rehabilitation interventions to reduce its impact.

FATIGUE AFTER STROKE

Clinical experience and an emerging body of research point to the high prevalence and negative impact of fatigue in the stroke population. A substantial proportion of individuals with stroke report significant and persistent fatigue affecting their daily lives (3,4,6). There are many issues unique to stroke that might account for the pervasiveness of fatigue in this population. First, there is the direct damage to brain tissue, sometimes implicated in disruption of attention and sleep–wake patterns, as well as inducing feelings of generalized fatigue. Second, fatigue may be linked with other consequences of stroke, such as depression (2,6–8), or with other underlying disease states (3,9). Further, alterations of energy expenditure associated with hemiparetic gait also may contribute to fatigue (10), as may inactivity-induced cardiovascular and metabolic deconditioning (11). The association of sleep-disordered breathing and stroke risk is well established (12–14), and the persistence of sleep disturbances after stroke may further contribute to subjective symptoms of fatigue. Deficits associated with stroke may impose limitations on social function and self-efficacy and may contribute to isolation and the subjective experience of fatigue (10).

However, these physical and psychosocial associations with fatigue are inconsistent (4) and do not fully explain the widespread prevalence of fatigue in this population, nor do they clearly map a course of effective management. Understanding how fatigue relates to underlying pathology and impairment, and how it is manifested in functional and behavioral outcomes, may hold the key to preventive and remedial strategies in stroke rehabilitation.

Prevalence

The actual prevalence of poststroke fatigue is thought to range from 23% to 75%, depending on the definition of fatigue and the characteristics of the patients included (15). The frequency of self-reported fatigue is roughly twice as high in individuals with stroke as in matched controls and is not related to time after stroke, stroke severity, or lesion location (4).

Severity

Fatigue is frequent, often severe, and persists for months and even years after stroke (3). Significant numbers of individuals with stroke report that fatigue is either their worst or one of their worst symptoms (3). Ingles and colleagues (4) found that individuals with stroke attributed more functional limitations to their fatigue than did control subjects with fatigue. In one of the few studies to examine fatigue in

large numbers of individuals with stroke (3), self-reported fatigue was identified as an independent predictor for having to move into an institutional setting after stroke. Fatigue was also an independent predictor for being dependent in primary activities of daily living. This suggests that fatigue may reflect a decline in general health status and that fatigue accompanies reductions in functional independence.

Duration

Fatigue is known to persist over time. Stein and colleagues (16) showed that 76% of individuals at 8 months after stroke complained of fatigue. In the chronic phase of stroke, the number of individuals stating that they are "always" or "often" fatigued is consistently reported in the literature to be approximately 40% (4,10). The observation that fatigue persists over time in individuals with stroke further increases the likelihood that fatigue is an important clinical feature of a progressively disabling pattern of inactivity. Patients who continue to experience subjective feelings of fatigue are less likely to be physically active. In studies of patients with neurological conditions other than stroke, evidence was found for a negative relationship between subjective fatigue severity and physical activity (17,18).

Significance

Combined with the motor deficits, cardiovascular and metabolic deconditioning, sleep disorders, and social isolation that often accompany neurological impairment, poststroke fatigue is associated with disruptions in physical, occupational, and social functions. Fatigue may impede full participation in a rehabilitation program and promote and reinforce sedentary behaviors that contribute to learned patterns of disuse. The functional activity necessary to restore and maintain mobility and independence may be negatively affected by fatigue (10). Even though fatigue has been associated with deterioration of activities of daily living in individuals with stroke, the symptom has received relatively little attention.

What Is Fatigue?

The symptom described as fatigue is common to many medical conditions and is recognized to have serious functional and emotional consequences. To define fatigue, one may try to explain what it feels like, what it is caused by, or what it does. Most current definitions describe fatigue's multidimensionality and frequently include a behavioral or work performance decrement, a physical or biochemical dimension, and a subjective or symptom–sensory aspect (19–21).

One definition by Aaronson and colleagues (22) applies to poststroke fatigue particularly well. Fatigue is depicted as "the awareness of a decreased capacity for physical and/or mental activity resulting from an imbalance in the availability, utilization, and/or restoration of resources needed to perform activity" (p. 46). This definition affirms that fatigue occurs when systems are out of balance, and there are insufficient resources because of either excess demand or deficient supply. The definition also makes it clear that fatigue is not the same thing as tiredness, which is remedied by the restoration of resources when the individual rests. Poststroke fatigue is a new life experience that differs from ordinary tiredness and seems to be a significant problem in the stroke survivor's struggle to regain a new normalcy (23).

Stroke imposes serious restrictions on the ability to activate, use, maintain, and restore physiologic and psychosocial resources, thereby promoting the imbalance that is felt as subjective fatigue. For example, the increased energy expenditure of hemiparetic gait results from the inability to activate normal movement patterns. There is disproportionately large use of cardiovascular and metabolic capacity to produce ambulation (24), often compounded by the existence of deconditioning, underlying disease, and changes associated with aging. Because individuals with hemiparetic stroke have very little margin of unexpended reserves, their ability to restore physiologic resources is diminished. Add to this the sleep disturbances associated with stroke, and the balance of demands and reserves is further threatened.

Fatigue is characterized by distress and decreased functional status related to reduced energy and behavioral adaptations to reduce symptom distress. Persons experiencing fatigue might describe it as a sense of weakness, exhaustion, tiredness, lack of pep and energy, and/or low vitality. Other descriptions of fatigue include feeling drained of energy, more susceptible to pain, experiencing helplessness or loss of control, having difficulty with concentration, and irritability. Individuals may use terms such as tired, weak, exhausted, weary, worn-out, heavy, or slow. In whatever way it is described, fatigue is a multicausal, multidimensional sensation that affects sensory, affective, behavioral, and physiologic realms. Indeed, individuals with stroke clearly describe and differentiate their experience between tiredness as an ordinary life event and fatigue as a poststroke life condition (23).

MECHANISMS OF POSTSTROKE FATIGUE

In defining fatigue, much attention has been paid to describing its origins. Sources of fatigue differ from person to person and from time to time. They may include physical causes, such as pain, disease, anemia, inactivity, and other health problems. Fatigue may be associated with depression, overdoing, or trying to compensate for a disability. Erratic sleep and too much stress may contribute to the development of fatigue as well. Environmental surroundings and accessibility issues, such as noise, air quality, stairs and other architectural barriers, weather, and uncomfortable furnishings, may add to fatigue (25).

Out of these observations came the idea that there are specific types of fatigue and that their mechanisms of

development and actions are distinct. Theories materialized in the attempt to organize and explain the complex and elusive nature of fatigue. One theory distinguished physical and psychological fatigues as two separate types (26,27). Another theory attempted to differentiate the fatigue associated with disease from that associated with exertion (28,29). Piper (19) proposed that there were two types of fatigue, acute and chronic, where acute fatigue occurs as a natural and protective response to a single cause, and chronic fatigue comes from multiple, additive, or unknown causes and is deemed abnormal.

Each of these theories characterized fatigue as falling into two discrete categories. As the body of fatigue-related research expanded over the past decade, multidimensional factors became incorporated into the descriptions and measurement of fatigue. Fatigue could no longer be completely and accurately categorized by types. The contributions of physiologic and psychological functioning as well as social and cultural factors had to be acknowledged (22), as did the outcomes of fatigue (30–32) and the interactions of an assortment of variables (33,34).

Physiologic and Biochemical Mechanisms

There are a number of physiologic and biochemical issues associated with stroke that increase the likelihood that fatigue will develop. A neurophysiologic model explains fatigue in terms of central and peripheral nervous system components (35). Strokes create impairments of the central nervous system because of direct damage. For example, impairment of the central component can lead to decreased transmission of messages from brain and spinal cord and exhaustion of brain cells in the hypothalamic region. One study suggests that individuals with caudate infarcts are more likely to develop fatigue than individuals with damage to other areas (36). Post-polio research about fatigue has explored the effects of viral damage to the neurons of the reticular activating system, which may be pertinent to certain types of stroke with damage to these areas. Damage to the reticular activating structures impairs the ability to maintain attention and leads to experiences of diminished concentration and drowsiness that polio survivors have aptly called "brain fatigue" (25). However, imaging studies have not been able to establish a direct connection between areas of brain damage and the development of poststroke fatigue; instead, these studies tend to find numerous other variables that contribute to fatigue, supporting its multidimensional characteristics (37). Some anticonvulsants and analgesics used to manage stroke-associated sequelae may further exert their effects on the central nervous system and can compound the symptom of fatigue for stroke patients.

Impairment of the peripheral neurological component can alter complex biochemical interactions between nerve and muscle that generate the force and power of movement. In individuals who have experienced strokes, there may be significant damage to the central components, and concomitant effects on peripheral components because of immobility, weakness, or spasticity. The peripheral components are likewise compromised because of lack of innervation and the inability to recruit motor units (38).

Another physiologic model of fatigue explains that changes in concentrations of metabolites interfere with force produced by muscle contractile proteins, leading to reduced muscle function and feelings of fatigue. The accumulation of lactic acid in working muscle is also implicated in the development of fatigue, which signals the body to rest to restore biochemical equilibrium. Other explanations of the organic etiologies of fatigue have included looking at the causal role of physiologic conditions such as decreased pulmonary function, decreased muscle strength and endurance, and increased oxygen consumption demands. Additional fatigue-related factors include the presence of pain (39) or vitamin B_{12} deficiencies, particularly in lacunar strokes (40). High serum levels of glucose and IL-1beta, and low IL1-ra and IL-9 may predict fatigue after ischemic stroke, indicating that the development of poststroke fatigue might be accounted for by a proinflammatory response. These findings support a possible cytokine theory of fatigue after stroke (41,42).

Other important physiologic fatigue-related issues after stroke include sleep–wake disturbances, disruptions in circadian patterns, and sleep-disordered breathing, discussed elsewhere in this text.

A further physiologic model of fatigue that warrants discussion in the context of chronic stroke is that of the stress response and the activation of the corticotrophin-releasing hormone and the sympathetic nervous system. Persons with chronic disease of any kind can be expected to experience a high degree of stress (35), springing from a variety of social, psychological, and physical sources. The stress response triggers the release of hormones (ACTH and corticotrophin) that act upon specific areas of the brain to coordinate behavioral responses. It is thought that in the presence of chronic disease, the sustained stress response may lead to defective releases of corticotrophin, giving rise to behavioral depression and subjective fatigue (35,43). Sources of chronic stress in this patient population might include physical issues such as immobility, gait problems, pain, spasticity, perceptual and communication deficits, and unaccustomed energy expenditures. The stress response might also relate to psychological, social, and role adjustment issues (44).

Work Performance and Behavioral Components of Fatigue

In the many definitions of fatigue, one common observation is its negative effect on work performance. When fatigued, people are less able to engage in physical, mental, or social activity. In the case of hemiparetic stroke, there appears to be a two-way relationship between fatigue and the work performance decrement. Subjective fatigue reduces activity levels, and reduced activity levels contribute to deconditioning and loss of function. Using ambulation as an example, one can discern the multiple triggers for the development

of fatigue. First, there is the increased workload and energy expenditure in hemiparetic gait, stemming from the inability to control the functional and efficient manipulation of body segments through space (45). Adjustment of gait in hemiparesis includes reductions in walking speed, cadence, and step length (46), as well as musculoskeletal adjustments that shift the center of gravity and produce decreased velocity, decreased support time on the affected limb, and decreased weight transfer through the limb, all resulting in increased energy costs (46).

The greater the deficits and movement difficulties, the more body systems are involved in compensation: neurologic, motor control, musculoskeletal, ligamentous, and cardiopulmonary. The increased recruitment of other systems to compensate for missing function leads to increased energy demand and fatigue, which can be seen with ambulation as decreased velocity and increased heart rate (47).

The development of fatigue in the face of mobility impairment and cardiovascular deconditioning is logical when one considers that reduced physical activity can be both an antecedent to and a consequence of fatigue. A reciprocal and perpetuating association may exist between impairments in functional ability and fatigue. For example, neurological deficits that compromise gait and balance increase energy expenditure and cardiovascular and metabolic demand for mobility-related activities of daily living tasks, and cause patients to use a greater proportion of their physiologic fitness reserve to ambulate (48,49). The depletion of energy may result in subjective fatigue, and patients may respond to symptom distress by limiting their activity. Inactivity further disrupts gait and balance through losses of muscle strength, and lowered cardiovascular and metabolic activity tolerance (48). Inactivity may also contribute to social isolation and loss of confidence in the performance of activities of daily living. Thus, a cycle of reduced activity and loss of fitness and mobility is propagated in the presence of fatigue (50,51).

There are also behavioral components of the work performance dimension that perpetuate the fatigue experience in individuals with stroke. Many individuals experience reduced motivation when their functional recoveries are slow or absent. This may contribute to social isolation and a disinclination to participate in household or community activities. The need to navigate architectural barriers may confine individuals to their homes. Fear of falling is also implicated as a behavioral limitation that has effects on the amount of activity in which individuals with stroke engage (52,53). With increasingly sedentary behavior patterns, individuals with stroke are at risk for fatigue associated not only with energy costs of hemiparetic gait but also with cardiovascular and metabolic deconditioning.

Paradoxical, however, is the likelihood that individuals with stroke who experience fatigue actually reduce their physical activity levels to maintain perceived fatigue levels within an acceptable range, in the same way that older adults in general interpret fatigue as a signal to rest (54). This can explain fluctuations in subjective fatigue report or difficulties in evaluating or quantifying fatigue.

Psychosocial Factors

Psychosocial and behavioral factors may be as important as physical health variables in affecting stroke survivors' ability to function normally in their everyday lives. Social support appears to play a significant role in explaining differences in subjective functioning (55). After stroke, high levels of family support, instrumental and emotional, are associated with progressive improvement of functional status (56). Peer influence is powerful: social networks may subtly or directly influence physical activity and simultaneously reinforce a sense of belonging, purpose, and self-worth, thereby promoting mental health that may be reflected in low self-perceived fatigue and positive activity levels (57). Social support may also be influential in reducing the impact of depression and perceived disability (58). For example, in patients experiencing chronic fatigue, lack of social support was identified as a perpetuating factor of fatigue severity and functional impairment (59). In evaluating the relationships of mobility deficit severity, cardiovascular fitness, ambulatory activity and the effects of fatigue, inclusion of social measures adds a valuable dimension.

Symptom–Sensory Dimensions

Several characteristics are common among all symptoms and all patient populations: intensity, timing, level of perceived distress, and quality (60). In the case of fatigue in individuals with stroke, very little is known about the specific dimensions of the symptom. Intensity has been measured using scales that were developed for other populations and may not capture the distinct characteristics of stroke-related fatigue. The timing of fatigue in individuals with stroke is known mainly in terms of its persistence and has not been measured according to situational or temporal fluctuations. We also know little about the course of fatigue development after stroke. Rough estimates of the level of distress have been made based on how much patients report that fatigue affects their function and how often they describe fatigue as their worst or one of their worst symptoms (4). Recently, the development of poststroke fatigue has been linked to attentional and executive impairments, as well as depression and anxiety (61). More work is needed to fully describe the symptom of fatigue in the stroke population.

Behavioral Adaptation

Another way to look at fatigue is in the context of adaptive response. In response to a condition or stimulus, fatigue might actually serve a protective purpose (22). For example, in severely deconditioned patients, the perception of fatigue might curtail activity that would otherwise exceed their physiologic reserves. In individuals with stroke, the loss of cardiovascular and metabolic fitness results in reduction of exercise capacity. Individuals with stroke use a greater proportion of their physiologic reserve to perform everyday activities. This energy expenditure is compounded when

gait and balance deficits increase the workload of functional ambulatory activity. Fatigue may be a warning sign of reaching the limits, causing patients to slow down or stop their actions, thereby protecting their diminished energy reserves and maintaining balance. Recently, attention has been directed toward the phenomenon of *fatigability*, which attempts to identify the point at which individuals report activity-associated changes in perceived fatigue and the performance decrement that occurs in response (54).

SIGNIFICANCE

With the evidence of fatigue's prevalence and persistence in the lives of persons living with stroke and its potential contribution to negative functional outcomes and disability, finding ways to prevent, manage, or respond to fatigue is imperative. The causes of fatigue in the chronic stroke population are many. Attention must be directed toward understanding the link between fatigue and the ability to engage in activities and also toward appreciating fatigue's relationship to specific functional outcomes such as ambulatory activity patterns. By building knowledge about fatigue after stroke, it may be possible to identify strategies for prevention, remediation, and/or compensation, thereby improving and preserving function, independence, and quality of life.

Predictors of Poststroke Fatigue

To anticipate risk for poststroke fatigue and implement proactive preventative strategies, it is important to identify factors that predispose or predict the likelihood that an individual with stroke will experience fatigue. Predisposing factors include advanced age and female gender, along with several physiologic issues such as level of functional disability, the presence of prestroke fatigue, medical comorbidities, medications, continence issues, sleep disturbances, and nutritional problems (15). Psychological and cognitive predictors can include the presence of depression and cognitive dysfunction, and also organic conditions such as damage to particular brain areas with consequent neurochemical alterations, perfusion deficit, and neuroinflammation (15).

Manifestations of Fatigue After Stroke

Numerous features can be observed or measured in a person who is experiencing fatigue. Manifestations of fatigue include perceptual, physiologic, biochemical, and behavioral signs. Contributors to fatigue may include innate host factors such as age or gender. They also may reflect the accumulation of certain metabolites, for example, in muscle fatigue with the rise in lactic acid that follows strenuous work. There may be pattern changes in energy and energy substrates, which can be seen in the mismatch of energy expenditure to reserve in hemiparetic gait. Disturbances in regulation and transmission patterns may result from injury to brain tissue and lead to subjective fatigue. Changes in activity and rest patterns may contribute to the experience of fatigue, as can disruptions in sleep and wake cycles, the presence of disease, or certain treatment effects. We may recognize the outcomes of fatigue in many areas of daily life in individuals with stroke. For example, individuals with poststroke fatigue are more likely to have difficulties with basic and instrumental activities of daily living than those without fatigue (62).

Psychological, social, and life events also have a role in the development of fatigue. Because the physical environment assumes greater importance in the presence of functional impairments, it must not be overlooked as another dimension of fatigue. For individuals with stroke, fatigue-inducing disruptions may occur in many areas and at many levels simultaneously. It has also been demonstrated that poststroke fatigue is an independent risk factor for poor physical health 18 months after stroke (63). As we noted earlier, self-reported fatigue was identified as an independent predictor for having to move into an institutional setting after stroke (3).

Fatigue plays a role in poststroke quality of life as well. Like other distressing symptoms, such as pain or depression, fatigue has a lot to do with how individuals rate their quality of life. Importantly, low health-related quality of life is actually associated with increased mortality (64). For example, in young individuals with ischemic stroke, the presence of fatigue was predictive of early mortality (65).

Assessment of Fatigue

In individuals who have had strokes, the assessment of fatigue is complex. Its presence as a distinct symptom may emerge in the evaluation of other issues, such as weakness or depression. For instance, individuals may experience significant weakness as a result of stroke yet not describe themselves as fatigued. But when individuals are fatigued, their weakness may be more pronounced (3). In individuals with stroke, somatic signs of depression may not always be accompanied by depressed mood and, in fact, may be more indicative of fatigue (7). Even when individuals do not have feelings of depression, the presence of fatigue may have a negative effect on their recovery (4). For individuals with stroke, fatigue should be anticipated, recognized, differentiated, evaluated, monitored, documented, and managed at all stages, from acute event through treatment and rehabilitation to long-term recovery. To do so, we need to have accurate methods to assess and measure fatigue in stroke.

Fatigue may be measured in a variety of ways. To judge the presence and severity of fatigue, or to determine if our interventions have had any effect on that experience, we may use measurement tools in conjunction with patient report, history, and observation of signs. Poststroke fatigue is most frequently measured by self-report, using general fatigue scales such as the Fatigue Severity Scale or a Fatigue Visual Analogue Scale, as no stroke-specific scale has yet been developed to measure fatigue (66). Widely used in

stroke research, most scales were originally developed for use in other patient populations, although similarities have been established between fatigue in stroke and that occurring with Parkinson's disease or multiple sclerosis (67).

Researchers call for a uniform taxonomy in addressing fatigue, which includes standardized ways to quantify it (68). It is very likely that many research questions may be better addressed by using multiple measures to capture the many dimensions of fatigue after stroke.

A promising development in the assessment of fatigue has arisen from studies of fatigability in older adults. *Fatigability* describes the relationship between self-reported fatigue and the level of activity with which the feeling of fatigue is associated (69). It also can be objectively measured by evaluating changes in performance at intervals during a standardized walking test. *Perceived fatigability* can actually be quantified by looking at the difference in pre- and posttest self-ratings of fatigue. *Performance fatigability* is reflected in serial measurements of performance to identify at what point performance changes as a result of fatigue (54). Making the connection between subjective fatigue and other physiologic and functional factors that affect performance may be extremely useful in stroke.

Table 32.1 offers a summary of selected instruments for measuring fatigue and fatigability in individuals with stroke.

Because fatigue is multidimensional, its assessment must also be multidimensional. Patient report of fatigue symptoms is the starting point. A careful history should be gathered to characterize the individual's fatigue experience and to identify contributing factors. Assessments of fatigue in individuals with stroke should include evaluation of:

- *Onset, duration, and intensity of fatigue*: How does the patient describe and interpret the fatigue? How has it impacted desired activities, independence, and function?
- *Aggravating and alleviating factors*
- *Disease process*: Which area of the brain has been affected by the stroke? How long has it been since the event? What has the course of recovery been like? Have there been any complications?
- *Current medications*: In particular, does the patient take anticonvulsants, antispasmodics, or pain medications?
- *Sleep and rest patterns, relaxation habits, rituals, customs*
- *Nutritional status*
- *Effects of fatigue on functional status*, including mobility, activities of daily living, cognitive and social activities, job and role performance. Has the patient had any falls?
- *Presence of depression or other psychiatric condition*
- *Complete physical examination*: Are there other disease processes, such as anemia, inflammatory disease, cardiac or respiratory disease?
- *Adherence to treatment plan*, such as therapy, use of adaptive devices, precautions

TABLE 32.1 Selected Instruments for Measuring Fatigue After Stroke

NAME OF INSTRUMENT	DOMAINS MEASURED	COMMENTS
Fatigue Severity Scale (1)	Physical and psychological function	• Patients select rating from 1–7 to signify agreement with statements • Functional impact of fatigue
Visual Analog Scale (VAS) (86)	Single item	• Simple, real-time measure • Cannot be evaluated by many forms of statistical analysis
Multidimensional Fatigue Inventory (MFI) (87)	General Physical Mental Motivation Activity	• Multidimensional
Piper Fatigue Scale (19)	Severity Temporal Affective Sensory	• Multidimensional • Complicated format • Presumes the presence of fatigue
Profile of Mood States—Fatigue (POMS-F) (88)	Intensity	• Measures only one aspect of fatigue
Fatigue Assessment Instrument	Global severity Triggers Situations that modify fatigue	• 1–7 Likert scale • Measures fatigue in the past 2 weeks
Perceived Fatigability Severity (54)	Self-rating of fatigue before and after a standardized walk test	• Score obtained by dividing total distance walked by change in perceived fatigue
Performance Fatigability Severity (54)	Measures change in performance as an objective indicator of fatigue, and identifies at what point patient performance changes	• Percentage changes in walking speed over distance walked, calculated in 2.5-minute intervals over 10 minutes.

FATIGUE MANAGEMENT STRATEGIES

We need treatments for fatigue because it seems to persist in the long term and has an ongoing effect on health, function, and well-being (63). The initial level of fatigue is thought to be a main determinant of the increase in fatigue over time (70), so targeting fatigue soon after stroke may be important in preventing it from becoming established and difficult to change. The contributions of physiological, cognitive, and affective changes underlying fatigue are variable, and treatment is largely symptomatic and rehabilitative (71). Because the etiology and mechanisms causing and contributing to fatigue are multidimensional and interrelated, it is not surprising to find a considerable range of options for fatigue management. Approaches therefore must be individualized according to the features of fatigue, the impact, and the responses to treatments. Strategies may include cause-specific treatments, nonpharmacologic interventions, pharmacologic interventions, and education and counseling.

Cause-Specific Treatments

The literature suggests that the diagnosis of fatigue is one of exclusion and that, even though it is seen very often in clinical practice, fatigue should not be presumed to be a natural consequence of brain injury. Individuals with stroke who have been ill and inactive for periods of time may have nutritional and metabolic deficits resulting in abnormal blood counts, which in turn can contribute to reduced oxygen-carrying capacity of the blood, and fatigue occurs as an adaptation to loss of energy. Treating anemias and supporting nutrition may make a positive difference for these individuals. Correcting fluid and electrolyte imbalances may dramatically restore feelings of energy.

Because individuals who have strokes are more likely to be in advanced years, they may have comorbidities that contribute to fatigue, such as arthritis, changes in thyroid function, alterations in glucose metabolism, and respiratory or cardiovascular disease. Alleviating acute inflammatory processes and correcting physiologic imbalances also may lessen symptoms of fatigue.

Nonpharmacologic Interventions

The association between regular physical activity and reduced fatigue is well recognized in other patient populations (72,73). Reestablishing activity levels that maximize independence and function is a goal of rehabilitation after stroke. Each patient requires an individualized exercise prescription based on needs and abilities, which supports regular physical activity despite disability. For individuals with stroke, the use of appropriate adaptive devices and equipment may enhance participation in a regular exercise program and yield physical and psychological benefits, including reduced subjective fatigue. Treadmill training, among other treatments, improves fitness reserve and lowers the energy cost of hemiparetic gait, which could be useful in relieving fatigue (49,74).

Restorative activities offer dividends for individuals with stroke. Time spent in natural environments, in contemplation, and in social activities may ameliorate the effects of fatigue. Some complementary therapies may be especially useful in managing stroke-related fatigue, such as biofeedback (75), relaxation techniques, meditation (76), music (77), and pet therapy (78). Such therapies offer multiple benefits through distraction and stress reduction, as well as their inherent therapeutic effects.

The ways in which people think seem also to have an effect on the fatigue experience after stroke. Interventions to increase mindfulness have shown benefits across a range of psychological, physiological, and psychosocial outcomes, including anxiety, depression, mental fatigue, blood pressure, perceived health, and quality of life (79). Some cognitive fatigue-transforming strategies have been identified as being on a mission, settling for less, and stalling (80). Investigators have demonstrated that a cognitive therapy program can alleviate persistent fatigue after stroke, with the most powerful results occurring when cognitive therapy is augmented with graded activity training (81).

Pharmacologic Interventions

When there has been damage to brain tissue, caution is warranted in the use of any medications. For some individuals, however, the use of psychostimulants or antidepressants may afford some relief from fatigue symptoms. Fatigue is so often intermingled with depression that treatment of the latter may yield improvement in the former. However, the research findings about the use of antidepressant medications in reducing fatigue are mixed, but the general consensus is that antidepressants, although helpful in treating depression, seem to have little effect on poststroke fatigue itself (82,83). In any case, when considering medications for the management of fatigue symptoms in the context of stroke, it is important to start with the lowest available dose and titrate carefully according to effect, monitoring for any adverse reactions.

Patient and Family Education

An equally important rehabilitation intervention for the management of stroke-related fatigue is patient and family education and counseling. Providing anticipatory guidance about fatigue may diminish distress and misunderstanding if it occurs and help individuals and families maintain feelings of control. Identifying fatigue-provoking activities, problem-solving to modify these activities, and suggesting individualized environmental changes empowers individuals and families to take concrete actions for symptom management.

Persons with stroke may benefit from learning energy conservation strategies that include prioritizing, pacing,

delegating, or scheduling activities for periods of highest energy. They may also do well with structured daily routines that allow them to attend to one activity at a time, and that support scheduled rest times. Family members play an important part in helping to identify and reinforce successful compensatory strategies. Fatigue management group education is also a feasible model that has been shown to reduce fatigue severity, as well as improve social functioning and reduce anxiety (84).

Future Research Directions

Fatigue has been identified among the top 10 stroke research priorities, along with cognition, aphasia, vision, upper-limb function, and mobility (85). Rehabilitation research activities pertaining to stroke-related fatigue may help to substantiate its roots and remedies, determine its impact on function and independence, and strengthen the case for fatigue prevention and management as a worthy part of stroke rehabilitation. Growing from the knowledge that has been gained in the study of persons with other disease- and disability-related fatigue, fatigue assessments and interventions specific to individuals with stroke might be developed and refined. There is also a need for tools that measure the impact of fatigue on function, such as merging fatigue scales with functional independence measures or further developing our evaluations of performance-related fatigability (54). Instruments that can be used with individuals who have cognitive or communication impairments would also be useful.

SUMMARY

This chapter presented some key information about fatigue after stroke, using a relevant working definition of fatigue, with discussion of theories and mechanisms that may uniquely account for poststroke fatigue. Stroke-specific assessment of fatigue was outlined, along with management strategies to promote function and well-being. Much of what is known about fatigue has come from research in nonstroke populations. Further fatigue-related research is needed specific to stroke, to fully elucidate the symptoms, mechanisms, and unique features of poststroke fatigue. With this knowledge, providers may more effectively design and implement rehabilitation interventions to reduce symptom distress, control risk factors, enhance recovery, and promote function, independence, and quality of life for individuals living with stroke.

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33

Sleep Disturbances and Stroke

Ana Sanchez and Arif A. Kabir

Sleep disorders are common in the general population. Insomnia and obstructive sleep apnea (OSA) syndrome are identified in 15% and 4% of the general population, respectively (1). Patients with stroke have an even higher incidence of certain sleep disorders, and these sleep disturbances may be underdiagnosed. Sleep-disordered breathing, sleep–wake disorders, sleep-related movement disorders, and parasomnias have all been described in patients with stroke. Recognition and treatment of these sleep disorders affects outcome and quality of life.

SLEEP-DISORDERED BREATHING AND STROKE

Types of Sleep-Disordered Breathing in Stroke

Several types of sleep-disordered breathing, including OSA, central sleep apnea (CSA), and Cheyne-Stokes respirations (CSR), are seen in association with stroke. OSA is the most common type of sleep-disordered breathing and is characterized by recurrent episodes of partial or complete upper airway obstruction during sleep. OSA can also lead to nocturnal hypoxemia, arousals, and sleep fragmentation.

Sleep apnea is graded in severity based on the apnea hypopnea index (AHI) (2) (Table 33.1). The AHI is the number of apneas and hypopneas per hour of sleep. An *apnea* is defined as a greater than or equal to 90% diminution in airflow that lasts at least 10 seconds. A *hypopnea* is defined as a greater than or equal to 30% reduction in airflow with an associated oxygen desaturation of at least 3% or an associated arousal from sleep. The definition of hypopnea was revised by the American Academy of Sleep Medicine in 2012. Respiratory effort-related arousals (RERAs) are more subtle disordered-breathing events that do not meet the criteria for an apnea or hypopnea but are associated with a sleep disruption in the form of an arousal. RERAs are not recognized by Medicare as an indication for treatment.

Apneas can be obstructive, central, or mixed. Apneas are categorized as obstructive if there is evidence of persistent respiratory effort against an upper airway obstruction. Apneas are central in the absence of inspiratory effort and are mixed if there is an initial absence of inspiratory effort followed by an effort to breathe. CSR is characterized by a crescendo–decrescendo pattern of respirations with associated CSA and can be seen with bilateral or large hemispheric strokes as well as congestive heart failure (3).

OSA and Risk for Stroke

OSA has been found to be associated with an increased risk of stroke, transient ischemic attack, and death (4), with the highest risk in patients with severe OSA. OSA is now recognized as an independent stroke risk factor (4,5).

Recurrent obstructive apneas acutely cause episodic nocturnal hypoxemia, hypercapnia, cardiac arrhythmias, intrathoracic pressure changes, and postapneic arousals. In the long term, OSA is associated with raised sympathetic activation, endothelial dysfunction, oxidative stress, inflammation, increased platelet aggregation, and metabolic dysfunction (6) (Figure 33.1). Furthermore, OSA may be associated with a reduction in cerebral blood flow (7). These changes negatively influence cardiovascular and cerebrovascular disease.

OSA is associated with many of the modifiable risk factors for stroke, including hypertension, atrial fibrillation (AF), diabetes mellitus, cardiac conditions like coronary artery disease and congestive heart failure, and carotid stenosis.

The association of OSA and hypertension is well established. The Wisconsin Sleep Cohort study showed that the odds ratio of developing new hypertension at 4-year follow-up was 2.03 for mild OSA and 2.89 for moderate to severe OSA compared with 1.42 for patients without OSA (8), and there is a high prevalence of OSA in patients with medically refractory hypertension (9). The most recent Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure cites OSA as an identifiable cause of hypertension and resistant hypertension (10). The enhanced sympathetic activation seen with OSA and the subsequent vasoconstriction may at least in part be responsible for the associated systemic hypertension (6). Patients with OSA have also been shown to demonstrate "nondipping," a phenomenon associated with worse cardiovascular prognosis, where blood pressure fails to normally drop 10% to 20% during sleep (11–13).

TABLE 33.1 Severity of OSA

Normal: AHI <5/hour
Mild OSA: AHI 5–15/hour
Moderate OSA: AHI 15–30/hour
Severe OSA: AHI >30/hour

There is also convincing evidence of a strong association between OSA and AF. Various cardiac arrhythmias are seen in association with OSA, including sinus arrhythmia and bradycardia, and the increased incidence of AF is particularly notable in the stroke population. A nested case control study of more than 100 patients with OSA showed that those with ischemic stroke had a significantly higher rate of AF compared with controls with no history of stroke, even after adjusting for confounding factors, demonstrating the strong association between OSA, AF, and stroke (14). The Sleep Heart Health Study reported a four-fold higher prevalence of AF in patients with OSA (15,16). Moreover, patients with OSA have an increased risk of recurrent AF after cardioversion, and treatment with continuous positive airway pressure (CPAP) results in a lower AF recurrence (17).

The Wisconsin Sleep Cohort study was a large longitudinal study demonstrating the increased prevalence of type II diabetes in patients with moderate to severe OSA (18). However, obesity is a confounding factor, and a causal relationship has not been established. There is also speculation that CPAP may improve glycemic control, but interventional studies have had conflicting results. More study is needed to elucidate if there is a causal relationship between type II diabetes mellitus and OSA, as well as effects of therapeutic intervention.

There is a high prevalence of OSA in patients with coronary artery disease and congestive heart failure (15), and OSA is considered a risk factor for cardiovascular disease. Patients with OSA are most likely to experience sudden cardiac death during sleep (12 midnight–6 a.m.) in contrast to the circadian pattern of the general population or patients without OSA in whom 12 midnight to 6 a.m. is the nadir of sudden cardiac deaths and 6 a.m. to 12 noon is the peak (19). The severity of OSA and its subsequent hypoxemia is also independently associated with increased carotid artery intima-media thickness, which is a marker of systemic atherosclerosis (20). Therefore, sleep apnea may negatively influence cardiovascular and cerebrovascular disease risk.

Prevalence of Sleep-Disordered Breathing in Stroke

OSA is prevalent in the general population. In middle-aged Americans, 24% of men and 9% of women have at least mild OSA (21). The OSA syndrome, defined as an AHI greater than 5 with associated excessive daytime sleepiness, is present in 4% of men and 2% of women (21).

Higher prevalence rates are noted in the stroke population. Sleep-disordered breathing, encompassing OSA, CSA,

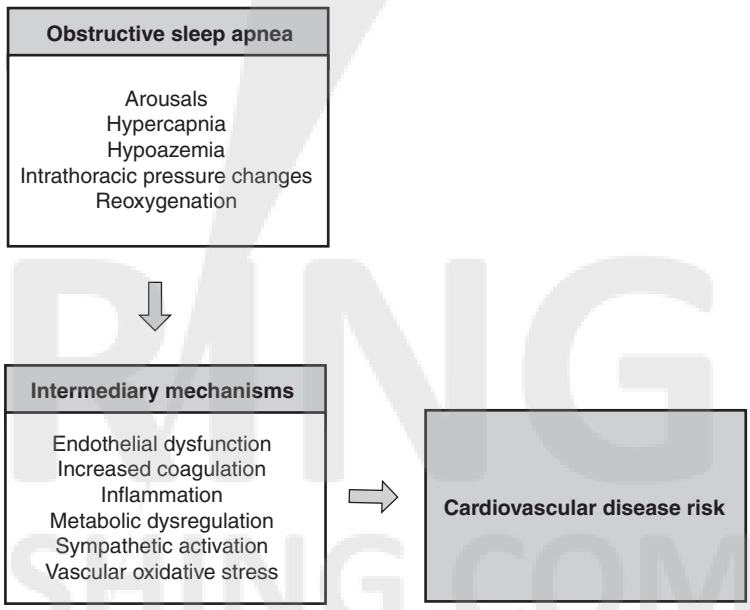

FIGURE 33.1 Mechanisms associated with obstructive sleep apnea that may increase the risk of cardiovascular disease.

Source: Adapted from Ref. (6). Shamsuzzaman AS, Gersh BJ, Somers VK. Obstructive sleep apnea: implications for cardiac and vascular disease. *JAMA*. 2003; 290(14):1906–1914.

TABLE 33.2 Clinical Features Indicating a Higher Risk of OSA

RISK FACTORS FOR OSA	SYMPTOMS OF OSA	ADDITIONAL CONSIDERATIONS IN STROKE PATIENTS
Males, postmenopausal women	Loud snoring	Diabetes
Obesity	Witness apneas	Sleep-related stroke
Hypertension	Gasping/choking	Macroangiopathy
Family history of OSA	Excessive daytime sleepiness	
Large neck circumference (>17" men, >16" women)	Morning headache	
Smoking, EtOH, sedatives	Dry mouth	
Upper airway or craniofacial abnormality	Difficulty concentrating	

and CSR, is present in 44% to 70% of patients with acute stroke (22–25). A meta-analysis of more than 2000 patients with ischemic stroke, hemorrhagic stroke, or TIA showed that 72% had at least mild sleep apnea and 38% had at least moderate sleep apnea (26). The sleep-disordered breathing identified in this population was predominantly OSA, with only 7% of patients with sleep apnea suffering primarily from CSA (26).

There are few studies addressing what risk factors predict the presence of sleep-disordered breathing in the stroke patient population specifically. In the general population, risk factors for OSA include male gender, postmenopausal status in women, obesity, hypertension, family history of OSA, large neck circumference, smoking, excessive use of alcohol or sedatives, and upper-airway or craniofacial anatomical abnormalities (Table 33.2). Generally, patients with OSA may report symptoms including a history of loud snoring, gasping/choking, witnessed apneas, and excessive daytime sleepiness. In the stroke population, neither the location of the stroke nor stroke severity predicts the presence or severity of sleep-disordered breathing (23,24), which may support the theory that OSA often precedes stroke. A prospective study by Bassetti et al. reported that the presence of diabetes, sleep-related stroke, and macroangiopathy may be variables that increase the risk of sleep-disordered breathing in stroke patients (24). Interestingly, in contrast to the general population, patients with stroke and sleep-disordered breathing are not typically symptomatic in terms of subjective sleepiness (27). Therefore, the absence of excessive daytime sleepiness by history does not necessarily lessen the possibility of sleep-disordered breathing in the stroke patient population.

There has been some study regarding the prevalence of sleep-disordered breathing in acute stroke versus the more stable subacute phase to determine if there is improvement of sleep-disordered breathing in line with stroke recovery. Parra et al. prospectively studied about 160 stroke patients admitted to a stroke unit. A portable sleep study was performed within 48 to 72 hours of admission and another follow-up sleep study was performed during the subacute phase at 3 months. The severity of OSA did not significantly change, but central events did improve (23). The authors concluded that this evidence indicates that OSA likely precedes stroke and that CSA as well as CSR occur subsequent to stroke as patients improve in the stable phase. CSA may result from brainstem stroke owing to the damage of central respiratory centers (28), although the Parra study did not show a statistically significant correlation between CSA and this stroke location (23).

OSA and Stroke Outcome

The presence of sleep-disordered breathing in stroke patients has been shown to be associated with a longer duration of hospitalization, worse functional outcomes, and higher mortality after stroke; it may also increase the risk of recurrent stroke (24,29–33). A prospective study by Kaneko et al. of about 60 patients admitted to a stroke rehabilitation unit showed that stroke patients with sleep-disordered breathing spent 2 weeks longer in the rehabilitation unit than patients with similar stroke severity but without sleep-disordered breathing (29). The presence of sleep-disordered breathing in patients with stroke has also been shown to be associated with acute worsening of neurologic status as well as worse short- and long-term outcomes (24,28,30–32,34).

One hypothesis is that the nocturnal hypoxemia, bradyarrhythmias, reduced cardiac output, and reduced cerebral perfusion associated with obstructive apneas may negatively influence the ischemic penumbra acutely (29). The worse outcomes in the short and long term are speculated to relate to the aforementioned factors, as well as to long-term complications of associated hypertension (35), sleep fragmentation, excessive daytime sleepiness, and worsened cognitive ability, which are typically thought to be associated with OSA. This might negatively affect a stroke patient's ability to participate in rehabilitation. However, in the study performed by Kaneko et al., there was no significant difference in sleep fragmentation, Epworth scores (a measure of subjective daytime sleepiness), or worsened cognition in stroke patients with or without sleep-disordered breathing. There have also been contradictory results regarding the presence of sleep-disordered breathing and long-term outcome, with some studies showing worse outcome at three months, six months, and one year (28,29,31), and others showing no association between outcome and OSA (24). The reason for this discrepancy is unclear and merits more study.

Treatment of OSA and Effect on Stroke Outcome

As OSA has been shown to be associated with worse outcomes in the stroke population, it will be important to determine if treatment of OSA improves outcomes. Options for treatment of OSA include weight loss, positional therapy if OSA is worse supine, surgery, oral appliances, and CPAP. Whereas surgery and oral appliances may be considered for patients with mild to moderate OSA, CPAP is the most commonly used therapy and the most effective for all severities of OSA. CPAP works by delivering compressed room air, via a hose, through a mask to prevent upper airway structures from collapsing; it thereby eliminates obstruction of airflow.

Treatment of OSA with CPAP in patients with stroke has been shown to be associated with better functional outcome, improved symptoms of depression, decreased blood pressure, and reduced mortality (27,36–38). Ryan et al. performed a randomized, open label, parallel group trial on stroke patients with OSA who were admitted to an inpatient stroke unit. Patients were randomized to CPAP or standard rehabilitation, and both groups spent the same time in therapy. Patients with neurological deficits, including anosognosia, receptive or global aphasia, were excluded owing to probable difficulty adhering to CPAP. There were no adverse events with CPAP, and compliance was high presumably because of the administration of CPAP in an inpatient setting. A significant improvement in functional and motor impairment as well as depression was demonstrated in the CPAP group compared to the control group, but neurocognitive recovery did not differ significantly. The patients in this study had Epworth sleepiness scale (a subjective assessment of sleepiness) scores that were within normal limits at baseline, but Epworth scores still improved with CPAP treatment. The authors speculate that the improvements seen in the CPAP group were not attributable to improved alertness but instead to increased oxygenation and fewer intrathoracic pressure swings, with subsequent enhanced cerebral blood flow (27).

Improvement of depression in patients with stroke and OSA could enhance rehabilitation and functional outcomes. Depression occurs in about 33% of patients with stroke (39), and treatment of depression may positively influence stroke outcome (40). A study by Sandberg et al. showed that patients with severe stroke and OSA who were treated with CPAP for one month had fewer symptoms of depression (36), and Wessendorf et al. found that patients with stroke and OSA who were compliant with CPAP while in an inpatient rehabilitation facility reported improvement in well-being (41).

Various studies demonstrate that effective treatment of OSA with CPAP lowers blood pressure. CPAP was shown to reduce mean arterial blood pressure by 3 mmHg in patients with moderate to severe OSA (37), and this translates into a reduction in stroke risk by 15% to 20% (35). A prospective study by Wessendorf et al. of about 100 patients with stroke and OSA being treated with CPAP during inpatient rehabilitation also reported improvement in nocturnal blood pressure (41), and CPAP was shown to improve systolic blood pressure in patients with heart failure and OSA (42).

Martinez-Garcia showed that patients with stroke and moderate to severe OSA who were compliant with CPAP had fewer new vascular events than patients who were not compliant with CPAP (43). Then another prospective study by the same group demonstrated that patients with ischemic stroke and moderate to severe OSA had an increased risk of mortality and that those who were compliant with CPAP had a significantly lower risk of mortality at five-year follow-up than patients who were not compliant with CPAP. Compliance with CPAP was defined as usage for more than 4 hours per night for more than 70% of nights. There was no difference in mortality for the groups without OSA, mild OSA, and those compliant with CPAP. A limitation of this study was the low overall compliance with CPAP, which was only 30% (38).

CPAP Compliance in the Stroke Population

Despite CPAP being highly effective at eliminating disordered breathing events, adherence is a significant obstacle to optimizing therapy. In the general population of patients with OSA, less than 60% are compliant with at least four hours of usage on a nightly basis (44); in stroke patients, compliance is thought to be even lower (28). Wessendorf et al. prospectively examined the acceptance of CPAP in a population of 100 or so patients with stroke and OSA in a rehabilitation facility. In this study, 70% accepted treatment with CPAP, which is similar to the rate of compliance in moderate to severe OSA patients in the general population. The primary reasons that 30% of patients did not accept CPAP in this study were mask discomfort and sleep disturbance. The presence of aphasia and severe motor disability was also associated with CPAP noncompliance. The authors hypothesize that difficulty adjusting the mask because of motor and cognitive impairment, mask leak because of facial weakness, trouble understanding the importance of CPAP owing to cognitive difficulties, and lack of the symptom of excessive daytime sleepiness in the stroke population may negatively affect compliance (41). Other studies have shown lower CPAP compliance rates in the stroke population (24,35,38). In the general population, the early acceptance of CPAP is one of the factors that predicts long-term adherence (44). Therefore, if CPAP is initiated during inpatient rehabilitation for stroke, compliance may be established early and improve adherence at home.

Guideline to Screen Stroke Patients for OSA and Considerations for Treatment

Given the high prevalence of sleep-disordered breathing in the stroke population, and given that OSA may increase the risk for recurrent stroke and worsen stroke outcome, an evaluation for sleep-disordered breathing should be considered in all stroke patients. A history of loud snoring, witnessed apneas, obesity/weight gain, large neck circumference, crowded oropharynx, and comorbid hypertension raises suspicion of OSA. In addition, if the patient has comorbid diabetes and a history of sleep-related stroke, that may further

increase the probability of OSA in a stroke patient (24). Stroke patients with OSA differ from the general population in that they may not report excessive daytime sleepiness (27), so this symptom should not be used as a reliable predictor of OSA in this particular patient population.

The evaluation for sleep-disordered breathing requires a sleep study. A *sleep study* is a continuous recording of various bioparameters, including electroencephalography, electro-oculography, electromyography, oral and nasal airflow, oxygen saturation, electrocardiography, and respiratory effort. There are different levels of sleep studies that range from recording a full set of these physiologic variables with a sleep technician attending the patient in a lab setting (Level 1) to recording one or two bioparameters, such as oxygen saturation and airflow, in an unattended portable setting (Level 4). Although an overnight Level 1 full polysomnography in the sleep lab is the gold standard for the diagnosis of sleep-disordered breathing, there are various other portable sleep studies that are adequate for the diagnosis of OSA and are more practical for use at the bedside in the inpatient setting in a rehabilitation facility or at home when travel is difficult. A meta-analysis by Ghegan et al. reported that portable sleep testing provides diagnostic information similar to the Level 1 in-lab sleep studies but may underestimate the severity of sleep apnea (45).

The optimal time to perform a sleep study on a stroke patient is not clear. As CSA may improve in the subacute phase of stroke (23), one might consider waiting until then to perform a sleep study. However, there is also evidence that OSA may worsen acute neurologic status (34), so diagnosis and treatment of OSA early in the course may be beneficial. These areas warrant more study.

TABLE 33.3 Treatment of Stroke-Associated Sleep-Wake Disorders

SLEEP–WAKE DISORDER	TREATMENT
Obstructive sleep apnea	CPAP Weight loss Positional therapy Oral appliance Surgery
Central sleep apnea/Cheyne-Stokes breathing	CPAP/BiPAP Adaptive servoventilation Oxygen
Hypersomnia Excessive daytime sleepiness Fatigue	**Stimulating antidepressants:** ■ Venlafaxine 37.5–150 mg/daily **Wake promoting agents:** ■ Modafinil 100–400 mg daily ■ Armodafinil 150–250 mg daily **Stimulants:** ■ Methylphenidate 5–60 mg daily
Insomnia	Cognitive behavioral therapy for insomnia **Nonbenzodiazepine receptor agonists:** ■ Zolpidem 5–10 mg qhs prn ■ Eszoplicone 1–3 mg qhs prn ■ Zaleplon 5–10 mg qhs prn **Sedative antidepressants:** ■ Amitriptyline 10–100 mg qhs ■ Trazodone 50–200 mg qhs ■ Mirtazapine 15–30 mg qhs Melatonin
Restless legs syndrome Periodic limb movements during sleep	**Dopamine agonists:** ■ Ropinirole 0.25–1 mg qhs ■ Pramipexole 0.125–0.75 mg qhs **Ca channel alpha 2 delta ligands:** ■ Gabapentin 300–1200 mg qhs ■ Pregabalin 50–300 mg qhs ■ Gabapentin encarbil 600–1200 mg qhs
REM sleep behavior disorders	Clonazepam 0.5–4 mg qhs Melatonin 3–12 mg qhs

Abbreviations: BiPAP, biphasic positive airway pressure; CPAP, continuous positive airway pressure.

Source: Adapted from Ref. (35). Hermann DM, Bassetti CL. Sleep-related breathing and sleep-wake disturbances in ischemic stroke. *Neurology*. 2009;73(16):1313–1322.

There are no formal guidelines regarding which patients with stroke and sleep disorders need treatment, although there are some recommendations regarding possible treatment strategies (Table 33.3). Hermann et al. recommend treatment with CPAP to stroke patients with moderate to severe OSA, symptoms of excessive daytime sleepiness, or other comorbid cardiovascular conditions such as hypertension (35). If a stroke patient is found to have CSA or CSR, the central component may improve in the subacute phase of recovery (23), or treatment with a more advanced mode of ventilation, adaptive servo-ventilation, may be considered (46). Further research may delineate which specific stroke patients with what particular type and severity of sleep-disordered breathing may gain the most benefit from treatment with CPAP or other modes of ventilation.

Sleep–Wake Disorders and Stroke

A number of sleep–wake disorders may be seen following a stroke. Patients with stroke may present with insomnia, hypersomnia, or excessive daytime sleepiness. *Insomnia* refers to recurrent difficulty initiating or maintaining sleep, early awakenings, or the inability to attain restorative sleep. *Hypersomnia* signifies excessive sleeping or sleepiness and may be present with the symptom of excessive daytime sleepiness. *Excessive daytime sleepiness* denotes the inability to stay awake or alert, resulting in drowsiness or naps, during the main waking periods of the day.

Insomnia After Stroke

A study of 277 stroke patients showed that 56.7% of patients complained of insomnia after stroke, which was a new complaint in 18.7% of patients (47). There are many reasons for the high incidence of insomnia in this population, including the initial reaction to having a serious medical condition, adjustment to physical and cognitive limitations, poststroke depression, and medication side effects (48). Sometimes insomnia is thought to result directly from the anatomic location of the lesion. Lesions to sleep centers such as the preoptic nucleus of the hypothalamus, brainstem, frontal lobe, basal ganglia, and paramedian thalamus may be associated with insomnia and cause changes to sleep architecture (49–51).

There are various treatments for insomnia, including behavioral approaches and medications. Good sleep hygiene should always be promoted and cognitive behavioral therapy for insomnia may also be utilized. Underlying depression or anxiety should be addressed and treated. In terms of hypnotic medications, one may consider treatment with a nonbenzodiazepine receptor agonist (non-BZRA) such as zolpidem or eszopiclone. The non-BZRA hypnotics will not worsen underlying sleep-disordered breathing. Other medications used to treat insomnia include benzodiazepines and sedating antidepressants in patients with comorbid depression (Table 33.3).

Hypersomnia After Stroke

Hypersomnia may also be seen after stroke (52). This is most commonly noted when strokes are in the distribution of wake-promoting regions such as the hypothalamus, brainstem, and basal forebrain. In addition, there have been reports of hypersomnia directly following ischemic lesions of the pontine tegmental reticular formation and the paramedian nuclei of the thalamus (48). Excluding anatomical lesions, hypersomnia can also be caused by medications used in the poststroke regimen, as well as by OSA or other sleep disorders.

One frequently used measure of excessive somnolence is the Epworth Sleepiness Scale. It is a subjective validated scale asking patients to evaluate the chances of dozing off in eight different scenarios. A score greater than 10 is considered pathologically hypersomnolent. Other more objective standards for assessing hypersomnia include the mean sleep latency test (MSLT) and the maintenance of wakefulness test (MWT).

The most common treatments for poststroke hypersomnia, not otherwise attributable to another condition, are the wake-promoting agents modafinil and armodafinil. Other reported therapies in stroke patients include methylphenidate, levodopa, and bromocriptine (53–55).

The presence of sleep–wake disorders may affect the stroke patient's ability to participate in rehabilitation and thereby negatively affect functional outcome, but there is insufficient evidence to support this hypothesis.

Movement Disorders and Parasomnias in Patients With Stroke

Restless legs syndrome (RLS) is a sleep-related movement disorder, and REM sleep behavior disorder is a parasomnia that can be seen in association with stroke. According to one study, the prevalence of RLS associated with stroke was 12%. RLS symptoms developed within one week of the stroke and were more common with strokes affecting the basal ganglia, corona radiate, and pons. The RLS symptoms were either bilateral or contralateral to the stroke (56). Dopamine agonists are typically first-line therapy to treat symptoms of RLS. There are also rare case reports of REM sleep behavior disorder seen after a pontine stroke that was successfully treated with clonazepam (57).

CONCLUSION

Sleep disturbances are prevalent in patients with stroke and may be underrecognized. Identification and treatment of these sleep disorders could improve functional outcome as well as quality of life and therefore warrant more attention.

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34

Malnutrition After Stroke

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Patients who have had a stroke are vulnerable to being malnourished. *Dysphagia*, defined as having difficulty swallowing (owing to central neurological injury in the case of stroke), is an important factor that may lead to eating difficulties. Other physical, cognitive, and perceptual issues often associated with advancing age and stroke may also contribute to malnutrition (Table 34.1). Awareness and proper management of the nutritional issues and problems associated with stroke can contribute to better outcomes. Identification and treatment of declines in nutritional status associated with stroke may counteract their known negative impact on survival and functional recovery (2–4). Malnutrition and hypoalbuminemia have been associated with poorer functional outcomes (2,5), higher complication rates (5), longer lengths of stay (2), and reduced functional improvement rates (2) in acute and rehabilitating stroke patients. In this chapter, the authors address the magnitude of the malnutrition problem, methods of screening and assessing stroke patients' nutritional status, and technical and clinical strategies for improving their food and fluid intake.

PREVALENCE

Malnutrition typically refers to protein–energy malnutrition resulting from a long-standing negative imbalance of both energy and protein, with metabolic requirements exceeding nutritional intake. The reported prevalence of malnutrition following stroke ranges widely, from 6% to 62% (4,6–23). Table 34.2 presents the results from 18 studies that assessed the nutritional status of patients following stroke using primary criteria to identify malnutrition. Many factors may have influenced the precision of the estimate, such as method and timing of nutritional assessment, differences in stroke subtypes (infarction vs. hemorrhagic, large vs. small, and cortical vs. subcortical infarcts), comorbid conditions, and use of medication. Although many of these studies showed declines in nutritional indices and increases in malnutrition in the weeks following stroke, it is unclear whether this represents further declines superimposed on preexisting (prevalent) malnutrition or whether these were incidental cases. Hama et al. (18) and Finestone et al. (9) reported that 57% and 49% of stroke patients, respectively, admitted to a rehabilitation unit were malnourished, which suggests that malnutrition develops as a consequence of stroke. The estimates of malnutrition assessed at admission to acute care hospitals are substantially lower, ranging from 8% to 19% (4,6,8,10,13,15–17,20).

ENERGY REQUIREMENTS FOLLOWING STROKE

Hypermetabolism has been defined as an increase in metabolic rate associated with a diseased state greater than that predicted, using equations accounting for age, sex, height, and weight (24). Metabolic rates 140% to 200% above predicted values have been described for burns, sepsis, and head injury (24), reflecting increased oxygen consumption associated with severe injury. However, it is unclear whether stroke results in similar metabolic perturbations. Several studies have been conducted to measure the resting energy expenditure of patients following stroke. Three studies focusing on patients receiving mechanical ventilation have given disparate findings. Bardutzky et al. (25) reported that in 34 sedated intensive care patients, total energy expenditure was not elevated and could be estimated using the Harris–Benedict equations (regressions using height, weight, age, and sex to estimate basal metabolic rate in noninjured or nondiseased states). Furthermore, energy expenditure was similar between those with ischemic stroke and those with hemorrhagic stroke. In contrast, in 14 patients with intracranial hemorrhage, 79% of whom were sedated, median energy expenditure appeared elevated at 126% of basal energy expenditure (26). Frankenfield et al. (27) reported that critical care patients with hemorrhagic stroke (n = 36, 58% with craniotomy or craniectomy and 11% with coil embolization of an aneurism) had higher metabolic rates than those with ischemic stroke (n = 30, 20% with decompressive craniotomy). When compared to the metabolic rate predicted by the Mifflin equation for healthy individuals (28), hypermetabolism (more than 15% above Mifflin) was observed in 60% and 86% of those with ischemic and hemorrhagic stroke, respectively.

In other studies, energy expenditure was elevated by 10% to 15% above predicted values, which suggests that stroke patients are not at increased risk for malnutrition caused by

TABLE 34.1 Factors Contributing to Eating Difficulties and Nutritional Impairments After Stroke

PRIMARY FACTOR	SECONDARY FACTORS
• Dysphagia	• Factors affecting ability to feed self (e.g., visuospatial perceptual deficits, upper-extremity paralysis or paresis, and apraxia) • Cognitive changes affecting eating behaviors (e.g., attention–concentration deficit or forgetting to eat, combativeness or throwing food, eating too fast or too slowly, forgetting to swallow, and chewing constantly or overchewing food) • Right and left disorientation • Visual neglect or denial of the paralyzed extremity • Disturbance of sensory function • Depression • Agnosia • Dygeusia (109)

Source: Modified from Ref. (1). Buelow JM, Jamieson D. Potential for altered nutritional status in the stroke patient. *Rehabil Nurs.* 1990;15(5):260–263.

the effects of hypermetabolism in the early poststroke period. Weekes and Elia (29) found that patients were not hypermetabolic in the acute recovery period after stroke. Finestone et al. (30) studied 91 normally nourished patients recovering from stroke from hospital admission at 3 weeks and at 90 days. Although much individual variation existed, patients were not noted to be hypermetabolic. Their resting energy expenditure during the study period was, on average, approximately 10% higher than the values obtained using a standard prediction equation developed with the Harris–Benedict formula. In fact, the energy expenditures of subjects with stroke were similar to those of control subjects who had not experienced a stroke. The authors concluded that a "stress factor" specific to stroke was not evident. In a pilot study comparing 10 stable chronically tube-fed stroke survivors, resting energy expenditure was approximately 90% of weight-based predicted levels (31). It was also lower in the stroke survivors than in healthy controls, even after adjustment for lower fat-free mass owing to hemiparesis and/or prolonged bed rest.

Although there is conflicting evidence that stroke patients receiving mechanical ventilation may have increased energy expenditure, it appears that hypermetabolism is not evident in stroke survivors who do not require ventilation. Furthermore, longer-term stroke survivors who are chronically tube-fed may have lower energy needs than predicted levels. Finally, energy requirements will also vary with the stroke survivor's ability to participate in an active rehabilitation program with physical therapy (32). The nutritional state of stroke patients should be evaluated on an individual basis and be based on their estimated energy expenditure. Detrimental patient outcomes may arise from both insufficient and excessive calories.

PROTEIN REQUIREMENTS FOLLOWING STROKE

There has been very little research on protein requirements of stroke survivors. Evidence of increased protein catabolism following acute stroke was noted by Mountokalakis and Dellos (33) when they compared nitrogen loss, expressed as urea:creatinine ratio, in stroke patients and in surgical patients before and after surgery. Though the ratio rose significantly in both groups, it exceeded the upper limit of normal only in the stroke patients. The ratio reached its peak in that group between the 4th and 10th days. Chalela et al. (34) reported that, of 27 severe stroke patients (median National Institutes of Health Stroke Scale of five) receiving goal rates of enteral nutrition because of depressed consciousness or at risk for aspiration or intubation, 44% were in negative balance while receiving 25 to 30 nonprotein Kcal/kg per day and 1.5 to 2.0 g of protein/kg per day. The authors concluded that "critically ill stroke patients are being underfed."

There is evidence of elevated acute-phase reactants following stroke (35–37), and this has been summarized elsewhere (38). The acute-phase response includes a hypermetabolic, hypercatabolic state in which lean body mass and body fat are catabolized for energy. Other factors, such as insufficient energy intake leading to a breakdown of muscle tissue to satisfy the body's need for energy (gluconeogenesis) and muscle atrophy owing to immobilization, can also contribute to negative nitrogen balance in stroke patients. However, though protein requirement can increase during times of metabolic stress or catabolism, the extent to which the requirement associated with stroke increases the need is not yet known. Protein requirements of 0.8 g/kg per day have been previously recommended for healthy adults aged 19 years or older, including elderly people (39), yet it may be insufficient to meet the needs of stroke patients, particularly in the presence of concomitant infections.

SCREENING AND ASSESSMENT OF NUTRITIONAL STATUS

Nutritional Screening

Nutritional screening can be diagnostic, intended to identify individuals who are considered to be malnourished or at nutritional risk and who would benefit from nutritional interventions. It can also be used as a prognostic tool to identify patients who may be at increased risk for

TABLE 34.2 Studies Assessing the Nutritional Status of Patients Following Stroke

AUTHOR/YEAR	PREVALENCE OF MALNUTRITION AND TIMING OF ASSESSMENT	INDICATORS AND CUT-OFF POINTS OR INDICES USED TO ASSESS NUTRITIONAL STATUS	CRITERIA USED TO ESTABLISH MALNUTRITION
Axelsson et al. (1988) (6)	16% at hospital admission, 22% at hospital discharge	Serum albumin < 38 g/L (male) or 37 g/L (female) Prealbumin < 0.18 g/L Transferrin < 1.7 g/L (male) or 1.5 g/L (female) Body weight < 80% relative body weight, tricep skinfold thickness (four levels based on age), and arm muscle circumference (four levels based on age)	Two or more variables below reference limits
DePippo et al. (1994) (7)	6.1% at any point between rehabilitation hospital admission and discharge	Albumin < 25 g/L, sustained ketonuria without glycosuria > 2 weeks	At least one variable below reference limits
Unosson et al. (1994) (8)	8% on admission to hospital	Weight < 80% of reference value Tricep skinfold thickness < 6 mm (male) or 12 mm (female) Arm muscle circumference (four levels based on age and sex) Delayed hypersensitivity skin testing (< 10 mm induration) Serum albumin < 36 g/L Prealbumin < 0.20 g/L (male) or 0.18 g/L (female)	Three or more variables below reference limits, including one of each of the anthropometric, serum protein, and skin test measurements
Finestone et al. (1995) (9)	49% on admission to rehabilitation unit, 34% at 1 month, 22% at 2 month, and 19% at follow-up (2–4 months)	Serum albumin < 35 g/L Transferrin < 2.0 g/L Total lymphocyte count < 1800/mm^3 Body weight < 90% of reference weight or < 95% of usual weight or body mass index < 20 Sum of four skinfold measurements < 5th percentile of reference population Mid-arm muscle circumference < 5th percentile of reference population	Two or more variables below reference limits
Davalos et al. (1996) (10)	16.3% at hospital admission, 26.4% after 1 week, and 35% after 2 weeks	Serum albumin < 35 g/L Tricep skinfold or mid-arm muscle circumference < 10th percentile of reference population	Any single indicator below reference limits
Choi-Kwon et al. (1998) (11)	25% among patients with ischemic stroke, 62% among patients with hemorrhagic stroke assessed in acute period of stroke: 13% among control subjects	Lean body mass Abdominal skinfold thickness Subscapular skinfold thickness Triceps skinfold thickness (all < 80% of reference values) Body mass index < 20 Total lymphocyte count < 1500/mm^3 Hemoglobin < 12 g/dL Serum albumin < 35 g/L	More than one biochemical indicator and two or more anthropometric indicators below reference values
Aquilani et al. (1999) (12)	30% at admission to rehabilitation	Loss of usual weight ≥ 5% or 10% Arm muscle area < 5th percentile Serum albumin < 35 g/L Total lymphocyte count < 1800 n/mm^3	Loss of weight ≥ 10% but with actual weight lower than reference weight or Loss of weight ≥ 5% plus one other abnormal marker

(*continued*)

TABLE 34.2 Studies Assessing the Nutritional Status of Patients Following Stroke (*continued*)

AUTHOR/YEAR	PREVALENCE OF MALNUTRITION AND TIMING OF ASSESSMENT	INDICATORS AND CUT-OFF POINTS OR INDICES USED TO ASSESS NUTRITIONAL STATUS	CRITERIA USED TO ESTABLISH MALNUTRITION
Westergren et al. (2001) (13)	8% at admission (acute), 29% at 1 month, 33% at 3 months	Body mass index < 20 or body weight < 80% of reference weight or weight loss < 5% since admission Subnormal triceps skinfold and mid-upper-arm muscle circumference Serum albumin < 36 g/L	One abnormal weight measurement and at least two other abnormal markers
Westergren et al. (2001) (14)	32% within 6 days following hospital admission	Authors' modified version of Subjective Global Assessment (A = well nourished, B = well nourished but at risk of becoming malnourished, C = suspected of being malnourished, D = severely malnourished)	Subjective global class B or C or D = malnourished
Davis et al. (2004) (4)	16% at admission	Subjective Global Assessment	Defined by the instrument
Dennis et al. (FOOD I) (2005) (15)	7.8% at admission	Body mass index < 20 (more comprehensive assessment may also have been carried out in a portion of the patients, although details not provided)	Underweight versus normal versus overweight
Dennis et al. (FOOD II) (2005) (16)	8.6% at admission	Same as FOOD I	Underweight versus normal versus overweight
Martineau et al. (2005) (17)	19.2% at acute admission	Patient-Generated Subjective Global Assessment (PG-SGA)	Defined by the instrument
Hama et al. (2005) (18)	22%–57% at admission to rehabilitation, depending on criteria used	Serum albumin < 40 g/L Body mass index < 19	Either marker below reference value
Brynningsen et al. (2007) (19)	35% at 1 week after stroke 33% at 5 weeks 20% at 3 months 22% at 6 months	Serum albumin < 550 mcmol/L Serum transferrin < 49 mcmol/L Triceps skinfold < 10th percentile Arm muscle circumference < 10th percentile	Two or more abnormal nutritional variables
Yoo et al. (2008) (20)	12.2% within 24 hours of symptom onset 19.8% at 1 week	Weight loss of ≥ 10% for previous 3 months or ≥ 6% during first week of admission Weight index (actual weight in relation to reference weight) < 80% Serum albumin < 30 g/L Serum transferrin < 1.5 g/L Serum prealbumin < 0.1 g/L	Any single indicator below reference limits
Lim and Choue (2010, 2012) (21,22)	74% and 57.5% within 18 days of stroke onset	PG-SGA Mini Nutritional Assessment (MNA)	Malnourished = PG-SGA of B or C Malnourished = MNA < 17
Crary et al. (2012) (23)	32% at admission to hospital 33% at day 7	Serum prealbumin < 15 mg/dL	

TABLE 34.3 Prognostic Nutrition Screening Tools

INDEX/INTERPRETATION	DESCRIPTION/CALCULATION
Prognostic Nutritional Index (42)	15.8–16.6 (albumin)
Low risk: < 40%	0.78 triceps skinfold (mm)
Intermediate risk: 40%–49%	0.2 (serum transferrin)
High risk: > 50%	5.8 (maximum skin reactivity, scored from 0 to 2)
Prognostic Inflammatory Nutrition Index (44) Correlates with death in critically ill patients when > 30	A-acid glycoprotein (mg/L) × C-reactive protein (mg/mL)/ albumin (g/L) × prealbumin (mg/L)
Nutritional Risk Index (41) > 100: no malnutrition 97.5 to 100: mildly malnourished 83.5 to < 97.5: moderately malnourished < 83.5: severely malnourished	(1.519 × albumin [g/L]) + 41.7 (present weight/usual weight)
Instant Nutritional Assessment (43) Four degrees of nutritional state	Serum albumin (SA) and total lymphocyte count (TLC) 1st degree: SA ≥ 35 g/L, TLC ≥ 1500/mm^3 2nd degree: SA ≥ 35 g/L, TLC < 1500/mm^3 3rd degree: SA < 35 g/L, TLC ≥ 1500/mm^3 4th degree: SA < 35 g/L, TLC < 1500/mm^3

complications, longer hospital stay, or mortality (40). The distinction is important, as some nutritional screening tools, such as the Nutritional Risk Index (41), the Prognostic Nutritional Index (42), and the Instant Nutritional Assessment (43), were developed for prediction purposes and include components that may be depressed irrespective of nutritional state (Table 34.3). These tools may better reflect disease severity and inflammation. It is usually of greater clinical interest to identify patients who are malnourished. Routine nutritional screening is now considered to be part of evidence-based practice and is included in many clinical practice guidelines, particularly when a patient is dysphagic. Patients should be screened within 24 to 48 hours of admission by a nurse or dietary assistant using a valid tool. Patients with positive findings (i.e., those who fail the screen) should be referred to a registered dietician for nutritional assessment.

There are several valid nutritional screening tools designed specifically to identify inpatients who are malnourished or who are likely to benefit from nutritional intervention. Some examples include the Malnutrition Screening Tool (45), Nutritional Risk Screening 2002 (46), the Malnutrition Universal Screening Tool (47), and the Short Nutritional Assessment Questionnaire (48). All of these screening tools include a maximum of six items assessing recent weight loss and/or body mass index, appetite, and recent dietary intake; some also include an assessment of disease severity, the use of supplements or tube feeding, and age. Most of these tools were developed for use in a broad range of inpatients, including general medical/surgery, orthopedics, and oncology; none have been validated for use in patients recovering from stroke. Finally, the short-form Mini Nutritional Assessment (MNA-SF) (49) is a six-item subscale of the 18-item MNA, which was developed as a tool to identify geriatric patients at risk for malnutrition.

Nutritional Assessment

Interest in identifying and treating all patients perceived to be in a nutritionally compromised state was aroused during the early 1970s, when iatrogenic malnutrition was believed to be a significant cause of poor outcome and rising health care costs. During that period, a series of nutrition assessment methods, many of which are still in use today, were proposed and adopted. However, regardless of the patient population under study, nutritional assessment has never been fully standardized, and no consensus exists as to which method of assessment is best. Therefore, wide variations occur in clinical practice. The nutritional screening and assessment of patients can range from very elaborate methods relying on a variety of biochemical and anthropometric markers (measures of fat and muscle stores) to simple methods using only a single measurement, such as body weight.

The ideal nutrition assessment method applicable for use in the stroke patient would be sensitive to recent intake, unaffected by disease state, inexpensive, simple, and noninvasive. Unfortunately, no such method exists. This limitation can affect not only the initial determination of nutritional status but also subsequent efforts to evaluate the response to nutritional interventions. In the absence of an acute or chronic underlying disease and/or institutionalization, the identification of malnutrition is less complicated, and the condition is thought to be attributable to negative energy balance, where nutritional intake is lower than required. However, in most diseases, including stroke, other metabolic processes may influence the detection of malnutrition.

TABLE 34.4 Biochemical Markers of Nutritional Status

MEASURE	NORMAL VALUES	LIMITATION(S)
Serum albumin (half-life 14–21 days)	> 3.5–5.0 g/dL	• Large body pool, best used with other indicators • Slow response to nutritional repletion (3–4 weeks) • Poor specificity to nutritional status • Decreased during acute-phase response
Serum transferrin (half-life 8–10 days)	> 200 mg/dL	• Better indicator than albumin owing to shorter half-life, smaller body pool, and quicker response to changes • Not specific to nutritional status • Decreased during acute-phase response
Thyroxin-binding prealbumin (transthyretin: half-life 2 days)	20–50 mg/dL	• Responds to repletion in 2–3 days • Not specific to nutritional status • Decreased during acute-phase response
Retinol-binding protein (half-life 10–12 hours)	3–7 mg/dL	• With short half-life and small body pool, reacts rapidly to repletion of energy and protein • Not specific to nutritional status
Total lymphocyte count	2000–3500/mm^3	• Inexpensive screening tool • Can be used with total leukocyte count when interpreting results • Poor sensitivity and specificity • Not specific to nutritional status

Source: From Ref. (51). Chicago Dietetic Association, The South Suburban Dietetic Association and Dietitians of Canada. *Manual of Clinical Dietetics*. 5th ed. Chicago, IL: American Dietetic Association; 1996:21–22.

This interaction between nutritional status and severity of illness was recognized by the Board of Directors of the American Association of Parenteral and Enteral Nutrition and the Clinical Guidelines Task Force:

> There is an inextricable relationship between nutritional status and the severity of illness. Severely ill patients, no matter what assessment tools are used, will be identified as being malnourished. Whether this assessment in fact truly indicates malnutrition (a state induced by dietary deficiency that may be improved solely by administration of nutrients) or is merely a reflection of the severity of metabolic derangement caused by the underlying illness is arguable. (50)

Although sophisticated measurements, such as bioelectrical impedance analysis of body composition, antigen skin testing, and muscle strength, are available to aid in the assessment of nutritional state, they are often impractical for use in clinical practice. More frequently, a traditional approach is used. This method combines the results of biochemical tests, such as serum albumin and transferrin levels, and measurement of skeletal muscle mass and subcutaneous fat stores, collectively referred to as *anthropometric measures*. Examples of anthropometric measurements include body weight, mid-arm muscle circumference, and skinfold thickness, which can be measured using skinfold calipers and a measuring tape. With a traditional approach, the identification of malnutrition is usually inferred, based on a single value or multiple values falling outside specific population reference ranges or below a given percentile within these ranges. Several examples of this approach to nutrition assessment in the stroke patient are presented in Table 34.2. With a system based on cut-off values, a patient's state can change abruptly from one of being well nourished to one of malnourishment. These designations may be somewhat artificial, and additional information, including that obtained from questionnaires designed to assess premorbid nutritional intake, mood, functional status, or comorbid conditions, may be necessary to identify the truly malnourished patient.

Table 34.4 presents some of the biochemical indicators more commonly used in nutrition assessment, their normal reference ranges, and their limitations. Although declines in the serum levels of these indicators may be associated with the development of malnutrition, many are affected independently by factors associated with stroke or any other acute illness. For example, the hepatic production of albumin, transferrin, and prealbumin is downregulated during periods of acute illness, resulting in depressed serum values (52,53). This effect is likely mediated by cytokines, such as tumor necrosis factor and interleukin-6, which have been reported to be elevated following stroke (35,37,54–57). The presence of concurrent infection or temperature elevation is also associated with depressed serum levels of the same proteins. With respect to albumin in particular, transcapillary escape resulting from systemic inflammation may be manifest as hypoalbuminemia (58,59). Whereas serum albumin levels can fall abruptly, recovery of levels may take time, owing to its relatively long half-life of 14 to 21 days; therefore, response to nutritional interventions can be slow (60). Moreover, several reports failed to demonstrate an association between serum albumin levels and adequacy of protein and energy intake (61–63). Using serum albumin as one of two nutritional indicators, Davalos et al. (10) reported that early, appropriate enteral feeding did not prevent the development of malnutrition during the first week after hospital

admission. Similarly, levels of serum transferrin as an acute-phase protein fall in response to physiological stress. Although serum transferrin's half-life of eight days is shorter than that of albumin, its specificity as a nutritional marker is similar to that of albumin (64). Of all of the visceral proteins used for nutritional assessment, serum prealbumin has the shortest half-life, at two days; therefore, it is more sensitive to changes in both disease severity and nutritional intake than either albumin or transferrin. Prealbumin also correlates with nitrogen balance. A dramatic decrease in serum prealbumin level can occur following three to five days of inadequate protein and energy intake or after significant physiological stress (64). Therefore, the serum concentration of prealbumin will normalize with resolution of the stressful insult if nutritional intake is adequate, but it will remain depressed in the presence of adequate intake if stress or inflammation persists.

There are also limitations associated with anthropometric measurements, which can remain static and may be insensitive to recent change in nutritional intake. Skeletal muscle losses may also occur over prolonged periods as a result of atrophy or secondary to immobility, and they can be difficult to distinguish from those with a nutritional cause (65,66). Specialized equipment, training, and practice are required to ensure that reproducible measurements of body composition are obtained, and appropriate reference population norms must be available to ensure proper interpretation.

Several nutritional assessment tools have been validated and are used in clinical practice. Subjective Global Assessment (SGA) (67) is a technique for assessing nutritional status that relies exclusively on the physical examination and history to determine whether a patient is well nourished, moderately malnourished, or severely malnourished. This technique was originally validated in a population of surgical patients (67). Although it has been adapted for use in other diseases such as kidney and liver disease and cancer, it has never been validated with stroke patients. Some of the components of the evaluation may be less applicable to this population because they were developed to identify malnutrition associated with progressive gastrointestinal conditions before surgical intervention, whereas stroke represents a distinct event. The more general items, such as weight and dietary intake history, are likely to be more useful to the clinician than items such as the presence of ascites or a history of nausea and vomiting, which pertain more specifically to patients with significant gastrointestinal disorders.

A variation of SGA, the scored Patient-Generated Subjective Global Assessment (PG-SGA) (68), was adapted from SGA and has also been validated. This tool was designed specifically for patients with cancer and includes a more detailed history section. Items related to weight change, food intake, functional capacity, and gastrointestinal symptoms can be completed by the patient using check boxes. A physical examination is then performed by a health care professional. Each component of the PG-SGA is scored from 0 to 4 according to the impact of the symptom on nutritional status. The total score is used to identify patients at risk for malnutrition and to triage them for nutritional interventions, based on four categories. A global score based on the SGA classification system (i.e., A, B, or C) is also provided as an overall representation of the patient's nutritional state. Like SGA, the PG-SGA has not been validated for use in stroke survivors.

The MNA includes 18 items related to anthropometrics, dietary assessment, self-perceived health and nutritional state, mobility, medication, depression, and lifestyle (69). Items are scored from 0 to 1, 0 to 2, and 0 to 3. An overall score of less than 17 indicates malnutrition, 17 to 23.5 indicates risk of malnutrition, and 24 to 30 indicates normal nutritional status. Both the MNA-SF and the full MNA may be difficult to complete if the patient has cognitive or language deficits secondary to stroke. Also, as the tool was designed for use in geriatric patients, it may be less appropriate for use in younger patients.

In summary, the nutritional assessment of stroke patients is imperfect, affected by the lack of a gold standard or consensus with respect to the most appropriate method of assessment. There are limitations associated with almost all routinely used indicators of nutritional status, whether used alone or in combination. When evaluating the nutritional state of a patient who has sustained a stroke, the clinician is advised to incorporate the history, physical examination, and body weight, as well as objective and subjective biochemical and anthropometric data. The use of serial assessments is encouraged to monitor the nutritional status of patients over time (see Table 34.2 for examples) and to evaluate the response to nutritional interventions.

NUTRITIONAL INTERVENTION STRATEGIES

The major diet strategies for patients undergoing rehabilitation for stroke are dysphagia diets, enteral feeding, high-energy (-calorie) and high-protein diets, energy-reduced diets, diabetic diets, low-saturated-fat diets, low-sodium diets, and high-fiber diets.

Dysphagia Diets

The word *dysphagia* is derived from the Greek words *dys*, meaning "difficult," and *phagein*, meaning "to eat." If not diagnosed and treated, dysphagia can lead to loss of the basic pleasure of eating, impaired nutritional status, or death caused by aspiration pneumonia (70,71). The diagnosis and treatment of dysphagia in patients who have experienced a stroke are discussed in Chapter 11. This section outlines the various dietary—oral and enteral—options available to the stroke patient with dysphagia.

Prescription and Implementation

The approach to the treatment of dysphagia is often multidisciplinary, with the team including nurses, speech–language pathologists, dieticians, and occupational therapists (72). Signs and symptoms of dysphagia observed during and between meals are given in Table 34.5. Stroke patients should be screened initially for swallowing difficulties by a nurse, and those suspected of being dysphagic should be referred

TABLE 34.5 Signs and Symptoms of Dysphagia During and Between Meals

- Drooling, excessive secretions
- Excessive tongue movement, tongue thrusting, or spitting food out of mouth
- Poor control of tongue
- Facial weakness
- Pocketing of food in cheek, under tongue, or on hard palate
- Slurred speech
- Coughing or choking while eating[a]
- Regurgitation through nose, mouth, or tracheostomy tube
- Wet, gurgly voice after eating or drinking, or frequent clearing of throat
- Hoarse or breathy voice
- Complaints of food getting stuck in throat or chest
- Delay or absence of laryngeal (Adam's apple or thyroid cartilage) elevation with swallowing
- Recurrent pneumonia (owing to aspiration)
- Prolonged chewing or eating time
- Reluctance to consume particular food consistencies or to eat at all
- Poor dentition, poor dental hygiene, or dental caries
- Breathing difficulties while eating
- Multiple swallows with single bite
- Effortful swallowing, gulping
- Unexplained weight loss
- Report of dysphasia

[a]Caveat: Aspiration very commonly occurs without coughing. The presence or absence of the gag reflex does not indicate whether the swallowing reflex is intact.

Source: From Refs. (70,72,73).

to a speech–language pathologist for assessment. Speech–language pathologists have extensive training in swallowing disorders. It is within the scope of practice in some jurisdictions for dieticians who have received advanced training to perform screening and dysphagia assessments as well (74). A bedside clinical assessment is usually performed first if the patient is alert and sufficiently conscious to participate. A videofluoroscopic examination (called a videofluoroscopic swallowing study [VFSS] or modified barium swallow [VFMBSS]) may be performed if there is uncertainty with respect to clinical management. Based on the results of these assessments, diet recommendations are made, which usually include modification of solids and liquids. The clinical dietician helps ensure adequacy of energy, macro- and micronutrients, and fluid, and assesses indicators of nutritional status; he or she may also recommend the type, rate, and route of enteral feeding. Nursing staff may assist or supervise the patient at mealtimes. Where possible, this can be done in a common dining room to enhance the social atmosphere and allow for monitoring of eating difficulties, such as coughing, choking, or food pocketing. The occupational therapist can provide recommendations for feeding techniques, upper-extremity positioning, and adaptive equipment to assist with mechanical aspects of feeding. The physical therapist can help determine any requirements for external support during feeding, such as positioning of the bed and wheelchair, and can aid with implementing swallowing strategies (72).

Types of Dysphagia Diets

Dysphagia diets are characterized by modifications of the texture of food and viscosity of fluids. The goal of the diet is to reduce the risk of aspiration and its possible sequela (pneumonia) by facilitating a safer swallow. Dysphagia diets are individualized according to the degree and site of the oral–pharyngeal impairment. Solids may be puréed, ground/minced, or soft/moist (72,73). The puréed diet includes mashed or blenderized foods that are smooth, dense, and homogeneous, with a pudding-like consistency. The minced (pieces up to ¼") or ground texture diet includes soft foods that are chopped and moist enough to form a bolus (for example, shepherd's pie) but require little chewing. The soft/moist diet includes easy-to-chew "bite-sized" foods such as minced, diced, or tender thin-sliced meats. Adequate chewing and dentition are necessary. Patients with dysphagia at the mild oral and/or pharyngeal phase would benefit from this diet; however, tolerance to mixed textures should be assessed (72,73).

Thin fluids are difficult for the dysphagic patient to control, as they can enter the pharynx prematurely and leak into the airway (72). Thicker fluids can be sensed and controlled more readily. Thickened fluid viscosities generally vary from those of nectar to honey to spoon-thick (73). Commercial prethickened products are available. Thin liquids are most often thickened with commercially prepared starch-based products, although other food ingredients such as skim milk powder, puréed fruit, or infant cereal may be used. It is important that food items maintain their thickness until swallowed. For example, ice cream must be held at a sufficiently cold temperature to maintain its thick consistency.

Dysphagia diets are nutritionally adequate, provided that patients consume sufficient quantities to meet their energy requirements. Regular consultation with a registered dietician is essential. Patient compliance and acceptance of the diet are known to be poor, and many institutions provide thickened, high-calorie, high-protein supplements as a standard component of the dysphagia diet. For this reason, the diet should be as liberal as possible, both for psychological reasons (75) and to enhance palatability. Swallowing status should be reassessed frequently enough to avoid needless dietary restrictions.

Enteral Feeding

In cases where the patient is unable to meet his or her nutritional requirements by mouth for a prolonged period, regardless of diet type, or if the risk of aspiration is high owing to dysphagia, enteral nutrition should be considered. By far, the greatest number of patients receive enteral nutrition because of unsafe swallowing. During the transition from enteral to oral intake, both types of feeding may be provided, with the enteral portion gradually being decreased as the oral portion is increased. Nonoral feeding may be discontinued once the adequacy of oral intake has been established.

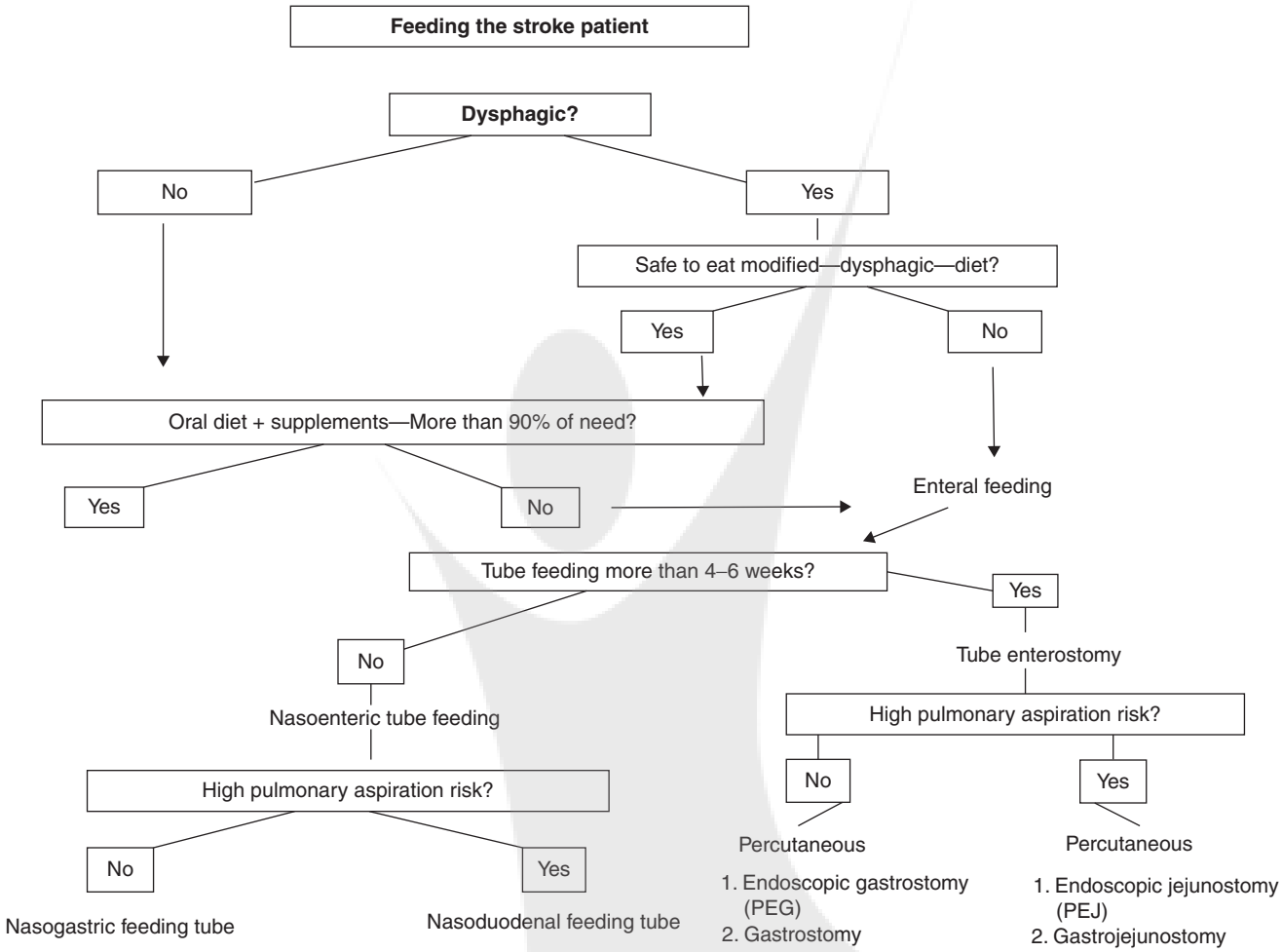

FIGURE 34.1 Algorithm for determining the optimal type of enteral feeding.

Although most patients recovering from stroke are potential candidates for nonoral feeding, it is contraindicated in those without a functional gastrointestinal tract (e.g., because of gastric or intestinal obstruction or paralytic ileus) and those with intractable vomiting or severe diarrhea. The choice of feeding tube and the route of access are dictated by the patient's medical conditions and the expected length of use. An algorithm for determining the optimal type of feeding is given in Figure 34.1. This flowchart takes into account the adequacy of oral intake, anticipated duration of enteral support, and risk of aspiration.

Enteral Formulations

Although enteral formulas vary in their energy density, osmolality, and molecular form of the substrates, most stroke patients do well with a standard polymeric formula (1.0–1.2 Kcal/mL). These nutritionally complete formulas can be titrated to meet patients' energy and protein requirements. Patients with impaired renal function, compromised pulmonary function, or diabetes can be given specialized formulas when required. A clinical dietician should be consulted for advice on the management of patients who are being fed enterally.

Routes of Access

Feeding tube access can be achieved through either nasoenteric or enterostomy routes. Figure 34.2 illustrates the location of these sites. Nasoenteric feeding includes nasogastric (tube from nose to stomach, which is, by far, the most common), nasoduodenal (tube from the nose through the pylorus and into the duodenum), and nasojejunal (tube from the nose through the pylorus and into the jejunum, usually placed radioscopically) feeding. The latter two are seldom used in patients with stroke. Nasogastric tubes were not found to affect swallowing in Japanese or German populations (76,77). Enterostomy tubes can be inserted percutaneously or, less frequently, surgically. Common routes include the prepyloric gastrostomy and postpyloric jejunostomy. A gastrostomy involves tube placement into the stomach. Tube size and techniques vary. Jejunostomy involves the creation of a jejunal stoma that can be catheterized intermittently via needle catheter placement or direct tube placement. This, too, is performed only rarely in the stroke patient. The rationale for wanting to deliver tube feeding to the stomach is that it is more "physiologic." Patients with severe reflux, however, may benefit from postpyloric tube insertion to prevent tube-feeding-related aspiration.

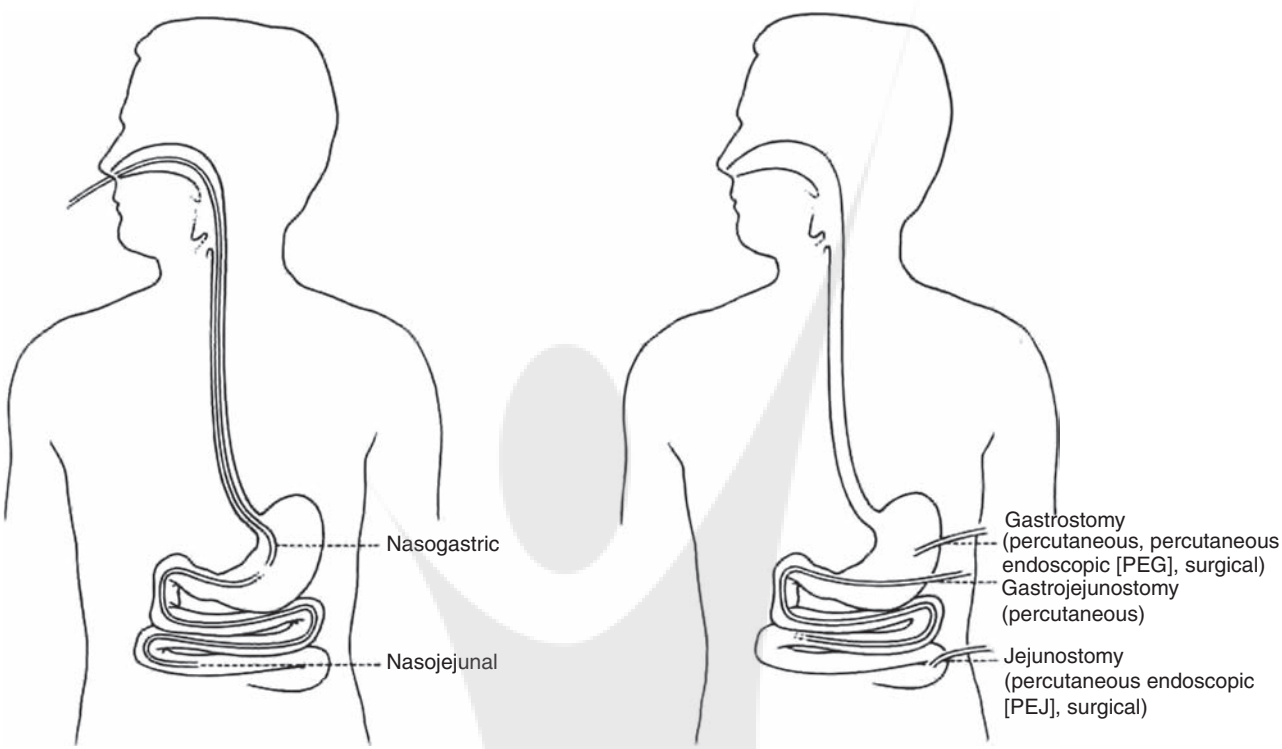

FIGURE 34.2 Common enteral feeding access routes.

Source: Reprinted from *Principles of Neurologic Rehabilitation*, edited by Richard B. Lazar, by permission of The McGraw-Hill Companies.

Percutaneous endoscopic gastrostomy (PEG) and jejunostomy are procedures in which the feeding tube is inserted percutaneously under endoscopic guidance into the stomach or jejunum. The tube is secured by rubber bumpers or an inflated balloon catheter. These procedures are often performed with local anesthesia by a gastroenterologist. Percutaneous gastrojejunostomy involves the percutaneous insertion of a guidewire followed by a feeding catheter into the jejunum via the stomach. This procedure is usually performed by a radiologist under fluoroscopic control, and only local anesthetic is required. Often, local experience and expertise will determine which method of tube insertion is chosen.

Methods of Administration

Feeding formula can be delivered by gravity drip or, for better volume accuracy and tolerance, infusion pump set at a constant rate. Feeding may be provided on a continuous basis, usually over a 24-hour period. This method reduces the possibility of pulmonary aspiration.

Intermittent infusions are equally divided feedings infused at intervals four to six times throughout the day (78). They can be given by gravity drip over 30 to 60 minutes or by infusion pump. This type of feeding frees patients from tube-feeding equipment between feedings, so it is convenient for those undergoing active rehabilitation and those at home. It is also used in patients who are not critically ill. A cyclic method of intermittent infusion may be used wherein the tube feeding is administered at a high infusion rate over 8 to 20 hours. This may be helpful in the transition from tube feeding to oral diet, with tube feeding delivered at night and oral diet ingested by day (78).

Bolus feeding involves the rapid delivery of a feeding into the gastrointestinal tract by syringe or funnel. It is suited to rehabilitating patients who are receiving gastric feeding in a rehabilitation facility or at home. Feeding is completed over a short period, for example, 200–300 mL over 5 to 15 minutes, followed by a flush of 30 mL of water. The advantages are freedom of movement and breaks from feeding. Disadvantages include risk of aspiration, volume intolerance, and delayed gastric emptying (78). Similar volumes of enteral feeding delivered into the jejunum are usually not tolerated by the stroke patient.

Feedings should begin with a full-strength formula, usually at a rate of 25 mL/h and advanced by 25-mL increments every 4 hours to goal rate, as tolerated (78). The residual gastric volume is often monitored every four hours when continuous feeds are administered. Occasional episodes of high-residual volume do not necessarily indicate that there is dysfunction. However, if a high volume (e.g., 200 mL) occurs frequently and is associated with symptoms of cramping, the rate of formula administration should be reduced. Once the problem has resolved, rate increases are then slowly attempted. Diarrhea, a common problem, can be treated by slowing the rate of infusion or adding loperamide or codeine to the formula. In some cases, changing the formula (for example, to a lower fat content) proves effective.

Alternative methods of administering and/or delivering enteral feeding have been proposed. These include transnasal PEG placement without sedation (79); use of a novel nasal loop to better secure a nasogastric tube (80); and feeding intermittently via an oroesophageal tube, whereby enteral fluids, for example, are introduced into the esophagus, with the patient often placing the tube himself or herself (81). Beavan et al. (82) performed a trial of a looped nasogastric tube to improve delivery of feedings and fluids. Key findings were that the nasogastric tube group required fewer tubes and had less minor nasal trauma and fewer electrolyte disturbances than the control group. The authors of this chapter do not have experience with this technique. In general, these studies were small, and, although interesting, there are no apparent standards for the use of the methods described.

Complications

Complications associated with tube feeding can usually be detected and controlled through attentive monitoring. Complications largely fall into three categories: mechanical, gastrointestinal, and metabolic (78). Mechanical complications include tube blockage, local skin infection at the site of tube insertion, and inadvertent insertion in the trachea or lung parenchyma. Nasopharyngeal area erosion with prolonged nasogastric tube feeding can occur, especially if poor taping technique is practiced. PEG tube insertion can lead to burying of the bumper subcutaneously at the abdominal insertion site (buried bumper syndrome), causing local pain and swelling (78). Gastrointestinal complications include peritonitis and free air in the abdomen. Gastrointestinal hemorrhage is also a potential complication of tube feeding (16). Pathophysiological changes of the gastrointestinal tract in ischemic stroke have been reviewed (83). A few studies indicate increased incidence of hemorrhage or decreased transit time, but the area warrants further study. Pruthi et al. (84) recently studied the incidence and independent predictive factors of tube-associated gastrostomy complications including deaths in six Canadian hospitals. Of 418 patients, 102 (24%) had complications, including peristomal cellulitis, tube dislodgement or inadvertent removal, tube blockage, peritonitis, and pressure necrosis at the skin insertion site. In multivariate analysis, complications were more likely to occur in patients with radiological percutaneous tubes and after insertions by physicians with the lowest procedure volume.

Metabolic complications in tube-fed populations are often related to fluid balance, electrolyte deficiencies, and hyperglycemia. Glycemic control in stroke rehabilitation patients being fed enterally can be difficult, especially when the patient requires insulin, and enteral feeding is being provided largely at night to avoid interference with daytime rehabilitation activities. Carbohydrate-reduced formulas may prove useful for diabetic patients. The authors have found that the common practice of providing two-thirds of the subcutaneous insulin in the morning and the remaining one-third in the evening must be reversed. Kerr et al. (85) discussed a structured enteral feeding program for diabetic patients with a specific subcutaneous insulin regimen, which precedes three enteral feedings per day. Dehydration, another metabolic complication, may result if daily fluid requirements are not met. On average, standard polymeric formulas contain 85% free water; therefore, additional water must usually be provided to meet patients' needs. Water may be added directly to the feed or may be provided by way of tube flushes. If fluid losses are excessive because of fever, diarrhea, or vomiting and fluids are not replaced, dehydration may also result. Patients who present with preexisting malnutrition resulting from a prolonged period of poor intake and those who have had food withheld for an extended period of time may be at risk for refeeding syndrome, a potentially life-threatening complication that can occur with rapid introduction of carbohydrate-containing feedings. In this syndrome, acute decreases in serum levels of potassium, magnesium, and phosphorus can appear, owing to intracellular shifts of electrolytes, with possible resultant cardiac, neuromuscular, and other dysfunction (86).

A comprehensive listing of potential adverse reactions to tube feeding, together with potential causes and management, is available from the American Society for Enteral and Parenteral Nutrition (78).

Home Tube Feeding (87)

Several factors should be considered before discharging a patient on a home tube-feeding program. The experience can prove overwhelming for patients and their families. The cognitive and functional ability of the patient or caregiver should be assessed to ensure that all tube-feeding-related tasks can be carried out correctly and safely. The compatibility of tube feeding with the home-life schedule should also be considered. The availability of funding to cover, or partly cover, the cost of formula, infusion pump (if required), and associated supplies also must be explored. Finally, the availability of support personnel and a mechanism for home monitoring, follow-up, and support must be established.

Patient instructions should include the following, with written guidelines provided:

- Proper sanitation techniques for preparation
- Storage and infusion of formula
- Proper sanitation of equipment
- Rate and strength of feedings
- Time of administration
- Body position and length of time to remain in position
- Formula temperature
- Maximum hanging time
- Maximum time to keep open formula
- Amount of fluids to flush between feedings
- How to deal with complications
- Care of the tube and exit site

The reported incidence rates of death, aspiration pneumonia, and complications associated with home enteral nutrition vary among studies but are generally low (88–90). In time, most patients are able to resume a regular diet.

High-Energy (High-Calorie), High-Protein Diets

Patients with preexisting malnutrition and those at nutritional risk owing to poor intake may benefit from a high-energy, high-protein diet. The rationale behind this diet is that the augmented protein intake supplies amino acids required for the building, maintenance, and repair of body tissue. Supplemental calories are needed to spare the protein from being used as a source of energy. At the same time, the energy level is increased to maintain body weight or promote weight gain.

High-energy/high-calorie supplements, which come in many forms (liquids, bars, and puddings) and flavors, may be offered. For dysphagic patients, liquid supplements can be thickened so that they can be consumed safely. Supplements may be given at mealtime along with reduced portions or between meals. The medication pass supplement program (med-pass), which provides a nutrient-dense supplement (60 mL four times daily), has been shown to be efficient (91,92). Most oral supplements contain approximately 250 to 300 Kcal and 8 to 13 g of protein per 250 mL serving. Efforts should be made to provide a pleasant atmosphere for inpatients and to offer appealing food that reflects the patient's food preferences. Six small meals per day, including snacks and nutritional supplements, may augment energy intake (93).

Energy-Reduced Diets

Although some patients may develop malnutrition following stroke, weight gain and obesity are encountered more frequently. *Obesity*, defined as body mass index greater than 30, adversely affects functions such as transfers and ambulation and places extra stress on caregivers. Furthermore, following stroke, patients' mobility and, consequently, energy requirements are often reduced.

Excess weight is treated by a reduction in total energy intake, whereas other nutrient requirements remain age-appropriate (39). Behavior modification, such as serving smaller portions, serving food on a smaller plate, instructing the patient to eat slowly (as it takes approximately 20 minutes to feel a sense of satiety), and increasing activity appropriate to the medical condition, may help the patient reduce energy intake. In addition, strategies to deal with contributing factors such as boredom and depression should be developed. Medications, such as antidepressants and steroids, should also be evaluated, as increased appetite may be a side effect (94). Unfortunately, weight loss can be difficult to achieve following stroke. A collaborative team approach, which may include a psychologist and recreation therapist, may be helpful.

Diabetic Diets

Diabetes is a risk factor for stroke. Many patients enter the rehabilitation program with a diagnosis of diabetes and require special dietary attention. Promoting good glycemic control during the hospital stay will support the patient in his or her daily physical and mental activities. Stroke rehabilitation is also a good time to provide patients with additional diabetic education and to connect them with appropriate community resources.

Low-Saturated-Fat Diets

After a stroke, many patients are prescribed medication to lower their blood lipid levels. In conjunction, a diet low in fat, particularly saturated and trans fats, is introduced to maximize achievement of the blood lipid targets.

Low-Sodium Diets

Following stroke, a therapeutic sodium-restricted diet may be used to manage hypertension. The level of sodium restriction will depend on hypertension severity and treatment; it generally varies between 1500 to 2400 mg per day. For the control of hypertension, a diet high in fruits and vegetables to provide potassium and high in low-fat or fat-free dairy products to provide calcium and potassium is also recommended. Alcohol should be restricted to not more than two drinks per day for men and one drink per day for women. A drink is equal to 150 mL of wine, 355 mL of beer, or 45 mL of liquor. This approach is sometimes called the DASH (Dietary Approaches to Stop Hypertension) diet (95,96).

High-Fiber Diets

Constipation may be associated with stroke. Reduced mobility, lack of dietary fiber, and inadequate fluid intake are the most common reasons. The degree of hydration should be assessed. Fluid intake should be recorded, and urine output and color noted. Fluid intake of at least 1500 mL (six 8-ounce glasses) should be encouraged, provided there is no medical reason for fluid restriction (97). When commercial fiber supplements (for example, psyllium) are used, additional fluid intake is recommended. Dietary sources of insoluble fiber are particularly effective in increasing fecal bulk (98), and the clinical dietician can advise on this. Insoluble fiber is found in many fruits and vegetables, wheat bran, and products such as whole grain breads, pastas, and brown rice. Stool softeners such as docusate sodium, along with judicious use of oral and rectal laxatives, are helpful adjuncts in the treatment of constipation. Exercise opportunities should be provided. Attention to the urge to defecate and the establishment of a routine schedule for toileting should be encouraged. Constipation may be a side effect of certain medications (94), such as antidepressants and narcotic preparations.

DEHYDRATION AND FLUID REQUIREMENTS

Although the fluid requirements of elderly people and those of younger adults are similar, elderly people are particularly vulnerable to dehydration. Therefore, attention to intake and output data is critical in elderly people (99). Besides dysphagia, reasons for underhydration in elderly people include

a blunted thirst mechanism, renal changes, and decreased mobility to reach a fluid source (99,100). In addition, loss of lean body mass with aging contributes to decreased total body water as a proportion of body weight, as lean muscle mass holds 40% of total body water (100).

Dehydration after stroke is associated with poor outcomes (101,102), yet the risk of dehydration in stroke patients is often underdiagnosed, particularly in those with dysphagia who are receiving all their nutrition orally (103,104). For these patients, thin fluids—the most difficult food item to manipulate and control—are often restricted or replaced by those that are thickened. Dislike for the taste or texture of thickened fluids, dependence on others to provide and/or help consume fluids, and fatigue are all factors that increase the risk of dehydration (105).

In a prospective study on inpatients with dysphagia, the greatest contribution to oral fluid intake was from food, not beverages, whether the patient was receiving diet alone or diet with enteral or parenteral fluid support (106). Thus, providing fluid-dense foods rather than thickened beverages may increase the fluid intake of those with dysphagia. Supplemental enteral or parenteral fluid may be necessary to achieve minimum daily fluid requirements (20 to 40 mL/kg of body weight, or 1.0 to 1.5 mL/Kcal of energy expended) (99). For stroke rehabilitation inpatients, physicians should consider ordering overnight intravenous fluid administration or hypodermoclysis.

There is no "gold standard" measure of dehydration. The urea:creatinine ratio is the best indicator of hydration routinely available; however, it is not a specific measure. There are conflicting findings regarding the usefulness of urine specific gravity as an early indicator of hydration status (107,108). Further research is needed to develop a practical tool for the early detection of dehydration in stroke patients.

THE FOOD TRIALS: FEEDING INTERVENTION STUDIES IN PATIENTS WITH STROKE

In 2005, *The Lancet* published the findings of the Feed or Ordinary Diet (FOOD) trials, a long-awaited series of three related large randomized controlled trials (15,16). The investigators attempted to provide definitive answers to three clinically relevant questions regarding the nutritional management of patients in the acute poststroke period:

1. Does routine oral supplementation decrease the number of patients having a poor outcome and patients requiring enteral feeding?
2. Do those who receive early feeding have better outcomes than patients whose feeding is delayed?
3. Do patients with PEG tubes have better outcomes than those with nasogastric tubes?

The trials enrolled 5033 patients, but they were stopped before target numbers were reached owing to lack of funding.

Unfortunately, the trials led to limited new findings of practical use to clinicians. A few highlights include:

1. Routine supplementation does not reduce the odds of a poor outcome for all patients, regardless of nutritional state, but supplementation is still recommended for malnourished patients and those perceived to be at nutritional risk.
2. There is a greater risk of gastrointestinal hemorrhage with placement of any type of feeding tube but particularly with the use of nasogastric tubes. This finding has limited clinical applicability because the long-term use (i.e., more than four to six weeks) of a nasogastric tube for enteral nutrition of stroke patients is not practical; thereafter, a PEG tube would be recommended.

CONCLUSION

The high prevalence of malnutrition in stroke patients on admission to a rehabilitation service (9,12,18) suggests that the decline in nutritional status develops as a consequence of stroke. In turn, malnutrition may adversely affect recovery from stroke. In malnourished stroke patients, poorer functional outcome and prolonged rehabilitation stay have been reported (2–4). Therefore, the clinical goal is to prevent or to identify and treat inadequate nutritional states. Nutritional evaluation methodology, however, is far from a perfect science, and numerous types of evaluations are described. Validation in stroke populations is lacking.

The nutritional care of patients who have sustained a stroke is a relatively new field. Although much research in this area has occurred, there is room for further evaluation of the dietary needs of specific stroke diagnostic groups and of optimal methods of assessment, nutritional delivery, and therapy. Attending to nutritional issues is an important step toward helping stroke patients achieve their full rehabilitation potential.

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35

Bladder and Bowel Management After Stroke

Sylvia A. Duraski, Florence A. Denby, and J. Quentin Clemens

Of all the functional deficits experienced by the survivor of a stroke, incontinence is often an overlooked consequence, despite its huge impact on rehabilitation and recovery. Over the years, health care providers and researchers have concluded that those who experience urinary incontinence (UI) after stroke have a poorer prognosis, decreased functional outcomes, and an increased risk of institutionalization (1–6). This does not include other negative consequences that can result from UI, such as depressed mood, social isolation, increased risk of skin breakdown, infection, and falls with or without injury.

BLADDER MANAGEMENT

Urinary Incontinence

Prevalence

The prevalence of UI after stroke varies depending upon when the survivor is assessed. In the acute-stroke survivor, the prevalence of UI has been documented to range between 32% and 83% (1–6). Brittain et al. (7) specifically looked at nine studies conducted to identify the prevalence of UI after stroke. The studies showed that between 32% and 79% of stroke patients at admission experienced some form of UI. The huge variance in prevalence could be the result of two factors. One is the varying times between the onset of stroke and when the survivor is first assessed for incontinence. Some studies assessed the stroke survivor within days of the onset of the stroke, whereas others assessed the survivor from three months to two years after stroke. Still other studies did not list the time from stroke onset. The second possible factor for the large variance in prevalence of UI after stroke is the lack of information about the presence of prestroke UI. Borrie et al. (8) conducted one of the few studies to identify that 17% of their subjects were incontinent prior to stroke.

The prevalence of UI after stroke is significant even weeks after onset. Ween et al. (9) found that 41% of the poststroke survivors were incontinent on admission to rehabilitation. However, the prevalence of poststroke incontinence decreases over time. In 135 stroke survivors studied over a 6-month period, Brockelhurst and his colleagues (10) showed that 51% of their subjects were incontinent of urine during the first year after stroke. Incontinence resolved 8 weeks after stroke in 55% of the subjects, and by 6 months, 80% of stroke survivors were continent. Borrie and his colleagues (8) similarly demonstrated a downward trend in the number of incontinent survivors over time. In 151 patients with 154 strokes, 55% were incontinent after 1 week, 32% were incontinent after 4 weeks, and 21% were incontinent after 12 weeks. Brittain et al. (11) cited rates of UI in hospitalized stroke patients between 32% and 79% at the time of admission, 25% and 28% at discharge, and 12% and 19% several months after onset. Patel et al. (3) reported that in 235 stroke survivors, 40% were incontinent on initial assessment, 19% at 3-month follow-up, 15% after 1 year, and 10% after 2 years. The method used to manage the incontinence was not identified in any study. Therefore, it is unknown if any particular intervention or if natural recovery led to the decrease in UI.

Prognostic Factors

Numerous studies have reported on UI and its prognostic factors in stroke mortality and recovery. Wade and Hewer (12) showed that incontinence had an overall predictive value of 78% for death. Nakayama and his colleagues (5) looked at 935 acute-stroke patients admitted to the hospital over a 19-month period. Of those with some degree of UI on admission, 68% died before discharged, and 25% died within 6 months of discharge. Brittain and her colleagues (7) concluded that 52% of the patients who experienced UI were dead within 6 months, compared to only 7% who were continent.

UI may affect functional status and recovery in rehabilitation. Jongbloed (13) reviewed 33 studies conducted between 1950 and 1985 to identify factors predictive of improvement in stroke survivors. He concluded that the presence of UI on admission was an adverse prognostic factor for functional outcome (13). Wade and Hewer (12) and Ween (9) also found that UI is an important prognostic factor affecting rehabilitation. In these studies, UI was associated with a more severe stroke, an inability to communicate, an inability to transfer, fecal incontinence (FI), and a greater risk of infection. Other studies confirm that UI is a strong predictor of functional recovery (5,12). In stroke survivors younger than 75 years of age, UI was the best single predictor of disability at 3 months.

Risk Factors

It is unclear whether UI results from time lost from therapeutic treatment; the survivor's advanced age or gender; severity, location, and type of stroke; and/or cognitive, language, or functional impairments (14). In 1987, Reding and his colleagues (14) documented possible comorbid reasons for UI in the stroke survivor. This study concluded that there was an association between UI and the presence of aphasia, or the combination of hemiplegia, visual association, and cognitive impairment and incontinence. Gelber et al. (14) assessed 51 patients with unilateral ischemic hemispheric strokes admitted to a neurorehabilitation unit. They concluded that the presence of aphasia, cognitive impairments, and poorer functional status strongly correlated with incontinence in the stroke survivor (14).

Owen et al. (15) performed a retrospective review of 225 patients admitted to a rehabilitation center in a tertiary medical center during a 14-month period of time. Their findings compared characteristics of incontinent stroke survivors to those of continent stroke survivors. More than 90% of subjects who remained incontinent experienced dysphagia, lower functional independence measure (FIM) scores, and significant impairments in orientation to time, memory, and problem solving. Nakayama et al. (5) found that patients with initial UI were older, female, and had more comorbid conditions. Ween et al. (9) concluded that the incontinent group in his study had significantly lower admission average FIM scores (43 vs. 75) when compared with that of the continent group. In a nonrandom sample of 45 continent and incontinent stroke survivors, Gross (16) found that the group that remained incontinent had significantly lower admission and discharge FIM scores. Although the incontinent group improved in all measures in this study, they still had lower mean FIM scores (16). All of these researchers agreed with previous studies showing that stroke survivors who were incontinent experienced more disabling strokes. Though incontinent stroke survivors do make functional gains, those gains are not as great as in the continent stroke survivor. This not only impacts functional outcomes but also affects the length of hospital and rehabilitation stays, as well as discharge destination.

Discharge Destination

Whether the result of UI alone, or combined with the severity of stroke or other medical comorbidities, numerous studies have documented that discharge destination for stroke survivors is negatively affected. Van Kuijk et al. (17) studied a cohort of 143 stroke survivors admitted for postacute rehabilitation. They showed that in the incontinent group, 8 survivors went home and 6 went to nursing homes, whereas in the continent group, 119 went home and 8 went to nursing homes. They found that the difference in discharge destination was statistically significant, suggesting an association between UI and admission to a long-term nursing facility (17). Ween et al. (9) similarly found that of patients with UI on discharge, 61% went to nursing homes, compared to 18% of patients who were continent (9). Patel et al. (3) found that if stroke survivors remained incontinent over time, institutionalization rates were even higher. In one study that did not find a correlation between incontinence and discharge destination, the majority of patients in both the continent and incontinent group went home after discharge (16).

Neural Control of the Lower Urinary Tract

Components of normal lower urinary tract function include the storage of urine at low pressure without leakage (storage phase), interrupted by the periodic, voluntary expulsion of urine (voiding phase). These processes involve the coordination of the peripheral autonomic, somatic, and central nervous systems (18,19). Sympathetic autonomic activity promotes urine storage, whereas parasympathetic activity promotes voiding.

Preganglionic parasympathetic efferent neurons exit the spinal cord at S2–4 and travel in the pelvic nerve to ganglia located in the bladder wall. These parasympathetic fibers modulate detrusor muscle contraction. Sympathetic efferent fibers exit the spinal cord at T10–L2 and travel in the hypogastric nerve. Alpha sympathetic fibers modulate contraction of the urethral smooth muscle and bladder outlet, and beta sympathetic fibers inhibit parasympathetic activity to the detrusor muscle. Somatic efferent fibers exit from S2–4 and travel in the pudendal nerve to the striated urethral sphincter. These fibers modulate voluntary urethral sphincter contractions. Afferent fibers from the urethra and bladder are distributed throughout the pelvis in the pelvic, hypogastric, and pudendal nerves. Coordination of the bladder and urethral sphincter appears to be accomplished in the pons, as experimental electrical stimulation of the pontine micturition center (PMC) causes detrusor contraction and urethral relaxation (20). The PMC receives input from multiple areas, including the cerebellum, basal ganglia, thalamus, hypothalamus, and cerebral cortex. Signals from these areas provide inhibition of the PMC and allow voluntary expulsion of urine when socially appropriate.

When the bladder fills, stretch receptors in the bladder wall cause afferent signal transmission to the spinal cord. These signals result in increased sympathetic activity (contraction of the urethral sphincter and bladder neck) and decreased parasympathetic activity (detrusor muscle relaxation; Figure 35.1). When voiding is desired, cortical signaling triggers a switch from storage to voiding function. PMC activity then leads to a coordinated relaxation of the urethral sphincter (decreased sympathetic activity) and contraction of the detrusor muscle (increased parasympathetic activity; Figure 35.2). After completion of voiding, the storage phase resumes.

Detrusor muscle contractions are mediated by muscarinic cholinergic receptors in the detrusor muscle cell wall (21). Parasympathetic neurons release acetylcholine, which binds to muscarinic receptors and triggers an increase in intracellular calcium. This in turn triggers downstream intracellular processes that cause muscle contraction.

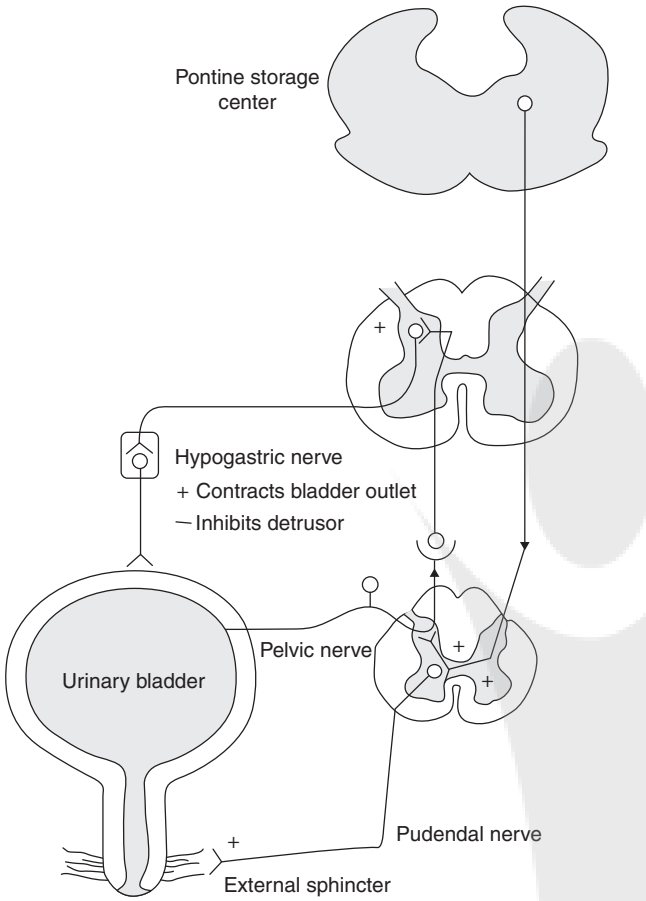

FIGURE 35.1 Storage reflex afferent signals from the bladder wall to the spinal cord result in relaxation of detrusor muscle and contraction of the bladder neck and urethral sphincter.

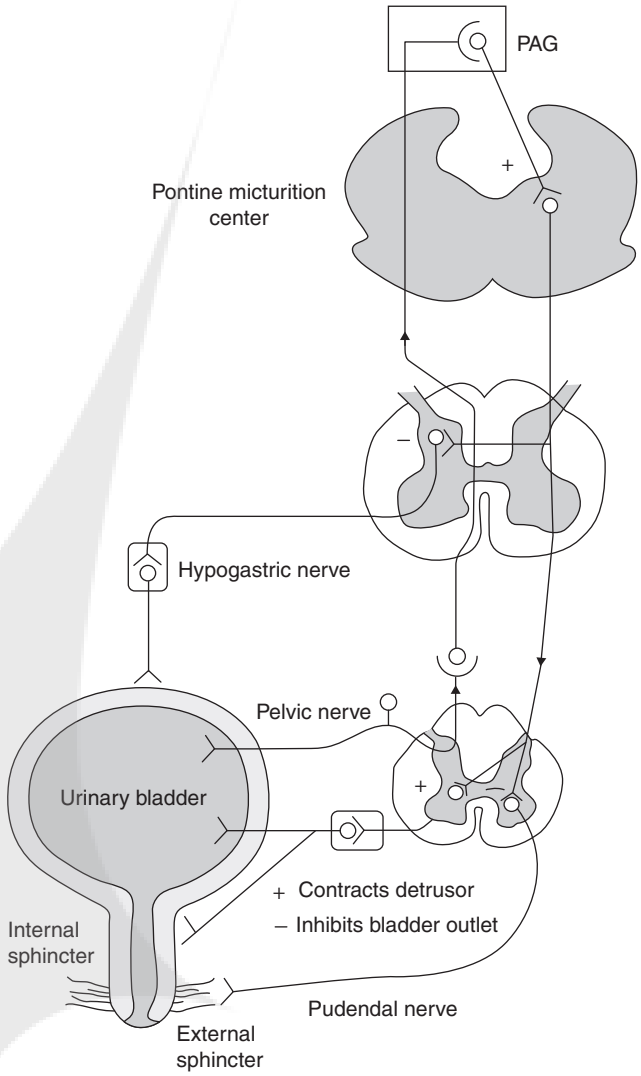

FIGURE 35.2 Voiding reflex cortical signaling leads to relaxation of the urethral sphincter and contraction of the detrusor muscle.

Classification of Voiding Dysfunction After Stroke

Researchers have concluded that the degree of voiding dysfunction after stroke is dependent upon the size, the location, and the time from onset of the stroke.

Early Phase

After the onset of stroke, areflexia has been documented as the most common detrusor dysfunction. Detrusor areflexia presents clinically in the stroke survivor as urinary retention or overflow incontinence, a problem of bladder emptying. Oftentimes referred to as "cerebral shock," this term is used to describe the loss of reflexes below the level of the lesion, much as "spinal shock" is used to describe what is experienced in someone with an acute spinal cord injury. The neurophysiology of cerebral shock is unclear (22). Some speculate that persistent areflexia in the stroke survivor may be the result of a lesion in an area of the brain that is responsible for voiding (23). Others believe that detrusor areflexia is caused by an impaired level of consciousness or a temporary detrusor failure resulting in overdistention (24).

Whatever the cause, many studies of detrusor activity after stroke have concluded that detrusor hyporeflexia immediately after the onset of stroke is common. Reports of the incidence of urinary retention after stroke vary and are estimated as high as 47% when survivors are assessed within 72 hours after the onset of stroke (25). Gelber and his colleagues followed 19 stroke survivors with unilateral ischemic stroke admitted to a neurorehabilitation unit. Urodynamic studies were performed on all of the survivors. Gelber concluded that bladder hyporeflexia occurred in the early phase of acute hemispheric stroke, with a gradual increase in bladder tone as the survivor recovered (14). In 1996, Burney and her colleagues followed 45 men and 15 women between the ages of 32 and 80 years of age 3 days after the onset of stroke. Forty seven percent (47%) of patients who were evaluated presented with retention and overflow incontinence. The cause of retention was reported to be detrusor areflexia (26). This study correlated the increased frequency of detrusor areflexia

with rapid assessment time from onset of stroke. Other studies varied in the amount of time from stroke onset to assessment. Those that assessed more chronic stroke survivors found less detrusor areflexia in cystometric testing.

One study found that a large number of those who experienced detrusor areflexia were diagnosed with lesions of the cerebellum, but no other study has been able to duplicate these results (26). Other potential causes of detrusor areflexia have been assessed. Several studies looked for other causes of urinary retention, such as urinary tract infections, anticholinergic medications, diabetic neuropathy, and benign prostatic hypertrophy. Given the average age of the stroke survivor, other factors may contribute to the retention. It has been estimated that approximately 50% of men by the age of 60 years and 80% of men by the age of 80 years have benign prostatic hypertrophy (BPH) (27). Some of the potential problems that also cause retention, such as BPH, may have existed prior to the stroke, but it is not until the stroke occurs that the individuals exhibit symptoms they can no longer manage. Most studies concluded that true detrusor areflexia with normal smooth sphincter function was common immediately after stroke. Smooth sphincter function is generally unaffected by stroke (22).

Late Phase

Just days to weeks after the onset of stroke, the most common detrusor dysfunction observed is hyperreflexia. The cause for this change is thought to be the result of the release of spinal micturition reflexes secondary to injury to the cerebral inhibitory centers of voiding (23). During this phase, the stroke survivor generally has intact sensation and presents with urgency, frequency, and urge incontinence as a result of the inability to suppress bladder contractions even at low detrusor filling volumes. This is a problem that can be categorized as a failure to store, secondary to bladder overactivity. Some studies demonstrate via cystometric testing that stroke survivors who are incontinent may have symptoms of hyperreflexia, not urgency. Tsuchida et al. performed cystometric studies on 39 stroke survivors. The time of stroke onset ranged from 11 days to 13 years. They concluded that urinary frequency or urge incontinence was the most commonly observed symptom in this population (28). Khan and his colleagues found that the most common cystometric finding in this group was detrusor hyperreflexia (29). Kong et al. studied 27 stroke survivors admitted to a rehabilitation center in a 3-month time period. Cystometric studies demonstrated that 11 patients had detrusor hyperreflexia, one patient had detrusor areflexia, and 15 patients had normal results (1). Of interest, the one patient who had detrusor areflexia was identified with the condition only 12 days after stroke.

Though it is still not completely understood what part of the brain controls voiding, lesions of the cerebral cortex, particularly the frontal lobe, have been identified as impairing the stroke survivor's ability to suppress detrusor contractions. Several studies concluded that cerebral hemispheric lesions most commonly cause detrusor hyperreflexia (14,26,29). Sakakibara et al. followed the urinary history and cystometric test results of 72 acute hemispheric stroke patients. They concluded that voiding dysfunction is common in frontal lesions and infarctions of the anterior cerebral artery territory (30). Burney et al., Khan et al., and Tsuchida et al. concluded that stroke lesions in the cerebral cortex, internal capsule, and basal ganglia resulted in detrusor hyperreflexia (26,28,29). Other researchers also concluded that there was no difference between voiding dysfunction and dominant and nondominant hemisphere lesions.

Incontinence has also been documented in stroke survivors with normal cystometric testing of the detrusor muscle. As there is no true voiding dysfunction in these stroke survivors, how is incontinence in this group explained? Health care professionals have concluded that neurologic deficits of the stroke contribute to incontinence (25). For example, motor deficits prevent the stroke survivor from getting to the bathroom for toileting. Sensory deficits interfere with the awareness of the need to void. Cognitive deficits interfere with remembering what to do to stay dry. Communication deficits interfere with the survivor asking for assistance with toileting.

Management

Initial management consists of supportive care and management of life-threatening sequelae of the stroke. It is common for an indwelling urethral catheter to be placed at this time. When the patient is medically stable, the catheter is removed and a voiding trial is begun. If the patient is able to void, postvoid residual volumes should be obtained. If the residual volumes are less than 100 mL after 2 to 3 voids, no additional measurements are needed. In a patient with an unsuccessful voiding trial, a urine culture should be obtained, and any bacteriuria should be treated with 3 to 7 days of appropriate antibiotics.

Cerebral Shock Phase (Failure to Empty)

During the cerebral shock phase (6–12 weeks), it is common for patients to fail decatheterization trials. When the catheter is removed, these patients may be unable to void, or they may void but only partially empty the bladder. Management of these patients consists of supportive care, medications, and catheterization.

Supportive Care

Intensive stroke rehabilitation is paramount, as immobility, polypharmacy, delirium, and pain may contribute to voiding dysfunction. As performance status improves, the ability to void also improves. Therefore, the timing of catheter removal must be individualized, as it may not be appropriate to remove an indwelling catheter in patients who remain severely disabled (e.g., cannot get out of bed).

Medications

Medications to decrease bladder outlet resistance and increase bladder contractility may be prescribed (Table 35.1). These

TABLE 35.1 Medications Used to Treat Lower Urinary Tract Symptoms

GENERIC NAME	TRADE NAME	DOSE	INDICATION
Bethanechol	Urecholine	5, 10, or 25 mg po TID to QID	Increase bladder contractility
Tamsulosin	Flomax	0.4 mg po qD	Reduce bladder outlet resistance
Alfuzosin	Uroxatral	10 mg po qD	Reduce bladder outlet resistance
Doxazosin	Cardura	1, 2, 4, or 8 mg po qD (must be titrated)	Reduce bladder outlet resistance
Terazosin	Hytrin	1, 2, 5, or 10 mg po qD (must be titrated)	Reduce bladder outlet resistance
Tolterodine	Tolterodine Detrol	2 mg po bid	Decrease urgency, frequency, and urge incontinence
Tolterodine	Detrol LA	4 mg po qD	Decrease urgency, frequency, and urge incontinence
Oxybutynin	Ditropan	5–10 mg po tid	Decrease urgency, frequency, and urge incontinence
Oxybutynin	Ditropan XL	5, 10, or 15 mg po qD	Decrease urgency, frequency, and urge incontinence
Oxybutynin	Oxytrol patch	3.9 mg—change twice weekly	Decrease urgency, frequency, and urge incontinence
Solifenacin	Vesicare	5 or 10 mg po qD	Decrease urgency, frequency, and urge incontinence
Darifenacin	Enablex	7.5 or 15 mg po qD	Decrease urgency, frequency, and urge incontinence
Trospium	Sanctura	20 mg po BID	Decrease urgency, frequency, and urge incontinence
Mirabegron	Myrbetriq	25 or 50 mg po qD	Decrease urgency, frequency, and urge incontinence

may help to decrease the duration of urinary retention. Reduction of bladder outlet resistance may be instituted with alpha-adrenergic blockers such as tamsulosin (Fomax), alfuzosin (Uroxatral), doxazosin (Cardura), and terazosin (Hytrin). These agents are used to treat bladder outlet obstruction caused by BPH and are commonly used as initial therapy in men with urinary retention. As alpha-adrenergic receptors are located in the bladder neck as well as the prostate, these agents could theoretically be used in both men and women, although very limited data exist regarding the efficacy on the latter.

After reducing bladder outlet resistance, bethanechol (Urecholine), an oral cholinergic agonist, theoretically may improve bladder contractility by stimulating cholinergic receptors in the bladder wall. However, data to support its clinical efficacy are very limited. Potential side effects include diarrhea, nausea, and bronchospasm.

Catheterization

Intermittent or continuous bladder catheterization must be used in patients who are unable to empty their bladders spontaneously. The choice of which method to use must be individualized based on the patient. Intermittent catheterization (IC) is often preferred, as it allows the clinician and patient to document voiding efficiency in an ongoing manner, and it appears to be associated with fewer infectious complications than those of indwelling catheterization (31). In the inpatient setting, nurses can perform IC, and the patient can attempt to void prior to each catheterization so that postvoid residual volumes can be assessed. Continuation of IC in the outpatient setting may not be possible, as the patient or caretaker may not be able or willing to perform the catheterization. If the patient is discharged with an indwelling catheter, arrangements must be made for follow-up visits for decatheterization trials.

Late Phase

Typically, urinary retention associated with cerebral shock is replaced by urgency, urge incontinence, and complete bladder emptying. This is felt to be caused by the loss of cortical inhibition of the voiding reflex (32). Therefore, the problem changes from a "failure to empty" to a "failure to store." Symptoms may be exacerbated by the loss of mobility that often occurs with a stroke, as more time may be required to get to the toilet. A moderate degree of urgency that is manageable for a healthy person may be quite troublesome for someone who requires more time to get to the toilet. Management of this problem is the same as for other patients with urgency and urge incontinence, although these treatments may be less effective following a stroke owing to the more severe nature of the symptoms.

Behavioral Therapy

Simple measures (use of a bedside commode, timed/prompted voiding, and avoidance of bladder irritants such as caffeine) may be used on virtually all patients. In studies using timed/prompted voiding, researchers have documented a decrease in UI from 80% to 20%. Unfortunately, those who use this therapy should know that one management method alone is not always sufficient or effective. This means that behavioral therapy for the management of UI may be very labor intensive and may require a great deal of time on the part of the caregiver to be effective or successful. A voiding diary completed by either the patient or caregiver also could identify the cause of incontinence. It is important that health care providers correctly identify the issue leading to UI because management techniques may differ based upon the cause (33). Other therapies, such as pelvic floor physical therapy, biofeedback, and electrical stimulation,

require a level of motivation and muscle control that may not be present in all patients. However, these measures may be quite effective in properly chosen patients (34).

Antimuscarinic Medications

These oral medications block the binding of acetylcholine to the muscarinic receptor, and result in decreased detrusor muscle contractile activity (35). Clinically, this receptor blockage causes a reduction in urinary urgency, frequency, and urgency incontinence. Examples of these medications include tolterodine (Detrol), oxybutynin (Ditropan, Oxytrol), solifenacin (Vesicare), darifenacin (Enablex), and trospium (Sanctura; Table 35.1). Side effects (e.g., dry mouth, constipation, dry eyes) are common, and clinical response is variable and unpredictable. The outcome appears to be better if these medications are combined with behavioral therapy (36).

Additional Diagnostic Tests

At times, patients may demonstrate incomplete bladder emptying or urinary retention that persists longer than would be expected after the initial cerebral shock phase. This may be because of a preexisting voiding dysfunction that was present prior to the stroke. In such patients, further evaluation with urodynamic testing and cystoscopy can be useful to determine if there is evidence of underlying bladder outlet obstruction (27). If obstruction is present, treatment with prostate resection can allow resumption of voiding, but these patients should be counseled that they may experience urge incontinence postoperatively.

Research Frontiers

The urgency and urge incontinence that often occur following a stroke can be more severe and difficult to treat than similar symptoms that occur in the absence of neurologic pathology. Two relatively new treatments that may be applied to these patients include sacral neuromodulation and detrusor injections of botulinum toxin.

Sacral Neuromodulation

Sacral neuromodulation was approved by the U.S. FDA in 1997 for the treatment of refractory urinary urgency and urge incontinence. Although the exact mechanism of action is not clear, the therapy appears to activate latent inhibitory reflexes to the bladder through stimulation of somatic afferent nerve fibers (37). The outpatient procedure is performed using sedation and local anesthesia, with the patient in the prone position. Under fluoroscopic guidance, a lead is placed percutaneously into one of the S3 sacral foramena. The lead is initially attached to an external battery, which is worn for a two- to three-week test period. If the stimulation results in a greater than 50% improvement in incontinence episodes, a second outpatient procedure is performed in which the external portion of the lead is removed, and a permanent subcutaneous battery is placed in the upper buttock. Multiple initial series demonstrated 70% to 80% success rates for the treatment of urgency and urge incontinence, although none of these focused exclusively on patients with these symptoms following a stroke (38). Potential complications include lead migration, pain at the stimulator site, and wound infection. No major neurologic complications have been reported to date. As with any metal implant, magnetic resonance imaging cannot be performed following the procedure. Most recently, in a series of 12 patients with refractory urge incontinence following stroke, Kuo found improvements in the grade of incontinence in 50% of patients after detrusor injections of 200 units botulinum toxin type A (39).

Injection of Botulinum Toxin

The use of botulinum toxin for medical purposes is well established in physiatry, but its use for urologic applications has been a very recent development. In 2000, Schurch and colleagues first described the cystoscopic injection of botulinum toxin type A into the detrusor for the treatment of neurogenic detrusor overactivity in individuals with traumatic spinal cord injury (40). Since then, multiple other investigators have reported excellent results for the treatment of both idiopathic and neurogenic urge incontinence (41,42). Significant improvements in incontinence episodes, pad use, and quality of life have been consistently demonstrated. Typical doses have been from 200 to 300 units injected at a random location into the bladder wall in 10-unit increments. To date, there have been no reports of de novo urinary retention. In those who respond to the treatment, the effects have been reported to last from 4 to 14 months. Botox® (onabotulinumtoxin A) was approved by the U.S. FDA for overactive bladder on January 18, 2013.

BOWEL MANAGEMENT

Introduction

Equally, if not more, distressing to the stroke survivor is FI. Those with FI have problems similar to those with UI, with poor prognosis, decreased functional outcomes, and the possible need for institutionalization.

Fecal Incontinence

There is a natural relationship between urinary and bowel continence. In a survey of 18,000 Wisconsin nursing home residents, UI was the greatest risk factor for developing FI, and FI was the greatest risk factor for developing UI. Decreased ability to perform activities of daily living, immobility, dementia, and specific diseases such as stroke and diabetes are also related to FI (43).

Bowel disturbances occur when the central nervous system is impaired. Uninhibited neurogenic bowel occurs when there is injury to the upper motor neurons located in the cerebral cortex, internal capsule, brainstem, or spinal cord. If cerebral control is interrupted, then the awareness of urge and ability to inhibit defecation are lost, resulting in FI. Sensory impulses travel through the sacral reflex arc to the

brain, but the brain is unable to read the impulses, resulting in a decreased awareness of the need to defecate and a decrease in voluntary control of the anal sphincter. Involuntary elimination occurs when the sacral defecation reflex is activated, but if sensation is not impaired, incontinence is coupled with a sense of urgency. In the uninhibited neurogenic bowel, the pattern of incontinence is characterized by a poor awareness of the need to defecate (44). In the general population, FI is the involuntary loss of anal sphincter control leading to the release of stool at any inconvenient or inappropriate time. There are three subtypes of incontinence: passive (the involuntary discharge of stool or gas without knowing); urge (the failed attempt to hold bowel contents); and fecal seepage (stool seeping out after a normal bowel movement) (45). FI increases the vulnerability for poor hygiene, skin breakdown, infection, depression, and social isolation. The etiology of FI may be the result of neuro–sensory–motor dysfunction of anal sphincter or pelvic floor; abnormal colonic transit; loose or liquid stool consistency; or decreased intestinal capacity with overflow. Multiple factors, including impaired consciousness and/or physical disability, influence bowel control after stroke (46,47).

Prevalence

In a U.S. householder survey of functional gastrointestinal disorders, 7.1% of the population reported fecal leakage, whereas 0.7% of the population experience fecal straining for more than 1 month. In the practice guidelines for diagnosis and management of FI, Rao summarizes its prevalence as ranging between 1% and 7.4% in the well population, and up to 25% in the institutionalized (45).

The prevalence of FI in community-dwelling individuals is reported between 1.4% and 15% in the adult population, and between 3.1 and 16.9% in individuals over the age of 60. The Chicago Health and Aging Project (CHAP) study of older biracial, geographically defined residents described the prevalence of FI by race, age, sex, the presence of stroke and diabetes, and the use of certain psychoactive medications. FI was significantly higher among persons with a reported history of stroke (21.5%) than in those with no stroke (8.3%, $P < .0001$). FI has a high association with stroke and diabetes. In a study using multivariate logistic regression analyses adjusted for age, sex, and race, the odds of FI was 2.8 times greater for persons who reported stroke (95% CI: 2.2–3.5) compared to people without stroke. Users of anticonvulsant, antipsychotic, hypnotic, antidepressant, and anti-Parkinsonian medications were two to three times more likely to have FI (48).

According to the Copenhagen Stroke Study, 40% of 935 stroke patients had FI at the time of admission, 18% at time of discharge, and 9% at 6-month follow up. Secondary to multiple risk factors, 62% of stroke survivors became incontinent during the 9 months after the 3-month acute phase (5). FI affects 56% of acute stroke survivors, 11% at 3 months after stroke, and less than 22% at 12 months (10,49). In a descriptive study of the natural history and independent associations of new onset FI in patients 3 months after stroke, the prevalence of poststroke FI was 30% at 7 to 10 days, 11% at 3 months, 11% at 1 year, and 15% at 3 years. One-third of the patients with FI at three months were continent at one year. Sixty-five percent of those who had been continent at three months were incontinent at one year (50).

Prognosis

In patients who were incontinent of feces at the time of admission, 53% died by the time of discharge, 27% had full FI, 6% had occasional incontinence, and 82% had no FI. At a 6-month follow-up, 5% of the responders had full FI, 4% had partial incontinence, and 91% had no FI (5).

Stroke patients who suffered total anterior circulation infarcts were more likely to be incontinent of feces at three months than those with partial anterior circulation infarct or posterior circulation or lacunar circulation infarct. No association was noted between FI and cerebral or subarachnoid hemorrhage versus infarct. Even though they are coexisting maladies, FI is less prevalent than UI. The strongest association with UI occurs at 3 months, with only 8% of stroke survivors having double incontinence. Identification of FI as a public health problem will continue to increase as the oldest age groups continue to grow. FI is associated with the presence of certain conditions: stroke, diabetes, aging, and the use of certain medications. Therefore, new-onset FI, common for stroke survivors, may be transient and treated. Drugs that cause constipation, fecal impaction or incontinence, decreased mobility, impaired proprioception, neglect, and inability to perform toileting activities are treatable risk factors (50).

Discharge Destination

In the Copenhagen Stroke Study, of patients with complete FI, 53% died prior to discharge as compared to 24% with partial FI, and only 3% of those with no fecal incontinence (5). Thirty-six percent of patients with new-onset FI died at 3 months after stroke, as compared to only 4% of continent patients. Of stroke survivors in nursing homes, 20% of incontinent patients died within 1 year, compared with only 8% of continent patients (50). Regarding discharge destination, FI at 3 months increased the risk of long-term placement, 28% versus 6%. FI is one of the most common reasons for nursing home placement in the United States, even more than dementia. Often caregivers are unable to manage the challenges of toileting, changing, and cleaning a dependent stroke survivor in the home setting (45,47). FI is directly related to functional disability after stroke and is more a result of poor functional recovery than a risk factor for death or institutionalization at six months (49,51). The more dependent the stroke survivor is on caregivers, the greater the loss of function, and the higher the rate of institutionalization or death.

For those patients returning home with FI, family training regarding bowel program management must be incorporated into the rehabilitation plan. The incontinent patient requires expensive disposable supplies, such as diapers, pads for bedding, and protective barrier creams.

Normal Bowel Function

Physiology of the Bowel

The gastrointestinal (GI) system consists of several organs, each with specialized anatomical functions, divided by autonomic muscular sphincters that compartmentalize each organ yet link together into one functioning system. Other body systems, such as the neural, lymphatic, endocrine, and vascular, work with the gut in serving the needs of the human body (52,53). The GI system transports food starting at the stomach and ending at the anus. Digestion of food occurs in the stomach, duodenum, jejunum, and ileum. Secretory glands positioned throughout the GI tract produce digestive enzymes and electrolytes that stimulate and contribute to digestion (44). The upper GI tract processes food by mixing it with pepsin and acid and breaking it down into smaller particles. The proximal stomach serves a storage function by relaxing to accommodate a meal. The distal stomach contracts and propels solid food remnants against the pylorus, where it is repeatedly propelled proximally for further mixing before it empties into the duodenum. The stomach also secretes intrinsic factor vitamin B_{12} for absorption. The middle of the GI tract extends from the duodenal papilla to the midtransverse colon, where digestion is completed. Absorption occurs in the small intestine and the proximal half of the colon. The colon is shorter in length and larger in diameter than the small intestine (44,52,54).

The large intestine anatomically is composed of the cecum; the ascending, transverse, descending, and sigmoid colon; the rectum; and the anal canal. The colon absorbs water and electrolytes from food matter and stores fecal matter until expulsion is convenient. The colon is bounded by the ileocecal sphincter at its proximal end, and by the anal sphincter at the perineum (54,55). Colonic mucosa prepares feces for evacuation by absorbing fluid from the stool, decreasing the daily fecal volumes from 1,000 to 1,500 mL delivered from the ileum to the 100 to 200 mL expelled from the rectum (52).

There are several layers in the wall of the colon (Figure 35.3). The inner layer of the mucosa is gut epithelium with subepithelial connective tissue. The mucosal musculature senses the stretch of the lumen wall. The submucosa layer is the submucosal plexus with stretch receptors between the mucosa and the middle layer. The middle layer consists of circular musculature, which contracts the lumen, causing mixing. The myenteric plexus is between the middle circular and the outer layers. The outer layer consists of longitudinal muscle layers and the serosa, which encapsulates and facilitates sliding (54) (Figure 35.4).

The Central Nervous System and Defecation

The colon's nervous system has two components: intrinsic and extrinsic. The colonic wall contains intrinsic elements that include the Auerbach's plexus and Meissner's plexus. Auerbach's plexus, also known as the *intramuscular myenteric plexus*, is located between the outer and middle muscle layers and controls GI motility. Meissner's plexus, located in the submucosa, is referred to as *submucosa plexus* and controls GI secretion (56). The intrinsic component is actually the enteric nervous system, providing the basic control for propulsion and fluid regulation. It coordinates the colonic wall, mixing and advancing stool

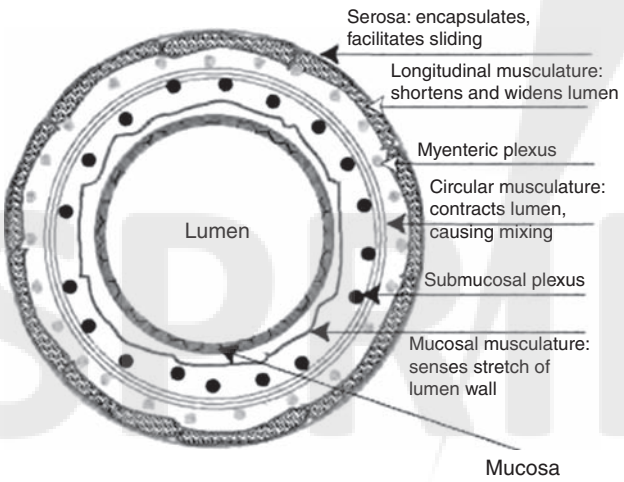

FIGURE 35.3 Cross section of GI wall diagrammatic depiction of the layers of the wall of the colon.

Source: Turner BH, Cowie RJ, Young JK. *The Functional Anatomy of Digestive and Urogenital Reflexes* [Powerpoint slides]. Retrieved from Howard University website http://www.medhoward.edu/anatomy/gas/wk6/lect19/gi

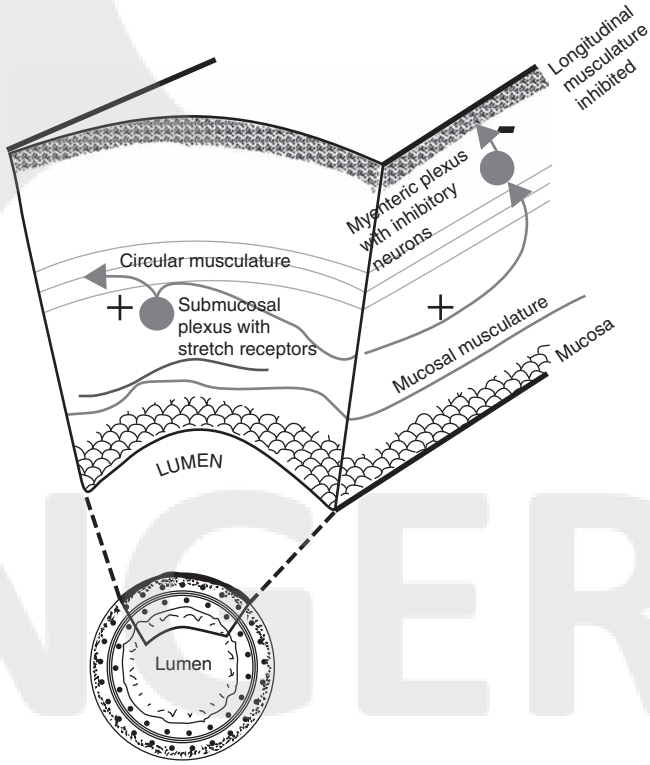

FIGURE 35.4 Cross section of colonic wall. Large intestine musculature of intestinal wall.

Source: Turner BH, Cowie RJ, Young JK. *The Functional Anatomy of Digestive and Urogenital Reflexes* [Powerpoint slides]. Retrieved from Howard University website http://www.medhoward.edu/anatomy/gas/wk6/lect19/gi

through the colon. The extrinsic neural input occurs through the autonomic nervous system's sympathetic and parasympathetic pathway, which provides volitional or involuntary control specific for each gut region (52,54,57).

Intestinal activity works with circular and segmental movements of the different sections of the intestinal tract. There are two types of movement in the colon. The propulsion of food matter, caused by a distended colonic segment forming a contractile ring around the colon to propel forward any material in front of it, is called *peristalsis*. The speed of peristalsis is greatest in the duodenum and jejunum and slowest in the ileum. To be effective, peristalsis requires an intact myenteric plexus. If peristalsis is weak, it may be that the myenteric plexus has been disturbed by disease or anticholinergic medication (54,57).

The second type of colonic movement, known as *haustrations,* is a mixing motion consisting of circular contractions digging into and rolling over the fecal material in the colon. Colonic movement depends on haustral contractions and mass movements. The gastroileal reflex stimulates the ileum to move semifluid contents into the cecum and gradually fill the ascending and transverse colon. Propulsion in the cecum and ascending colon is caused by the slow, haustral contractions. Movement of chyme from the ileocecal valve through the transverse colon requires 8 to 15 hours. Chyme evolves into a fecal, semisolid state as fluid is absorbed. This slows down the process for long intervals until a powerful mass movement of the transverse colon propels the contents into the lower colon. All of these processes remain involuntary (52,54,55).

Mass movements replace propulsion at the transverse colon and through the sigmoid colon. Gastrocolic and duodenocolic reflexes expedite mass movements that are strongest for about 15 minutes in the first hour after breakfast. In response to distention, usually in the transverse colon, a constrictive ring forms and mass movements begin. Twenty centimeters or more of colon distal to the constrictive ring lose the haustral contractions and move as a mass or unit. In response, fecal material in that colonic segment is forced down the colon to the rectum. Mass movements last for 10 to 30 minutes but may return in 12 or 24 hours. As feces move into the rectum, the need to defecate is felt (54).

Neurologic Control (Reflexes)

The GI tract is unique among other organ systems, as its function is influenced and altered mostly by the outside environment, not by direct control of the brain. Intrinsic nerves control most basic gut activities, whereas extrinsic nerves modulate visceral activity through sympathetic and parasympathetic functions (53). GI reflexes are mediated by extrinsic vagus or splanchnic nerve pathways. The brain–gut axis alters function in regions not under voluntary regulation. Stress caused by external forces can alter GI motility as well as the gut's immune function (56).

The enteric nervous system and its relationship with the sympathetic and parasympathetic systems support three types of GI reflexes essential for bowel control and defecation. The first group of reflexes occurs within the enteric nervous system and controls GI secretion, peristalsis, and mixing contractions. The second group of reflexes travels from the gut to the prevertebral sympathetic ganglia and back to the GI tract. Gastrocolic reflexes transmit signals from the stomach to cause evacuation of the colon. Enterogastric reflexes from the colon and small intestine inhibit stomach motility and secretion. Colonoileal reflexes prevent the emptying of ileal contents into the colon. The third group of reflexes travels from the gut to the brainstem and then back to the GI tract. These include reflexes in the stomach and duodenum that control gastric motor and secretory activity. Pain reflexes can cause general inhibition of the entire GI tract. Defecation reflexes produce colonic, rectal, and abdominal contractions needed for defecation (57).

Intrinsic neural control is altered by signals from the brain to the autonomic nervous system that innervates the GI tract. The enteric nervous system controls the automatic motor and secretory functions and allows the gut to continue to function in isolation from its extrinsic nerve supply. Intestinal activity relies on the coordinated action of various parts of the nervous system, including the intramural plexus in the bowel wall, the autonomic nervous system, and the voluntary nervous system. The human brain can inhibit the sacral spinal center to decrease peristaltic activity by voluntarily increasing anal sphincter tone and relaxing the colon, causing the urge to defecate to disappear (54).

Defecation requires the integration of the somatic nervous system (voluntary) and the autonomic nervous system (involuntary). Any interruption in the process can impair bowel function. The defecation reflex begins when mass movements propel fecal material forward, caused principally by the duodenocolic reflex that is initiated while the duodenum is filled. Feces enter the sigmoid colon and are kept there until right before defecation. The adult rectum is about four to six inches long and is usually empty of feces until defecation. Fecal bolus is propelled into the rectum by mass movement, causing distention and initiating the defecation reflex. The puborectalis muscle forms a sling around the rectoanal junction. To maintain continence, the puborectalis muscle must be contracted. The rectum contains vertical and transverse folds of tissue that help retain the feces. Each vertical fold contains an artery and vein. During defecation, sacral parasympathetic nerves relax this muscle and straighten the rectoangle. Rectal distention initiates temporary relaxation of the internal anal sphincter through intrinsic and reflex sympathetic innervation. The anal canal, which is about 1.5 inches long, contains an internal and external sphincter. Continual dribbling of fecal matter through the anus is prevented by tonic constriction of the internal sphincter, consisting of thick smooth muscle inside the anus. The external anal sphincter is composed of striated voluntary muscle that surrounds and extends distal to the internal sphincter. The external sphincter is controlled by nerve fibers in the pudendal nerve, which is part of the somatic (voluntary) nervous system (44,53,57). Reflexes to defecate are transmitted through the intramural nerve plexus and intensified by parasympathetic system signals or overdistention of the colon. Feces enter the

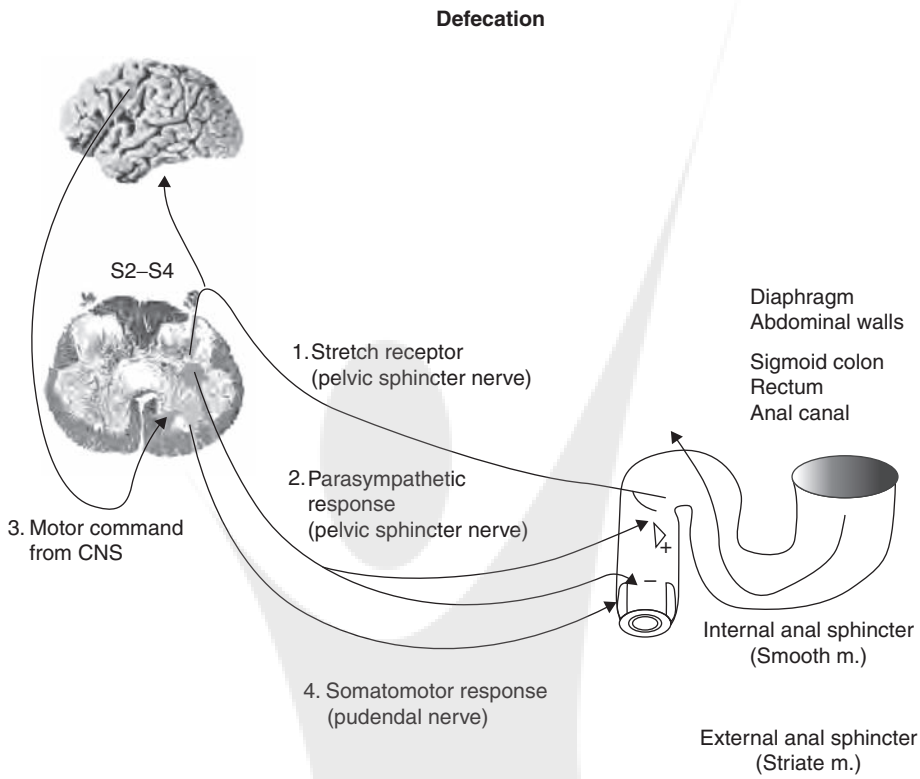

FIGURE 35.5 Colonic spinal afferents contribute to defecation. The sympathetic nerve supply to the internal (involuntary) anal sphincter is excitatory; the parasympathetic is inhibitory. The pudendal nerve supplies the external anal sphincter, which is maintained in a state of tonic contraction.

rectum, causing distention of the rectal wall and initiating afferent signals that spread through the myenteric plexus to start peristaltic waves in the descending colon, sigmoid, and rectum, forcing feces toward the anus. As the peristaltic wave moves toward the anus, the internal anal sphincter is relaxed by inhibitory signals from the myenteric plexus. As sigmoid and rectal contractions increase the pressure within the rectum, the rectosigmoid angle opens by more than 15 degrees. The external sphincter relaxes voluntarily and permits fecal defecation. Voluntary increases in intra-abdominal pressure (i.e., valsalva maneuver) can assist in defecation. If the intrinsic defecation reflex itself is too weak to be effective, it has to be supported by a parasympathetic defecation reflex that involves the sacral segments of the spinal cord. Parasympathetic nerve fibers in the pelvic nerves intensify the peristaltic waves, relax the internal anal sphincter, and convert the intrinsic defecation reflex from a weak movement into a strong defecation process (Figure 35.5). In the continent person, relaxation of the internal sphincter and forward movement of feces toward the anus initiate an instantaneous contraction of the external sphincter, temporarily preventing defecation until an appropriate time (52,57,58).

The GI tract has dual innervation. The small intestine is rich with sensory fibers. Vagal and spinal afferent nerves to the CNS carry information from activated sensory receptors. The extrinsic supply is divided into efferent and afferent branches. Information is transported in parasympathetic and sympathetic nerve tracts, provided by the vagus and spinal nerves. Most efferent parasympathetic and sympathetic fibers terminate in the myenteric plexus and form connections in enteric ganglia. Some sympathetic axons terminate directly on sphincteric smooth muscles. GI activities are carried out independent of external neural control. Cell bodies of these efferent nerves reside predominantly in the brainstem. The vagus nerve contains three groups of efferent fibers: parasympathetic cholinergic, cholinergic, and sympathetic (56). Stimulation of efferent vagal cholinergic neurons principally activates nicotinergic receptors within enteric ganglia, exciting motor activity. The vagus nerve informs the brainstem about activities of the gut. In humans, the enteric nervous system contains up to 100 million neurons, compared to only 2,000 efferent fibers in the vagus. This suggests that the intrinsic nerves direct reflexes and control activities, and extrinsic nerves serve to modulate function (59,60).

Effect of Stroke on Fecal Elimination

To improve the quality of life of patients with stroke, rehabilitation specialists need to have an understanding of how stroke may alter bowel function resulting in FI, diarrhea, and/or constipation. In addition to affecting speech and mobility, stroke can injure the cerebral areas responsible for

bowel control. Ischemic stroke can result in secondary functional changes in the peripheral organs that communicate with the affected vascular areas of the brain (60).

Incontinence

People with stroke who experience UI often have problems with bowel irregularity including constipation, diarrhea, bowel impaction, and FI. Both UI and FI after stroke are frequently the result of immobility, decreased consciousness, and/or functional dependency rather than the impairment of neural pathways. FI in stroke is often temporary and may resolve if the stroke survivor's recovery includes improved cognitive awareness and mobility (10).

Bowel problems in stroke survivors often result from multiple issues rather than a single factor. Needing help to use the toilet is one of the strongest predictors of FI after stroke. Poor mobility, impaired dexterity, changes in vision, decreased sensation, and communication can influence continence (61). Mobility and dexterity can be improved with physical and occupational therapy. The use of anticholinergic medications, including antipsychotics, tricyclic antidepressants, oxybutynin, or antiemetics, increases the risk of FI in stroke survivors by reducing contractility of smooth muscle of the gut by an antimuscarinic effect at acetylcholine receptor sites. In some cases, long-term use may induce chronic colonic dysmotility. As a comorbidity, stroke does not independently affect bowel continence in longer-term stroke survivors, but rather influences continence through associations with other clinical and functional factors. FI is not only a financial burden to caregivers and society but may also cause the stroke survivor the additional cost of social isolation and dependence. The degree of disability is the most important factor causing FI in stroke, but using constipating drugs and functional difficulties with toileting strongly influence FI at three months after stroke (50).

If incontinence is caused by external factors such as medications or mobility, it can be managed through education and therapy. A randomized controlled trial of constipation and FI management showed that one year after a nursing intervention, subjects were more likely to alter their diet and fluid intake to control their bowels and to receive different prescribed patterns of bowel agents. A single-encounter nurse-led intervention in stroke patients significantly improved measures of bowel dysfunction and changed bowel-modifying lifestyle behavior. Findings promoted structured management of bowel problems in stroke patients and encouraged health education (49). In summary, FI is the involuntary evacuation of rectal contents and is most often caused by neuromuscular disorders or structural anorectal problems. FI may be aggravated by diarrhea or urgency, but the causes of those issues must be identified separately (52).

Diarrhea

Diarrhea is the passage of atypical liquid or unformed stool at the rate of 3 or more bowel movements in 24 hours. Acute diarrhea lasts less than 2 weeks, persistent diarrhea lasts for longer than 2 weeks, and chronic diarrhea persists for more than 4 weeks. When diarrhea occurs, it is harder for the anal sphincter to hold liquid stool, as compared to stool in the semisolid state (62). Every 24 hours, the small intestine converts about 10 liters of fluid and digested food into 1.5 to 2 liters of ileal content. This volume is then converted into approximately 200 grams of solid stool by fluid absorption in the colon. When the balance between the absorptive capacity in the intestine and its secretory function is disrupted, diarrhea occurs (63). Malnutrition, tube feedings, and debility put the stroke patient at risk for diarrhea.

Infectious agents cause more than 90% of acute diarrhea. The other 10% is caused by medications, toxic ingestions, and other conditions. Infections are transmitted through fecal–oral direct personal contact, or ingestion of food or water contaminated with pathogens. Diarrhea is one of the most common sources of nosocomial infections in hospitals and long-term care facilities. There are many microorganisms in the hospital setting. Currently, the most persistent microorganism is *Clostridium difficile*. Hospitalization predisposes stroke patients to nosocomial infections. Common outbreaks usually occur through foodborne epidemics, sharing toilets, or rooming with patients with infective diarrhea. Impaired cognition, decreased mobility, and functional disabilities contribute to decreased personal hygiene. Antibiotics disrupt the gut's normal flora and break down the colon's immunity. Side effects from drug therapy are the most common noninfectious cause of acute diarrhea and can be easily determined by connecting the onset of symptoms with drug start date. In the stroke population, the most frequent diarrhea-causing drugs are antibiotics, cardiac antidysrhythmics, antihypertensives, nonsteroidal anti-inflammatories, antidepressants, antacids, and laxatives (63).

Constipation

According to the practice guidelines for the management of constipation published by the Rehabilitation Nursing Foundation, a proposed definition of *constipation* is "the passage of small amounts of hard, dry stool fewer than three times per week or a significant change in one's usual routine, accompanied by straining, and feelings of being bloated, or having abdominal fullness. Persistence of these symptoms for 3 months or longer is defined as chronic constipation" (54).

In the general population, the prevalence of constipation in North America is estimated to be between 2% and 27%. Approximately 42 million people in the United States meet the defined criteria for functional constipation (54). Twice as many women as men complain of symptoms of constipation. It is more prevalent in the elderly (older than 65 years), nonwhites, and individuals from lower socioeconomic or less educated groups. It is a serious problem in clinical practice, affecting up to 60% of those in stroke rehabilitation units (50,63). Chronic constipation is associated with GI motility and sensory disorders including functional dyspepsia, heartburn, and gastroesophageal

reflux disease (GERD). Twenty-nine percent of GERD patients also report functional constipation. Approximately 63 million people in North America meet the Rome II Criteria for constipation (64).

Constipation is linked to impairments of the central nervous system. In stroke, depending on the location of the lesion, weakness of the abdominal and pelvic muscles and hypomotility of the large bowel may occur (63). The rectum is bilaterally innervated on the motor cortex with asymmetric representation and unilateral dominance. It is uncertain if asymmetry accounts for difficulties in defecation after brain injury or if unilateral pudendal nerve injury causes a disturbance of pelvic floor function (56). Lesions affecting the pontine defacatory center disrupt the sequencing of sympathetic and parasympathetic components of defecation and impair the coordination of the peristaltic wave and relaxation of the pelvic floor and external sphincter. Drugs that contribute to constipation are diuretics, iron, antihypertensives, antipsychotics, anticholinergics, anticonvulsants, opioids, and ganglionic blockers (53,63). Tricyclic antidepressants can cause constipation induced by blocking the reuptake of norepinephrine or serotonin. Antidepressants such as amitriptyline, as well as the selective serotonin reuptake inhibitors, affect visceral sensitivity and motility (48). Ninety-five percent of the patients on opioids are constipated. Verapamil, a calcium channel blocker, causes constipation by delaying GI transit time. Antacids that contain aluminum cause constipation owing to the constricting agent. Diuretics causing fluid loss can constipate (53,63).

In patients with ischemic stroke, colorectal dysfunction is caused by a combination of lesions of the central or peripheral nervous system, immobility, or altered dietary habits. Constipation in patients with stroke has been suggested to be disruption of the neuronal modulation of colonic motility. Colonic transit time is prolonged, especially in the right colon. The mechanism of intestinal pseudo-obstruction in stroke may be defective enteric neurons, smooth muscles, or both. The exact cause of constipation after stroke requires further study. Disruption to the modulation of colonic motility must also be assessed. Because stroke is common in elderly patients, the aging effects of the GI tract have to be considered. GI changes with aging are very subtle (59,60). In conclusion, ischemic stroke may disrupt neural control of GI motility by interrupting or altering the flow of information between the cortex and the GI system. Future research utilizing positron emission test scans and magnetic resonance imaging may be able to demonstrate a relationship between bowel dysfunction and stroke (60).

History

The first component of bowel function assessment is to obtain a history from the stroke survivor. Unfortunately, this may not always be possible, because of cognitive or communication deficits. In these instances, the interviewer will need to rely on the family for information. In cases where the family is not present or unable to provide the necessary information, the nursing staff will have to be questioned.

Previous Bowel Habits

The assessment starts by obtaining information about the stroke survivor's previous bowel habits. Questions about previous bowel habits include: past problems with abdominal pain, bloating, and discomfort; hemorrhoids; episodes of constipation, diarrhea, or incontinence; frequency of occurrence; and use of medications for management. When asking questions about constipation or diarrhea, the interviewer should be specific. Often, misconceptions regarding normal bowel habits can interfere with obtaining accurate information. A scale developed at the University of Bristol, the Stool Form Scale, can be used to help improve communication. The scale provides pictures and descriptions of different stool consistencies so that the interviewer and stroke survivor are using the same terminology when discussing bowel habits. An incontinence problem that existed prior to the onset of stroke may make achieving continence more challenging.

Current Bowel Habits

Information regarding current bowel habits helps to contrast that of past bowel habits. Questions about current bowel habits include: the onset of FI; the number of incontinent and continent bowel movements; the consistency and size of the stool; the activity immediately preceding the incontinence; the ability to distinguish between passing of stool and gas; the presence of urgency, pain, or other symptoms; and the presence of blood in the stool. Changes in bowel habits may be because of stroke-related deficits, prolonged hospitalization, changes in diet, medications, or the development of a new medical problem.

Past Medical History

The health care practitioner should obtain information about a previous history of small bowel obstruction, inflammatory bowel disease, malabsorption syndromes and treatment, GI surgery, trauma to the abdominal area, neurologic diseases that affect the central or peripheral nervous systems, diabetes that can affect gastric motility, antibiotic therapy, and urology problems. With male stroke survivors, the interviewer should ask about the presence of sexual dysfunction that may suggest impairment of pelvic floor innervation (65). With female stroke survivors, the interviewer should ask about the obstetrical history. In multiparous women, stretch injuries or lacerations of the pelvic floor are common causes of anorectal denervation and sphincter damage (65). All of these could likely contribute to FI after stroke.

Fluid and Dietary Intake

The examiner should determine the amounts, types, and timing of fluids consumed. Decreased fluid intake, or the intake of diuretic fluids, can increase the risk of constipation. Fluid intake should be spaced throughout the day to ensure that 2 liters or 8 to 10 glasses of fluid are consumed. Stroke survivors drinking thickened liquids need to be encouraged to increase their fluid intake to prevent constipation. Inquiries about dietary intake should focus on the amount of dietary fiber consumed, potential dietary irritants, and food allergies.

Fluid and oral caloric intake must be monitored closely in stroke survivors on modified consistency diets or enteric feedings secondary to dysphagia. These individuals will have the same incontinence problems but present a bigger challenge because of their swallowing impairment.

Medication Review

With a hospitalized stroke survivor, it is much easier to monitor the medications he or she is taking, as rarely does one take anything other than that prescribed by the physician or administered by the nursing staff. With a stroke survivor who is at home, it is important to find out not only what prescription medications the person is taking, but also any over-the-counter medications, vitamins, and herbal supplements being taken. Not only can certain medications affect stool consistency and GI motility, but medications can also affect a person's level of alertness, balance, or coordination, which can contribute to incontinence.

Functional Status

Functional assessments performed by the rehabilitation team in all areas of mobility and activities of daily living are a necessary part of the bowel function assessment. Knowledge of the stroke survivor's cognitive status determines whether the person can identify the need to have a bowel movement and act upon it. It is important to know about the survivor's communication status. Aphasia or dysarthria may make it difficult for the survivor to communicate his or her needs for toileting. Sensory perceptual deficits may make it difficult to identify the bathroom, or to know what to do or where to go once in the bathroom. Visual deficits may make finding the bathroom difficult. Mobility or balance deficits will make it difficult to get to the bathroom, manage clothing, transfer to the toilet, and manage hygiene. If the environment is not wheelchair accessible, or if appropriate equipment is not available, establishing an effective program will be more difficult. For those stroke survivors who are home, it will be necessary to assess the environment and equipment available to assist with toileting.

Bowel Diary

In cases where the stroke survivor is unable to provide information to the interviewer about current or previous bowel habits, it may be necessary to keep a bowel diary. The diary is a document that will provide the interviewer with information about current bowel function. Any rehabilitation treatment team member can develop a form to obtain the necessary information. The team or family member completing the diary should record fluid intake and timing, continent and incontinent bowel movements and timing, and consistency of stools. The diary can also assist the rehabilitation professional with documentation once a program has been put into effect.

Physical Examination

The next component of the assessment is the physical examination. The examiner should always explain to the stroke survivor what is to occur throughout the assessment. The first part of the physical examination begins with a visual inspection of the abdomen. The examiner should observe for surgical scars that might indicate past GI surgery, or an enlarged, protuberant abdomen that may suggest gas, tumor, pregnancy, or fluid collection. The examiner then auscultates for bowel sounds. Hypoactive bowel sounds could be a sign of constipation, impaction, obstruction, paralytic ileus, or peritonitis. Hyperactive bowel sounds could be a sign of diarrhea or intestinal obstruction. The examiner then palpates the abdomen, assessing for tenderness, masses, and enlarged organs.

After examination of the abdomen, the stroke survivor should be asked or assisted to turn to his or her left side. The next portion of the physical examination is assessment of the anus and rectum. Using two hands, the examiner gently spreads the buttocks, looking for the presence of stool, hemorrhoids, fissures, skin breakdown, bulging, or gaping of the anal opening. These findings are suggestive of sphincter weakness and could help identify the potential cause of incontinence (45). Using a cotton-tip applicator, the examiner gently strokes the perianal area on either side of the anus. This should elicit a contraction of the external sphincter called the *anal wink*. The cotton-tip applicator can also be used to assess perianal sensation. The examiner then asks the stroke survivor to bear down gently, while looking for a bulging of the anus. A small amount of bulging is normal, but a large bulge, loss of stool, or organ prolapse is not. The examiner is now ready to perform a digital rectal examination. Using a lubricated, gloved index finger, the examiner gently checks the rectal vault for the presence of stool. At the same time, the examiner assesses anal tone. The examiner asks the stroke survivor to tighten the external sphincter around the gloved finger assessing for tone. The sphincter should tighten evenly around the gloved finger. Loss of rectal tone suggests that a significant neurologic problem is present.

Diagnostic Tests

There will be instances when some stroke survivors will require diagnostic testing. Diagnostic testing can provide additional information that will assist the health care practitioner determine the potential cause of FI. In stroke survivors with hypoactive bowel sounds, abdominal distention, or oozing of liquid stool upon examination, or when the exact date of the last bowel movement is unknown, a simple abdominal radiograph can identify the presence of stool or impaction in the GI tract. In the stroke survivor with hyperactive bowel sounds, abdominal discomfort, and large amounts of liquid stool, a stool culture can be obtained to rule out infection. Checking stool for occult blood also can help to rule out GI bleeding as a cause of incontinence or diarrhea.

Other diagnostic tests are available, but these are not performed frequently as part of an assessment. When there is a history of previous GI problems, neurologic complications, or the assessment does not help identify a problem, the stroke survivor should be referred to a gastroenterologist

for further testing. Additional testing may include upper or lower GI tract endoscopy, balloon expulsion testing, anorectal manometry, colonic transit testing, endoanal ultrasound and magnetic resonance imaging, and defecography (66).

Treatment

The management of FI after stroke is often easier to address than UI. Depending upon the problem, the stool may have to be softened for easier passage, or bulked up to increase sensory input. A regular toileting schedule may have to be devised. A combination of methods may be implemented. It is important to be realistic when establishing goals for the stroke survivor. It may take several months to achieve 100% continence. Initially, the goal may be to decrease the frequency of incontinence or simply to regulate the individual with a program.

Nonpharmacologic Treatment: Diet

Increasing the fiber content in a diet can add bulk to stool to help increase size and improve rectal sensation. Fiber taken appropriately can also prevent constipation. Fibrous foods are poorly digested and remain in the lumen of the GI tract. They help form viscous, gel-like substances (54). The American Dietetics Association recommends 20 to 35 grams of fiber per day to maintain normal bowel function (67). This amount should be built up slowly in those who do not normally consume this amount of fiber, to prevent abdominal cramping. In those individuals who cannot ingest that amount of fiber in their diet, supplemental fiber can be used. Various supplements and recipes of bran, prune juice, and applesauce can help to increase dietary fiber intake (68). Bran, psyllium, guar gum, and fiber concentrates can also be purchased to increase fiber intakes.

Fluids

The intake of fluid is very closely related to dietary intake. Although increased fiber intake is effective in managing constipation, diarrhea, and FI in stroke survivors, an insufficient intake of fluids (especially with increased fiber intake) can actually be more harmful than beneficial. The American Dietetic Association recommends that the average person take in 2 liters of liquid or 10 to 12 glasses of fluids per day. The type of fluid should also be carefully monitored. The stroke survivor should avoid caffeinated and alcoholic fluids. These fluids are diuretics and can worsen dehydration. In situations when the stroke survivor has an elevated temperature, diarrhea, and vomiting, fluid intake should be increased. Hot or warmed fluids help promote peristalsis and can be used to assist in achieving continence.

Activity/Exercise

Although research has been inconclusive regarding the effects of exercise and activity on bowel function, many health care practitioners will agree that remaining active helps improve appetite, shortens food transit time through the GI tract, and improves bowel function (54,68). In those who have just suffered a stroke, activity and mobility are severely impaired. Participation in a rehabilitation program will help improve activity. Any activity that helps with reestablishing muscle tone can help return bowel function (44). Walking, leg lifts, stationary bicycling, turning in bed, hip lifts, or a home program are just some examples of exercises that have been tested, but none has been found to be more effective than another (54).

Positioning is also an important part of bowel function. As soon as the stroke survivor can tolerate it, sitting at 90 degrees will help gravity empty the rectal vault and decrease the risk of incontinence. The use of raised toilet seats or bedside commode chairs helps to improve compliance. Bedpans should be avoided whenever possible because gravity will not assist in emptying and because of the increased risk of skin breakdown. In those with poor muscle tone, the use of a stepstool under the stroke survivor's feet can help promote emptying. A squat position with the knees slightly higher than the hips improves the passage of stool by increasing abdominal pressure (44). If the person has sufficient trunk control, bending at the waist also can help increase abdominal pressure. Abdominal massage from right to left can also assist with emptying (68). The valsalva maneuver or bearing down should be avoided in any stroke survivor with an unstable cardiac history.

Timing/Privacy

A regular toileting schedule should be established to help decrease FI in the stroke survivor. When setting up a program in the hospital or for the home, the stroke survivor's schedule should be considered. Toileting after meals can help use the gastrocolic reflex to the survivor's advantage. Initially, the stroke survivor may need toileting after every meal, but morning toileting programs have been found to be more effective (69). The stroke survivor should also be provided with plenty of time and privacy for appropriate evacuation. If the person is rushed while having a bowel movement, inadequate emptying may occur. Over time, this can lead to constipation and impaction. Privacy should also be provided to avoid embarrassing odors or sounds. If the stroke survivor anticipates embarrassment from odors or sounds that could be made during toileting, the defecation reflex may be extinguished, which can lead to or worsen constipation or FI over time.

Education

For a program to remain effective, it is necessary that methods implemented be carried over by the stroke survivor. The individual should be taught the importance of maintaining nonpharmacologic treatment methods to prevent constipation, diarrhea, or FI. Misconceptions regarding bowel habits should also be corrected. The stroke survivor should be educated on how to make changes to his or her program when ill or as bowel habits change over time. Rehabilitation staff

should be educated on how to explain the purpose of programs to stroke survivors and their families. Often stroke survivors and families do not understand the purpose of rectal medications and toileting programs to regulate the frequency of incontinent bowel movements. Education will help improve compliance and encourage family assistance. When the date of the last bowel movement is unknown, it will be difficult to establish if the stroke survivor is truly incontinent or simply impacted. It will be necessary to give a rectal or oral laxative to "clean out" the stool before establishing a program. Stroke survivors and families should be made aware of this to prevent misunderstanding on the use of laxatives. The treatment team should be educated on the need to work together to ease the burden of care in a program. Physical therapists can help train staff and families to ease the effort needed for toilet transfers. Equipment that will ease toileting should be issued to the stroke survivor. Occupational therapists can help families or staff identify appropriate clothing to make management and hygiene less difficult. Speech–language pathologists can work with staff and families on developing a communication system that will notify them when the stroke survivor feels the need to use the bathroom. Nursing staff can ensure that a program is in place and monitor the need for changes based on results.

Pharmacologic Treatment

There will be cases when nonpharmacologic treatment alone is not effective in achieving continence. In these instances, it will be necessary to combine nonpharmacologic and pharmacologic treatment to improve continence. When selecting a medication for the stroke survivor, careful attention should be paid to medical history, ease of administration, and availability of a caregiver. Those stroke survivors who use pharmacologic treatment should be monitored closely by a health care practitioner to ensure that the individual does not develop long-term problems.

Bulk-Forming/Hydrophilic Laxatives

This category of medications softens stool by increasing water content. This increases the frequency of stools. The site of action is the small and large intestine. As mentioned earlier, the stroke survivor should drink at least one 8-ounce glass of water with each dose of medication. The onset of action can be as little as 12 hours, or up to 3 days. The most common side effect is abdominal bloating. Bulk-forming agents should be avoided in those individuals with esophageal narrowing, intestinal adhesions, ulcers, or bowel stenosis (70). Several studies have used bulk-forming agents to manage constipation or decrease FI in stroke survivors (49,71). Examples include psyllium, methylcellulose, and calcium polycarbophil.

Stool Softeners/Lubricant Laxatives

This category of medications decreases the surface tension of the stool by adding water and fatty substances. This medication does not induce defecation; it simply softens stool, making it easier to pass. The site of action is the small and large intestine. The onset of action is as little as 6 to 8 hours, though it can take up to 3 days (70). The most common side effect is loose stool that ceases when the medication is discontinued. Examples include docusate sodium, docusate calcium, and mineral oil. Tramonte et al. cited multiple studies that used stool softeners and found them to be very effective in increasing the frequency of stools (71).

Stimulant Laxatives

This category of medication alters water and electrolyte balance, thereby stimulating intestinal motor function. The site of action is the mesenteric plexus. This category of medications includes rectal and oral forms. The onset of action in the rectal forms is 15 to 60 minutes. The onset of action in the oral forms is 6 to 12 hours. The most common side effect is abdominal cramping. This category of medication is not recommended for long-term use (53). Examples include senna, bisacodyl, and cascara.

Hyperosmotic Laxatives

This category of medication increases intraluminal pressure by increasing water content, thereby stimulating peristalsis. The site of action is the small and large intestine. This category of medications can be found in oral or rectal forms. The onset of action of the oral form is 1 to 2 days. The onset of action of the rectal form is 30 to 60 minutes. There are minimal side effects with the rectal preparations, but the oral preparations can cause abdominal cramps, diarrhea, and electrolyte imbalances. Examples include sorbitol, lactulose, sodium biphosphonate, and polyethylene glycol. Tramonte et al. reviewed three studies that found an increase in bowel movement frequency and improvement in stool consistency when lactulose is used in long-term care and outpatient settings (71).

Research Frontiers

Future research should focus specifically on the management of FI. A great deal of work has been done on the management of constipation, but little on its management specifically after stroke. Although many textbooks outline how to set up a bowel program, only Venn et al. (1992) (69) and Harari et al. (2004) (49) analyzed the use of nonpharmacologic and pharmacologic management and the effectiveness of bowel training. Even these authors recommended larger and longer longitudinal studies of patients who have effective bowel habits after discharge from rehabilitation. Traditionally, rehabilitation hospitals utilize rectal suppositories for the regulation of incontinent bowel movements, but this can be very distressing for the survivor and difficult for the family to understand. Research should also address the effectiveness of suppositories versus toileting programs, and whether stroke survivors achieve continence sooner with either or a combination of both interventions.

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VI

OTHER REHABILITATION THERAPEUTICS

36

Orthotic Management in Stroke

Stefania Fatone and Bryan Malas

The word "orthosis" is derived from the Greek word *orthos*, meaning "to make straight." The International Standards Organization (ISO 8549-1, 1989) defines an *orthosis* or *orthotic device* as "an externally applied device used to modify the structural or functional characteristics of the neuromusculo-skeletal system." The standardized nomenclature for orthoses is based on the principal joint or joints that the orthosis encompasses. For example, an ankle–foot orthosis (AFO) physically encompasses the ankle and foot and provides control principally at the ankle, whereas a wrist–hand orthosis (WHO) encompasses the wrist and hand and provides control principally at the wrist. Often, orthoses are further described based on the control exerted on the joints they encompass; for example, a plantar flexion stop AFO or dorsiflexion assist AFO. Orthoses may allow free motion, resist or assist motion, stop motion, or provide an adjustable hold or lock (1). The basic functional goals of orthoses are to provide support, correct deformity, or modify motion occurring at a joint, either assisting motion where it is insufficient or substituting motion where it is absent. Overall, it is generally intended that orthoses aid function.

Generally, orthoses are designed based on biomechanical principles, working primarily through the application of force systems to relieve unwanted forces or moments from the body. However, the amount of force applied by orthoses is limited by tissue tolerances so as not to cause tissue injury (1). Orthoses affect normal movements by applying selective forces in relatively limited directions (1). Control of joint motion is generally achieved through the application of one or more three-point for6ce systems, consisting of two counter (stabilizing) forces and one active (corrective) force applied proximally and distally to a joint to produce angular change in a specific plane (Figure 36.1). Generally, the more complex the impairment, the more three-point force systems are incorporated into the orthosis design. Orthoses may act directly or indirectly: an orthosis acts *directly* if it surrounds the segment or joint that it is attempting to influence, and *indirectly* if it attempts to modify the external forces acting on a joint beyond its physical boundaries (2). For example, during the stance phase of gait, an AFO acts directly on the ankle but indirectly on the knee by influencing the moments acting at the knee (Figure 36.2). Indirect action of the AFO at the knee is predicated on the closed kinetic chain occurring during stance phase and hence is not applicable during swing phase.

With respect to neurologic conditions such as stroke, orthoses may also incorporate design modifications based on neurophysiologic principles. These principles are derived from neurodevelopmental therapies such as those developed by Bobath (3) and used in inhibitive casting. Orthoses designed using neurophysiologic principles attempt to use sensory feedback (e.g., inhibition of reflexes, pressure over muscle insertions, active and static prolonged stretch, and orthokinetics—the physical effect of materials placed over muscle bellies) to decrease tone and improve isolated motor control, in particular facilitating movement patterns associated with decreased tone, while inhibiting movement patterns associated with increased tone (1,4). Tone-reducing modifications are commonly found in the footplate of lower-limb orthoses or the palmar area of upper-limb orthoses. Although there is some evidence to support the biomechanical effects of orthoses on joint motion and alignment (5,6), there is little evidence to support the neurophysiologic effects of orthoses on tone and spasticity (4,7,8).

Orthotic management of the lower limb in stroke is intended to facilitate function, primarily the ability to stand and walk as safely and efficiently as possible. In the upper limb, orthotic management is intended mainly to avoid the development of orthopedic complications because of muscle weakness and abnormal tone (9), although the use of orthoses to facilitate functional improvements is emerging (10,11).

The use of orthoses should be considered as part of an overall management plan during both the acute and chronic stages of stroke rehabilitation (12,13). Furthermore, as stroke recovery is a dynamic process, the use of orthoses should be intermittently reassessed to keep pace with the individual's changing abilities. Generally, the primary goal of orthoses during the acute phase is to maintain range of motion and prevent joint contractures that may interfere with eventual functional outcome (although this may change with increased understanding of the therapeutic benefits of functional electrical stimulation [FES] (14)). Prefabricated orthoses may be used initially during the acute phase as an interim measure while changes are occurring and a definitive

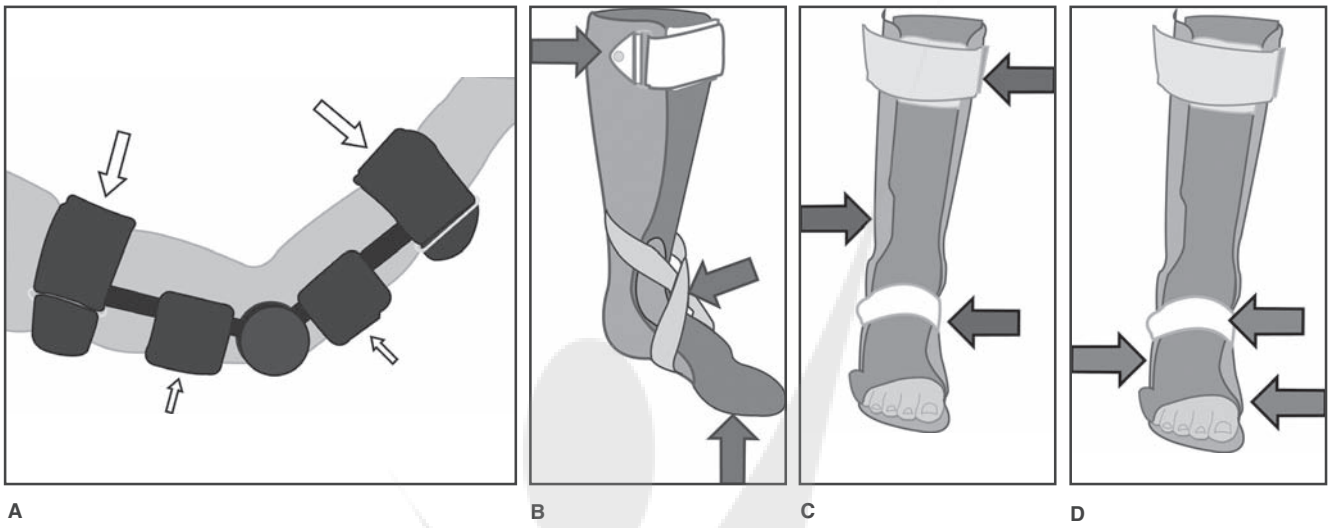

FIGURE 36.1 Examples of three-point force systems used in orthoses for the hemiplegic limb: (A) static progressive contracture management of an elbow flexion contracture with stabilizing forces at each end of the orthosis and the net corrective force acting immediately proximal and distal to the posterior elbow; (B) control of ankle dorsiflexion/plantar flexion using an AFO with stabilizing forces acting on the limb proximally at the posterior calf shell and distally under the plantar surface of the foot with a counterforce over the anterior aspect of the ankle, often through an ankle strap; (C) control of ankle inversion in spastic hemiparesis using an AFO with stabilizing forces acting on the medial arch and medial proximal calf, and the corrective force acting through a flange on the lateral distal tibia; and (D) control of forefoot adduction using an AFO with stabilizing forces acting on the medial aspect of the heel and along the first metatarsal shaft, with a counterforce on the lateral midfoot. Arrows indicate the application of forces.

prescription is unclear, or until a definitive, custom orthosis is ready (12). Adjustable orthoses are often preferred during the acute phase, because they can keep pace with the changes occurring such as with improvements in function. Individuals who demonstrate long-term need for orthotic treatment should receive custom orthoses to provide the necessary degrees of control, correction, and comfort, and the highest degree of compliance in use (13). Currently, no experimental evidence is available regarding optimum timing of orthotic management (12). Hence, we do not know yet whether early orthotic management is superior to waiting until most natural recovery has occurred before making a decision about orthotic management (1). As a result, clinically there appears to be a trend to providing individuals with articulated AFOs that are "uncut" and initially function as solid AFOs. As the person gains function, the same AFO can be cut and articulated to coincide with functional gains. These trends are not surprising and are consistent with recovery statistics for stroke showng that 50% to 70% of stroke survivors regain functional independence, whereas 15% to 30% are permanently disabled (15).

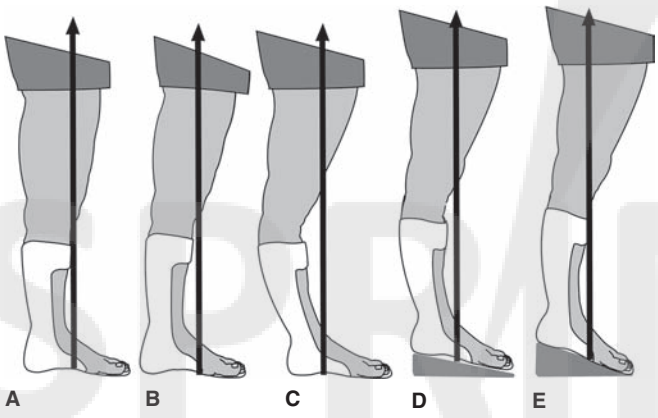

FIGURE 36.2 Indirect action of a nonarticulated, rigid ankle–foot orthosis on the knee during single limb stance: (A) AFO set at 90 degrees; (B) AFO set in dorsiflexion; (C) AFO set in plantar flexion; (D) AFO set in plantar flexion and supported by a small wedge; and (E) AFO set in plantar flexion and supported by a bigger wedge. Note the position of the vertical ground reaction force vector (arrow) with respect to the knee joint, which is indicative of the external knee moment.

For orthoses to be successfully used in the management of stroke, they must be safe, and there must be realistic outcome expectations and appropriate follow-up to ensure proper fit and function. There must be adequate strength and stability of the orthosis to ensure that anatomical joints are protected from unnecessary damage. Orthoses must also minimize the pressure and friction applied to skin and bony prominences by careful fitting and padding. Furthermore, the axes of mechanical joints must be aligned with those of anatomic joints to avoid undesirable torques and motion between the orthosis and the body (16,17). It is also important to realize that most individuals require a period of adjustment or training when receiving an orthosis to achieve maximum benefit (1).

The objective of this chapter is to provide an overview of current practice in the orthotic management of stroke for both upper and lower limbs, describing different orthotic treatments, when and why they are provided, and how they work.

ORTHOTIC MANAGEMENT OF THE UPPER LIMB

Orthoses play a role in preventing or correcting upper-extremity deformities in stroke that result from limited range of motion (18). After stroke, range of motion may be limited by, among other things, immobilization, paresis, increased muscle tone or spasticity, and myostatic contracture (18). Development of contracture is common in the hemiplegic limb, owing to the presence of spasticity and abnormal muscle tone that is inherently resistant to passive stretch (19). Most commonly, the presence of spasticity after the onset of stroke prevents adequate range of motion and, if left untreated, leads to deformity. Although orthoses can be used to prevent deformity, it is often important to treat the underlying spasticity when it is severe to enable safe use of an orthotic device to effectively position the limb. Such treatments may include pharmacologic intervention, serial casting, and surgery, either in isolation or combination. If spasticity is not controlled, the forces required within the cast or orthosis to position the limb may be so great as to cause tissue breakdown. Where spasticity remains, orthoses may have to completely encompass the limb to adequately control position while minimizing the risk of skin breakdown (18).

Paresis following stroke can also contribute to the development of various abnormalities and deformities, especially when coupled with spasticity. Subluxation of the glenohumeral joint is common after stroke, with a reported incidence of 81% to 85% in individuals with spasticity following stroke, and may result in pain and decreased function (20,21). Although shoulder pain is also very common in the hemiplegic upper limb, with a reported incidence of 38% to 84% of individuals with stroke, studies have been unable to establish a direct cause-and-effect relationship between shoulder pain and glenohumeral subluxation (20–25). Despite a lack of evidence regarding whether shoulder subluxation is the primary cause of pain in individuals with stroke (9,19), devices such as slings and wheelchair attachments may be prescribed to prevent subluxation and pain. Unfortunately, some of these devices also markedly restrict shoulder motion, which may diminish function and compromise hygiene. Though there is insufficient evidence to decide whether devices such as slings and wheelchair attachments prevent subluxation, decrease pain, increase function, or adversely increase contracture in the shoulder after stroke (26), a recent study suggests that wearing a vertical humeral cuff sling (similar to that shown in Figure 36.3B) may reduce the laxity of the inferior glenohumeral joint under external loading (27).

Paresis, disuse, and poor positioning of the upper limb may also result in painful edema of the hand. Where possible, the arm is elevated at or above heart level to assist with venous return. A person who is limited to a bed or wheelchair may benefit from pillows or foam wedges placed on a lap board to elevate the arm. In ambulatory individuals, compression gloves may be used to control edema of the hand and wrist. A sling may also be used to support the arm in a position that limits development of edema. However, slings also immobilize the arm and, depending on design, increase flexor tone (9) (Figure 36.3).

At the elbow, flexor spasticity and contracture are common and often severe. Flexion contractures are painful and can lead to breakdown of the antecubital skin and place traction or pressure on the ulnar nerve in the cubital tunnel (18). Similarly, at the wrist, spastic forearm flexors typically cause wrist and finger flexion deformities. Carpal tunnel syndrome is a common orthopedic problem in the hemiplegic arm (28). Orthotic treatment is primarily aimed at preventing wrist flexion so as to alleviate pressure on the median nerve.

Generally, upper-limb assistive devices, including plaster casts, slings, wheelchair attachments, and orthoses, are used following stroke to prevent or correct contracture, maintain limb position, and improve or assist function. Upper-limb orthotic devices are regarded as either static or

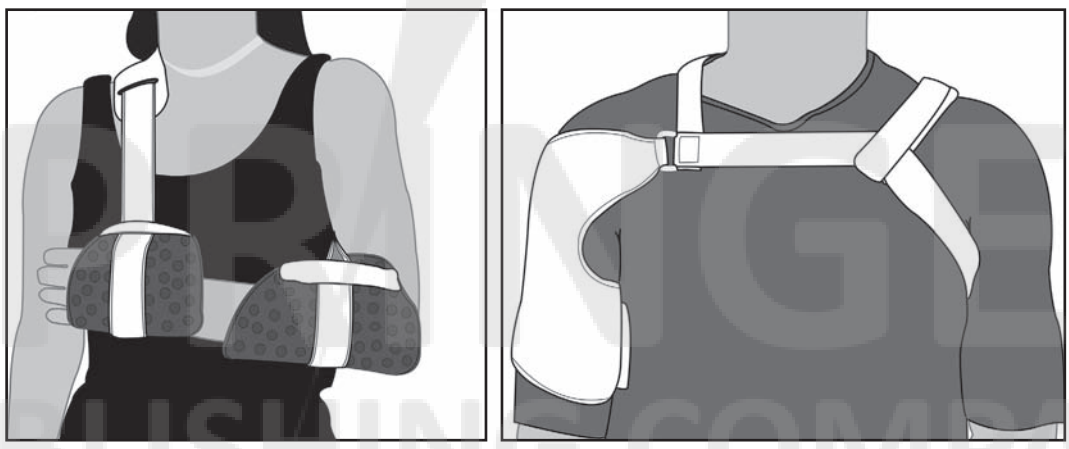

FIGURE 36.3 Examples of two slings: (A) the hemiplegic arm sling and (B) the vertical humeral cuff sling. Both slings attempt to reduce pain caused by shoulder subluxation by supporting the weight of the arm and reducing shoulder subluxation. However, they differ in the position in which the arm is held, with the hemi-sling encouraging a flexed posture.

dynamic. Static orthoses hold the joints in optimum positions to reduce painful motions, prevent or correct deformity, and facilitate function. Dynamic orthoses provide mechanical assistance to joint motion where muscles are weak or paralyzed or where muscle imbalance across joints is present (29). However, orthotic prescription for the upper limb remains primarily empirical, as few upper-limb orthotic devices have been subjected to controlled analysis (9). Furthermore, compliance with use of orthoses is often poor in individuals with hemiplegia, owing to the overall neglect of the involved limb and difficulty with donning and doffing of the orthosis. Many individuals simply use the uninvolved side for activities of daily living.

Contracture Management

Contracture management is important for both the upper and lower limb, as more than 50% of individuals develop contractures following stroke (30). Immobilization, muscle weakness or paralysis, and spasticity are the three main factors leading to the development of contractures that variously affect the joint, contractile tissue, and connective tissue (31). Along with other treatments, such as surgery, passive stretching, and botulinum toxin, casts and orthoses may be used to prevent and correct contractures. There are three main types of orthoses for contracture management: custom orthoses that hold the limb at the limit of range of motion but must be replaced when range of motion is gained; static progressive orthoses, which operate under the same principle as serial casting; and dynamic orthoses.

Casts

Three goals of casting for spasticity have been identified in the literature: increasing or preventing loss of passive range of motion by maintaining muscle fiber length, reducing hypertonicity by decreasing sensory input, and improving function. However, available evidence only supports the use of casts to improve passive range of motion (32). Traditionally, different types of short-term plaster casts (or casts made from other materials such as fiberglass) have been used, sometimes in conjunction with other spasticity management, to prevent or correct contracture. Circular casts applied while an individual is immobile prevent contracture formation, whereas serial casts applied and reapplied at frequent intervals (static progressive stretching) correct contractures. Types of casts include long-arm casts, typically for elbow flexion contracture; short-arm casts, typically for wrist flexion contracture; thumb spica casts for thumb-in-palm deformity (Figure 36.4A); and finger casts for flexion contractures of the interphalangeal joints. By holding the muscle in a lengthened position, both types of casts increase sarcomeres (31). However, the limb is also immobilized, which may allow the antagonists to atrophy and shorten, or lead to fibrous adhesions within the joint space and connective tissue inextensibility (31). Therefore, the challenge is to apply the correct amount of load and use it for the correct period of time to remodel connective tissue without causing further immobility.

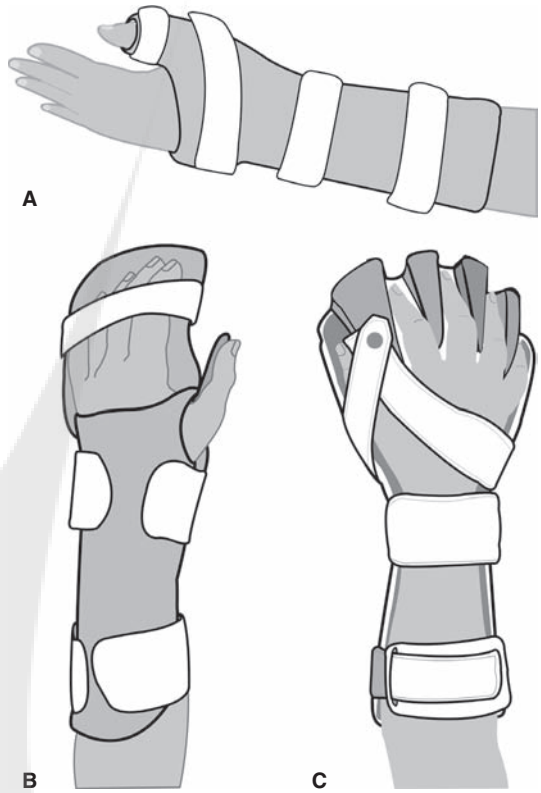

FIGURE 36.4 Examples of static wrist–hand orthoses (WHO): (A) thumb spica orthosis, (B) dorsal WHO, and (C) rigid volar WHO.

Dropout casts may be used when complete immobilization is unnecessary, as they allow movement into the desired range of motion but limit the progression of deformity by preventing motion in the opposite direction (18,31). Bivalved or clamshell designs allow casts to be removed for limb inspection, hygiene, or therapy, but should not be used in the presence of severe spasticity, as they do not provide sufficient immobilization of the limb to protect the skin from shearing and breakdown, nor should they be used where the limb is insensate or when cognition is impaired (18).

Static Progressive Orthoses

Orthoses can also be used to apply a static progressive stretch to joints with limited range of motion owing to contracture (e.g., Joint Active System [JAS], Thera Tech Equipment, Inc.™, Bloomingdale, IL; Air Cast, Vista, CA; turnbuckle orthoses) (33–35). Similar to serial casting, static progressive orthoses allow for incremental changes in joint position, which are then held constant for a prescribed period of time. However, static progressive orthoses also allow patient-directed therapy, as the stretch or force applied is typically increased by the patient to increase range of motion during the period of orthosis use. Static progressive stretch applied to contracted muscles is intended to restore the lost range of motion through the biomechanical principle of stress–relaxation (31); soft tissues respond to mechanical loads in

the same manner as a viscoelastic material, such that when stretched and then held at a constant length, the tendency to rebound gradually declines, leading to permanent plastic deformation rather than an elastic response (36). Static progressive orthoses are typically used for 30 minutes, two to three times per day, although it is possible for them to be applied for considerably longer periods (e.g., up to 6 to 12 hours). Unfortunately, there is scant evidence in the literature as to the most efficacious protocol for management of contracture in individuals with stroke. Joints that allow smoother incremental adjustment of joint position have replaced the use of ratcheting joints in static progressive orthoses, so that current orthotic technology allows the same degree of customization of joint position as casting.

Compared to serial casting, static progressive orthoses can be easily removed at regular intervals to allow inspection of the limb and maintenance of hygiene. Orthoses also reduce some of the risks of immobilization by allowing intermittent stretching of the antagonists, thus maintaining sarcomeres and some normal activity that helps reduce connective tissue accumulation (31). However, despite maximizing lever arms and pressure distribution wherever possible, individuals with both contractures and spasticity are particularly at risk for skin breakdown and may not tolerate a prolonged amount of time in a static progressive orthosis (19).

Dynamic Orthoses

Any technique that holds the joint in a fixed position, like static progressive stretching, will lose its stretching effect after a short period of time owing to relaxation of the connective tissue. Hence, dynamic orthoses were developed that apply a continuous stretch to contracted tissue and are commonly used for 6 to 12 hours (37). Dynamic orthoses attempt to stimulate continuous lengthening by operating under a different biomechanical principle than static progressive orthoses: that of creep rather than stress–relaxation. *Creep* is a loading condition where a force or load is held constant over a long period of time, whereas the displacement is allowed to vary (36).

Dynamic orthoses use a spring to generate torque at the contracted joint. There are three main types of springs used in dynamic orthoses, each with its own advantages and disadvantages: coil springs (e.g., Dynasplint®, Dynasplint Systems, Inc., Severna Park, MD), gas springs (e.g., ORLAU Contracture Correction Device, ORLAU, Oswestry, Shropshire, UK), and clockwork or flat springs (e.g., Advance Dynamic ROM®, Empi, St Paul, MN; Ultraflex Systems Inc., Pottstown, PA). Coil springs produce a linear force that is proportional to the change in length of the spring; in gas springs, the force produced depends on the gas pressure; and in clockwork springs, the torque produced is almost constant throughout the functional range (38). Because not all springs are capable of maintaining a constant torque throughout the joint range, they will need adjustment when range of motion improves if torque level is to be maintained (38). The advantages of spring mechanisms are that they provide an immediate dynamic response to activity by applying a controlled level of torque, and the spring tension can be set so that the user can overcome the stretching effect in the event of something like a spasm but will return to the stretched position (38). For the applied forces to be tolerable, dynamic orthoses should incorporate large interface areas located as far distally as possible from the joint undergoing stretch, to maximize the lever arm (38). It is important to be aware that the application of a mechanically generated load to a joint will generate relatively static compressive forces across the joint surface compared to normal physiological activity, which is more dynamic and results in periodic unloading of pressure from the joint surface (39). Hence, the prolonged use of orthoses should be undertaken with caution to limit compressive loading and its effect on cartilage (39). Although it has been reported that low-load prolonged stretch produces more increase in tendon length than a high-load stretch applied for a short time (40), the evidence is not definitively in favor of one protocol or the other (41).

To prevent contracture or maintain correction following resolution of contracture, static or fixed-position orthoses that hold the joint at the limit of its range of motion may be used (38). Such orthoses may be made from low- or high-temperature thermoplastics, depending on the expected life span of the orthosis (see the "Management of Limb Position" and "Management of the Hemiplegic Wrist and Hand" sections).

Management of Limb Position

Various devices can be used to improve or assist function by positioning the limb adequately for use. At the shoulder, proper positioning and support of the weakened or subluxed upper extremity may help to decrease pain, prevent inferior subluxation, and avoid the development of secondary problems. Individuals with paresis or spasticity of the shoulder, who are restricted to bed, tend to develop adduction and internal rotation contractures. In such cases, a foam abduction pillow can be used to position the shoulder in slight abduction and neutral rotation, preventing contracture and facilitating care and hygiene.

For nonambulatory individuals, the arm may be supported by a lap board placed over the arms of a wheelchair or by wheelchair-mounted slings and arm supports. Slings are the simplest and most common devices used with ambulatory individuals who require support of a flail arm to prevent inferior subluxation of the shoulder. Slings are inexpensive, lightweight, portable, and generally accepted by individuals. Examples include the hemi sling, figure-of-eight clavicular sling, the Bobath sling with axillary roll, the vertical humeral cuff sling, and the distal support sling that engages the thumb and wrist (Figure 36.3) (9). Although there are many different types of slings, no one type of shoulder support appears to be superior in reducing glenohumeral subluxation (9). The disadvantages of slings are that they immobilize the arm, have a tendency to increase flexor tone, and transfer a load that may adversely affect the neck and contralateral shoulder.

Management of the Hemiplegic Wrist and Hand

Upper-extremity orthoses have most commonly been used distally in individuals with stroke (1). The main goals of orthotic management of the hemiplegic hand are to reduce flexor tone at the wrist and fingers; avoid flexion contractures and deformities (e.g., thumb-in-palm and Boutonniere deformities of the fingers—where the proximal interphalangeal joint [PIP] is flexed and the distal interphalangeal joint [DIP] is hyperextended); maintain the hand and wrist in a comfortable, anatomically neutral position; and avoid carpal tunnel syndrome and hand edema (9,19). Avoidance of wrist and hand contractures not only serves a cosmetic purpose, it also allows adequate hygiene and skin care of the hand to be performed (9). Generally, rigid or static resting WHOs are used to position the hand in a "functional position," with 20 to 30 degrees of wrist extension, 35 to 45 degrees of metacarpophalangeal (MCP) joint flexion, 20 to 45 degrees of PIP joint flexion, 10 to 20 degrees of DIP joint flexion, and the thumb carpometacarpal joint partially abducted and opposed (42–44). Although such orthoses provide support for weak wrists and hands, they limit the range of motion and hence function. They are also constructed with rigid materials that are very unforgiving in the event of spasm or increased tone, especially if correction of the deformity is overly aggressive; moreover, it has been suggested recently that they often contribute to deformity rather than prevent it (42). Hence, it has been proposed that use of more flexible materials that provide support but "give" a little in the event of increased flexor tone, as well as positioning of the MCP, PIP, and DIP joints in neutral to stretch flexor muscles, and better strap placement to more positively secure the fingers (e.g., SaeboStretch, Saebo Inc., Charlotte, NC), would result in less deformity and greater compliance with orthotic management (42). Unfortunately, research as to the relative benefits between particular WHOs in the management of individuals with stroke has not been extensively performed.

Dorsal and volar WHOs are lightweight thermoplastic devices that utilize three-point force systems to maintain the wrist, thumb, and fingers in a functional position. The dorsal WHO primarily contacts the posterior surface of the forearm, providing a platform for finger support (Figure 36.4B). The volar WHO primarily contacts the anterior surface of the forearm, maintaining the wrist, thumb, and fingers in a slightly extended position (Figure 36.4C). Volar wrist orthoses are most commonly indicated after surgical lengthening of spastic extrinsic finger flexor muscles in a hand with modest volitional motion and are usually worn at night to maintain the hand in a corrected position (18). They should not be used in the presence of excessive spasticity, as they do not adequately control position and, if rigid, may cause skin breakdown or Boutonniere deformities of the fingers (18). Whether a dorsal or volar WHO design is selected, it is important to avoid forcing wrist/hand alignment that does not exist or is difficult to attain. If alignment is forced, the likely result is discomfort, possible skin breakdown, or discontinued use altogether. As the hemiplegic hand typically exhibits flexor tone, finger slings attached to the orthosis by springs (e.g., elastic bands or coiled wires) may be used within a dorsal WHO to create extension bias and a more dynamic device (9), where active contraction of the flexor muscles deforms the orthosis, and the orthosis returns the joints to a predetermined resting (static equilibrium) position when muscles relax (Figure 36.5). WHOs may also incorporate neurophysiologic principles to inhibit flexor tone, such as abduction of the fingers and avoidance of palm contact, to eliminate facilitation of the grasp reflex.

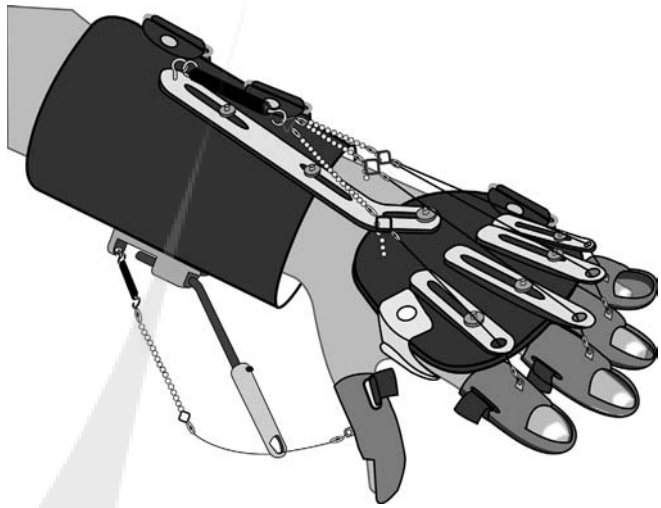

FIGURE 36.5 A dynamic finger extension WHO, the Saebo-flex (Saebo Inc., Charlotte, NC), for functional retraining of the hemiplegic hand. Springs on the dorsum provide resistance to finger flexion.

Dynamic finger orthoses or spring splints are used to correct flexion contractures of the interphalangeal joints but should not be used where flexor spasticity is present. The thumb abduction orthosis or thumb spica (Figure 36.4A) is a lightweight device that holds the thumb metacarpal in an abducted and slightly opposed position. It is used to avoid thumb-in-palm deformity and to improve thumb function, especially pinch. However, it has been proposed that the traditional "C" position of the thumb may actually encourage deformity. A less opposed position, though less functional, would lengthen the thumb flexor and adductor muscles rather than shortening them.

Recently, orthoses have been developed to aid in the retraining of function in the hemiplegic upper limb and hand (10,45,46). The SaeboFlex (Saebo Inc., Charlotte, NC) device uses springs to assist in hand opening for individuals with flexor hypertonicity and/or weak wrist and finger extensors. Use of the device is predicated on the functional task approach (47,48), wherein intensive, repetitive task-oriented training is used to improve function of the hand and upper limb by inducing long-term plasticity in the motor cortex (49–51). It has been suggested that this device potentially reduces tonicity/spasticity and improves range

of motion and motor control through functional tone management, a process whereby spastic muscle activation followed by relaxation teaches individuals how to modulate forces or "turn off" spastic flexors and lengthen them eccentrically (45). Similarly, electromyographic (EMG) signals have been used to trigger robot-assisted exercises and to control powered exoskeletal devices to provide assistance with movement (52). The Myomo device (Myomo Inc., Cambridge, MA) is an exoskeletal elbow orthosis that uses surface EMG signals to control a powered elbow to assist with movement of the paretic limb during therapy. In general, there is good evidence for the positive effect of repetitive function and strength training for the hand and upper limb (8), with mixed evidence as to whether orthoses provide an advantage for this type of therapy (10,45,53–55).

ORTHOTIC MANAGEMENT OF THE LOWER LIMB

Orthotic management of the lower limb is an important adjunct to the management and treatment of individuals with stroke during both the acute and the chronic stages of rehabilitation (12). During the acute phase, the primary goals are similar to orthotic management of the upper limb: that is, to maintain range of motion and prevent joint contractures. Adjustable AFOs may be used at night to prevent or correct contracture of the plantar flexors, whereas knee orthoses, which may or may not include the ankle, are often used to prevent or correct flexion contracture of the hamstrings. Contracture management of the lower limb is based on the same principles as described for the upper limb (see "Contracture Management" section). During both the acute and chronic phases, lower-limb orthotic intervention is linked closely to the functional requirements of ambulation. Generally, lower-limb orthotic devices provide lower-extremity stability and safety by controlling limb alignment and eliminating excessive joint motion; enhance motion when muscle activity is not adequate in strength, timing, or coordination; and inhibit or decrease abnormal muscle tone or cutaneous and postural reflexes either by controlling range of motion or by incorporating neurophysiologic modifications.

Lower-limb orthoses are ideally prescribed based on an assessment of walking to determine changes in limb alignment, motor control, and range of motion resulting from stroke that detrimentally affect function. The degree of sensation present (e.g., proprioception and touch) following recovery from stroke partly determines the ability to ambulate, as sensory deficits impair feedback with respect to limb position and placement (9). Therefore, decisions regarding orthotic prescription should also include assessment of sensation and cognitive status. Impaired balance, loss of trunk stability, proprioceptive loss, and/or loss of motor control may require the use of additional supports for walking, such as a walker or quad cane. Individuals who are unlikely to ambulate may nevertheless require lower-limb orthoses to prevent contractures that impede transfers or the ability to wear shoes.

Although the use of an orthosis may provide overall improvement in one functional task, it almost invariably also limits or resists other desirable movements, thereby hindering other tasks. Stroke affects not only the lower limb but half of the entire body, resulting in problems with proximal control and alignment of the trunk and pelvis. Proximal alignment affects distal function of the lower limb, and there are currently no lower-limb orthoses that can substantially influence alignment and function of the trunk and pelvis directly (56).

Lower-Limb Biomechanics and Function

Normal human walking is characterized by smooth, rhythmic patterns of motion that require relatively little effort by the individual. The functional requirements of able-bodied walking include gait initiation and termination, balance and upright posture, stance phase stability, shock absorption, execution of the stepping motion, forward progression/propulsion, and energy conservation (57,58). These requirements are variably disrupted by stroke.

Although common gait patterns exist, there is great variability among individuals with hemiplegia. Generally, hemiplegic gait is asymmetrical, slow, and uncoordinated owing to poor selective motor control of muscles on the affected side (9,59). Voluntary movement is often characterized by synergistic patterns corresponding to primitive extensor and flexor reflexes. Fortunately, these synergies are somewhat functional: by alternating synergy patterns, a hemiplegic person can walk, as the stance phase predominantly requires extension to create stability and the swing phase predominantly requires flexion to functionally shorten the limb for ground clearance. Unfortunately, following stroke, most individuals present with a predominant extensor synergy pattern in both swing and stance phases, leading to issues with limb clearance during swing and the adoption of compensatory gait patterns.

Compensatory gait patterns are commonly observed in individuals with hemiplegia. Inadequate knee flexion and dorsiflexion may require circumduction of the limb to prevent toe drag in swing (9). Circumduction, excessive posterior trunk bending, pelvic rotation, and hip hiking on the involved side and vaulting on the sound side may be used to assist in swinging the involved leg (59). Disruption in normal motion and alignment, along with compensatory maneuvers and increased muscle activity, lead to greater than normal energy expenditure during walking and fatigue over short distances (60,61).

Hemiplegic gait is generally characterized by shorter than normal step lengths bilaterally (with the uninvolved step length shorter than the involved), longer stance phase duration, and shorter swing phase duration during swing phase on the involved side (9,59). Weight bearing on the involved limb is often decreased because of weakness, fear, perceptual or sensory impairments, and disorientation to midline. Persistent equinovarus of the ankle and foot during stance on the involved limb decreases the base of support,

increasing instability. People with hemiplegia tend to walk with a retracted hemi pelvis, primarily because of perceptual and sensory deficits and secondarily because of altered muscle tone and weakness in the hip abductors, trunk, and abdominal muscles (59). Weak internal rotators and an inability to dissociate hip motion from a retracted pelvis lead to excessive external rotation of the hip during swing phase and excessive toe-out distally. Pelvic retraction can also lead to hyperextension at the knee. Equinus of the ankle–foot may lead to initial contact with the forefoot or a foot-flat position. Inability to achieve initial contact with the heel may result in an external extensor moment at the knee during early stance, leading to hyperextension. Forward flexion of the trunk is common, owing to tight hip flexors or weak hip extensors, and will also contribute to an increased external extensor moment at the knee during stance. Forward flexion of the trunk may also be a compensation for the lack of tibial advancement during stance resulting from tight plantar flexors. Weak knee extensors commonly result in knee instability and buckling, whereas weak dorsiflexors result in insufficient dorsiflexion and drop foot during swing (59).

Types of Lower Limb Orthoses

Shoe Modifications

Following stroke, shoe modifications may be used, alone or (more likely) in conjunction with lower-limb orthoses, to improve ankle–foot function (Figure 36.6). Velcro closures or elastic laces are commonly used to facilitate donning and doffing of shoes with one hand, as individuals with hemiplegia typically lack bilateral upper-limb function. Extra-depth footwear may be necessary to accommodate orthotic devices such as AFOs. When the stroke results in mild varus or valgus angulations of the ankle–foot complex, a high-top shoe may provide some control. Shoe modifications such as a cushion or beveled heel can be used to decrease loading rate of the limb at initial contact and during loading response. A cushion heel involves sandwiching a compressible material within the heel of a shoe, whereas a beveled heel involves beveling the posterior aspect of the existing heel (Figure 36.6A,B). Both modifications alter the point of application of the ground reaction force and serve to facilitate forward progression of the center of pressure, reducing the demand on the quadriceps by decreasing the external flexor moment acting at the knee during loading response. However, cushion and beveled heels are contraindicated in the presence of knee hyperextension unless a rigid, nonarticulated AFO or an articulated AFO with plantar flexion stop is used to provide control at the knee (see the following section on AFOs). Sole and heel wedges placed medially or laterally (Figure 36.6C,D) may be used to counteract undesirable coronal plane moments at the ankle and knee. Addition of a lateral border flare to the sole of the shoe increases the base of support and decreases the tendency for the foot to roll out laterally into varus during stance. Traditional metal AFOs often incorporate T-straps to control varus deformity at the

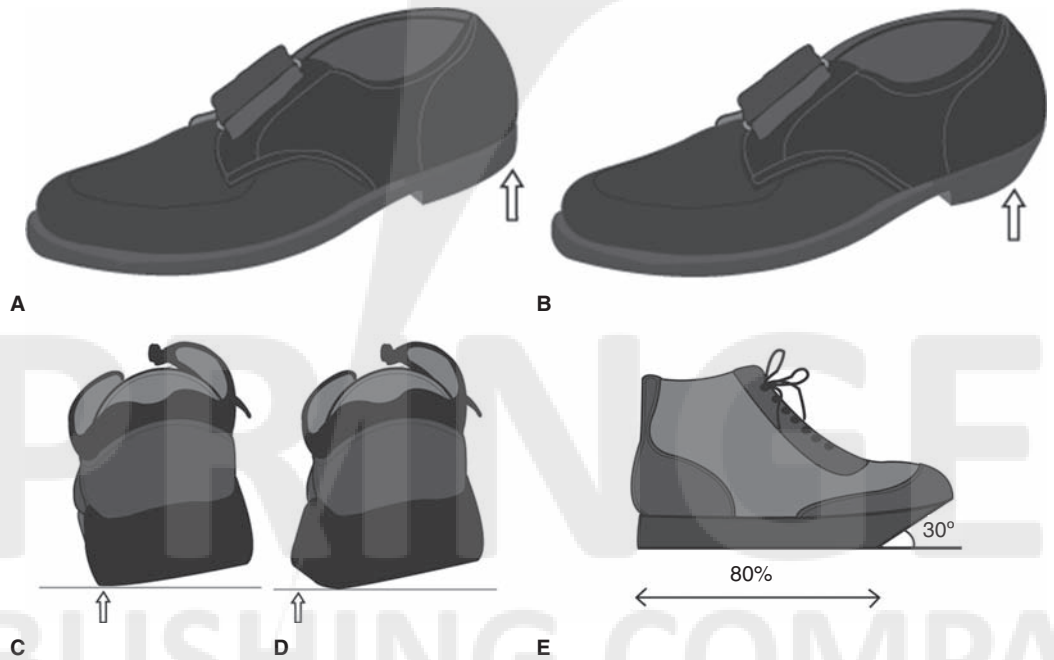

FIGURE 36.6 Examples of three shoe modifications: (A,B) side view of the beveled heel used to alter moments about the ankle in the sagittal plane, (C,D) posterior view of the lateral border flare used to alter moments at the subtalar joint in the coronal plane, and (E) side view of point-loading rocker (dimensions taken from Owen (62)). Arrows indicate point of application of the ground reaction force at initial contact in the unmodified shoes (A,C) and the modified shoes (B,D).

ankle. It should be noted that if initial contact occurs with the forefoot or with the foot flat, shoe modifications used in isolation, without other orthoses, are unlikely to be helpful.

Shoe modifications are also important when tuning segmental kinematics to improve standing balance and gait. A specific example, the AFO-Footwear Combination (AFO-FC) approach consists of a rigid, nonarticulated AFO in which modified footwear in the form of heel and toe rockers is used in addition to heel wedges under the AFO to adjust the shank-to-floor angle, that is, the position of the lower leg relative to the ground when standing (62–64). Subsequent "tuning" of the AFO-FC involves iteratively adjusting the intrinsic wedges and shoe modifications to manipulate the relationship between the ground reaction force and knee and hip joints, thus improving gait performance (65,66). In conjunction with a rigid, appropriately aligned AFO, stiff soles with point-loading (toe) rockers (Figure 36.6E) are used to facilitate terminal stance by allowing the heel to lift off the ground when the point of application of the ground reaction force reaches the point-loading rocker (62). The appropriate position of the point-loading rocker along the length of the foot and the toe spring angle must be determined for each individual. Although this orthotic approach is being advocated for use in stroke (67), only limited evidence exists regarding effectiveness in this population (65,66,68). Footwear modifications effectively increase the length of the affected leg, so some compensation for leg length in the form of a raise on the opposite limb may be required. Custom shoe modifications, though important, are often difficult to get covered by third-party payors in current practice. Where this is an issue, it is important for the medical team to be aware of alternate options, such as commercially available shoes that incorporate some of these design features to some extent.

Foot Orthoses

Foot orthoses (FO) encompass all or part of the foot but terminate distal to the ankle joint. They may extend the length of the foot or terminate at the toe sulcus or proximal to the metatarsal heads. FOs may be used to provide protection for insensate feet or corrective positioning (69). A rigid thermoplastic University of California Biomechanics Laboratory (UCBL) foot orthosis with neurophysiologic modifications may be used in the presence of stable subtalar and ankle joints to manage mild hypertonic foot reflex activity and toe clawing (Figure 36.7) (70). Since an FO such as the UCBL does not cross the ankle joint, it will not correct an equinovarus ankle-foot posture.

Ankle–Foot Orthoses

Equinovarus positioning of the ankle–foot complex is the most common deformity observed in the lower limb following stroke (71); hence, AFOs are the most commonly prescribed orthoses for management of gait abnormalities following stroke. AFOs may be made from a variety of materials, such as metals, thermoplastics, thermosets, or a hybrid of metal and plastic, depending on their particular application. Plastic orthoses are popular because they provide improved cosmesis and circumferential control compared with metal, although metal orthoses are indicated where fluctuating edema cannot be controlled by compression garments or medication (Figure 36.8). Plastic AFOs are generally comprised of an intimate fitting, posterior shell typically made from homopolymer polypropylene or a polypropylene/polyethylene copolymer (1). Polyethylene homopolymer is more flexible than polypropylene and typically is used for circumferential or nonweight-bearing orthoses such as upper-limb orthoses. Fiber-reinforced thermoset laminations, such as those incorporating carbon graphite, are appropriate when transverse rotational forces must be restricted. Despite resulting in stronger, stiffer, and lighter orthoses compared to polymers, thermosets are not used as widely because of their higher cost and more difficult fabrication process, although easier fabrication techniques using "prepreg composites" (i.e., fibrous material preimpregnated with resin, partially cured and ready for molding) are emerging that allow custom thermoset orthoses of varying flexibility and rigidity to be fabricated without the need for specialized facilities (72).

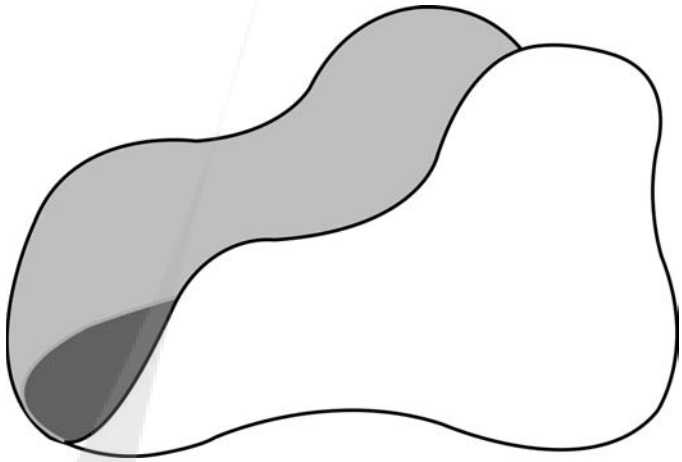

FIGURE 36.7 UCBL (University of California Biomechanics Laboratory) foot orthosis, side view with posterior aspect to the right.

AFOs act directly at the ankle and indirectly at the knee and hip, although there is less evidence for the effect at the hip than at the knee (12,73–76). The basic AFO design includes a proximal trimline that terminates 20 mm distal to the neck of the fibula, providing the longest possible lever arm for ankle motion control, which is particularly important if spasticity of the triceps surae muscle is present (29). AFOs differ substantially from ankle orthoses (AO). AOs are prefabricated orthoses intended to provide mediolateral stability at the ankle joint in the presence of ligamentous insufficiency. AOs provide only minimal support to prevent varus of the hind foot, but may be used transiently in mild cases until gait improves completely (9). Generally, AOs are inappropriate

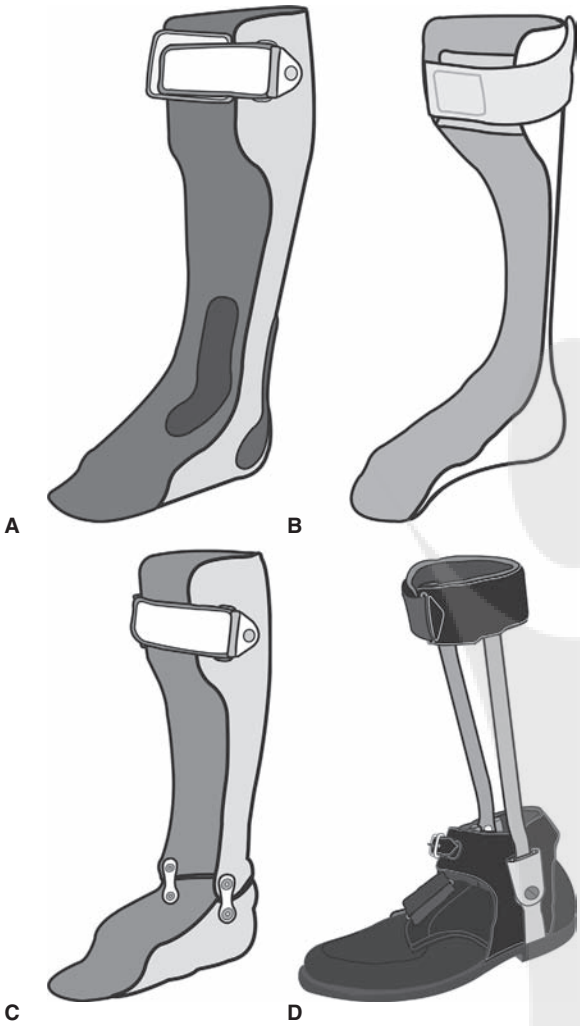

FIGURE 36.8 Four main types of AFO: (A) rigid nonarticulated, (B) posterior leaf spring, (C) polymer articulated, and (D) metal articulated. The articulated polymer AFO incorporates a plantar flexion stop, whereas the metal-articulated AFO has double-action ankle joints that use combinations of pins and springs anterior and posterior to the joint to provide a plantar flexion stop (pin in posterior channel), dorsiflexion stop (pin in anterior channel), dorsiflexion assist (spring in posterior channel), and plantar flexion assist (spring in anterior channel).

for individuals with stroke, as they lack sufficient lever arm in the presence of hypertonicity to adequately control ankle motion. However, when worn, AOs may have greater compliance than AFOs, as they are relatively inconspicuous and fit easily into regular footwear.

AFOs fall into two main categories: articulated and nonarticulated (Figure 36.8). As the name implies, articulated AFOs incorporate mechanical joints at the ankle that allow control of sagittal plane motion. Articulated AFOs may be used to control joint range of motion (e.g., using adjustable joints), provide assistance to motion (e.g., with a dorsiflexion assist joint), or limit motion (e.g., with plantar flexion or dorsiflexion stops). Although nonarticulated AFOs do not incorporate joints, they may or may not allow motion at the ankle in the sagittal plane, depending on their flexibility. In a nonarticulated polymer AFO, motion is determined by the rigidity of the orthosis about the ankle joint, which is usually a product of plastic thickness and geometry. Adding reinforcements about the ankle or an anterior shell may increase rigidity of the AFO. A nonarticulated AFO is generally rigid if the trimlines about the ankle are anterior to the malleoli, sometimes referred to as a *solid* or *rigid AFO*. The more posterior the trimlines are to the malleoli, the more flexible the orthosis becomes, such as in a polymer posterior leaf-spring AFO (PLS-AFO). In a PLS-AFO, motion occurs because of buckling or deformation of the plastic when a moment is applied. A PLS-AFO allows some plantar flexion at initial contact and dorsiflexion during mid-stance. It returns the ankle to neutral during swing phase when the only load acting on the orthosis is the weight of the foot. Hence, the PLS-AFO is contraindicated where there is spasticity, hypertonicity, or clonus of the plantar flexors, as the control of ankle position in swing is diminished if a plantar flexor moment is applied to the orthosis at that time (12).

AFOs may be either prefabricated or custom-made. Prefabricated or off-the-shelf AFOs are convenient, inexpensive, and adequate for some individuals. Although they may be used for training/evaluation or as interim devices, they are rarely recommended for long-term use owing to their generic fit (12), which also makes them unable to accommodate misalignment and deformity of the foot and ankle. Prefabricated PLS-AFOs are common because their limited biomechanical control easily accommodates a more generic shape; however, they are contraindicated where there is significant tone or spasticity, mediolateral subtalar joint instability, or problems at the knee or hip that have to be addressed (71). A fundamental requirement of all orthoses is that they contour well to the body segment(s) they encompass. Custom-made AFOs provide better biomechanical control than prefabricated orthoses because a more precise fit can be achieved, especially in the presence of complex deformities.

The primary indications for AFO use in stroke are inadequate dorsiflexion in mid to terminal swing, resulting in foot clearance problems and compromising the ability to achieve initial contact with the heel; mediolateral ankle–foot instability in stance and swing; and insufficient tibial control in stance. Table 36.1 summarizes indications for the three basic types of AFOs (rigid nonarticulated, articulated, and flexible nonarticulated) as applied to individuals with stroke (12).

It is not uncommon for a person with stroke to require greater stability during the initial acute phase but less stability as recovery occurs. In such cases, a progressive AFO, with biomechanical controls that can be altered as the individual's condition changes, may be useful. This can be a polymer AFO fabricated to include ankle joints but that has yet to be "cut" to allow articulation. Similarly, a knee–ankle–foot orthosis (KAFO) can be converted to an AFO as the individual's needs change (77). An AFO with adjustable ankle joints may also be useful during the acute phase, as

TABLE 36.1 Summary of Indications for AFOs

Nonarticulated AFOs (excluding leaf-spring AFOs) are indicated as follows:
- poor balance, instability in stance
- inability to transfer weight onto the affected limb in stance
- moderate to severe foot abnormality; equinus, valgus or varus, or a combination
- moderate to severe hypertonicity
- as above, but with mild recurvatum or instability of the knee
- to improve walking speed and cadence

Articulated AFOs are indicated as follows:
- dorsiflexor weakness only
- where passive or active range of dorsiflexion is present
- where dorsiflexion is needed for sit-to-stand or stair climbing
- to control knee flexion instability only; articulated AFO with dorsiflexion stop
- to control recurvatum only; articulated AFO with plantar flexion stop
- to improve walking speed and cadence

Posterior leaf-spring AFOs are indicated as follows:
- isolated dorsiflexor weakness
- no significant problem with tone
- no significant mediolateral instability
- no need for orthotic influence on the knee or hip

Source: From Ref. (12). *International Society for Prosthetics and Orthotics. Report of a Consensus Conference on the Orthotic Management of Stroke Patients.*

it allows the ankle joint to be locked in any position from dorsiflexion to plantar flexion or be free moving throughout the range. Dorsiflexion and plantar flexion stops can be used when partial range of motion is required. Such adjustability allows the mechanical ankle joints to accommodate changes in the range of motion as the individual progresses.

In AFOs, three-point force systems are used as needed in the sagittal plane to control plantar flexion/dorsiflexion and in the coronal plane to control hind foot inversion and/or forefoot adduction (Figure 36.1B–D). Shaping the AFO to match the foot ensures comfort while controlling deformity. The forces should be applied as far apart as possible to maximize lever arms and over large areas to reduce pressure (67).

When a rigid nonarticulated AFO or an AFO with a plantar flexion stop is used, it is important to account for footwear heel height when casting and keep the heel height of the shoe constant, as changes in footwear heel height can alter the indirect effect of the AFO at the knee (78). Rigid devices may be used to maintain the ankle in a fixed position and prevent spasticity, as a spastic response tends to rapidly diminish when joints are immobilized but may persist with even small amounts of motion. Although it has long been considered standard practice to cast the ankle at neutral (i.e., 90 degrees), recent literature suggests that the angular relationship between the shank and floor is more important for function, especially in a rigid nonarticulated AFO (5,63–65,67) and that gastrocnemius length should be considered when deciding ankle alignment (79). When sagittal alignment of the foot cannot be fully corrected owing to tight plantar flexors, wedging can be added to the underside of the AFO to accommodate the lack of range but still create a stable base of support (67) (Figure 36.2).

A tuned AFO-FC consists of a rigid, nonarticulated AFO in which ankle angle and shank to vertical angle are considered separately. *Ankle angle* refers to the angle of the ankle in the AFO and is based on measurements of muscle length (79), whereas *shank to vertical angle* refers to the angle of the tibia with respect to vertical during standing and walking (64). Modified footwear is used in addition to wedges under the heel of the AFO and/or shoe to "tune" the shank to vertical angle (63). "Tuning" focuses on manipulating segment kinematics, in particular shank (i.e., tibial) kinematics, to improve the relationship of the vertical ground reaction force vector to the knee and hip during stance. When the AFO positions the tibia in a vertical alignment, the ground reaction force cannot be simultaneously aligned in front of the knee and behind the hip, unless the knee hyperextends, which is undesirable. Progressively adding wedges under the heel to incline the tibia can optimize ground reaction force alignment at both joints. The rationale for this approach is that controlling tibial alignment and progression in mid to late stance transfers forward momentum to the thigh, facilitating knee and hip extension in terminal stance if there is sufficient gastrocnemius length, placing the limb in a more appropriate alignment for transfer of body weight to the contralateral limb, and commencing swing phase with the ipsilateral limb. There is some evidence that alignment of the orthosis at terminal stance and/or preswing will influence step length, gait symmetry, speed, and energy consumption (67,80). However, when using a tuned AFO-FC, additional gait training may be required to derive maximum benefit. Use of the AFO-FC approach has been advocated for stroke (67), with plans proposed for a randomized control trial to investigate the effect of tuning on gait (81).

AFO alignment can also be used to enhance knee stability during stance where the knee extensors are weak and unable to support body weight during single support. Floor reaction or ground reaction AFOs (FRAFO or GRAFO) are rigid, nonarticulated AFOs that hold the ankle in slight plantar flexion to create an external knee extension moment during stance. For these designs to be effective, they must provide good rotational control and should not be used in the presence of a knee hyperextension deformity.

AFOs that incorporate neurophysiologic modifications are sometimes referred to as *dynamic* or *tone-reducing AFOs*. In these orthoses, control of muscle tone may be attempted by positioning the toes in extension, applying pressure points over strategic locations on the plantar surface of the foot and muscle insertions, providing static immobilization through total contact, and stimulation of antagonist muscle groups (7,8). For example, a toe spreader or toe separator may be used independently or in conjunction with an AFO to inhibit tonic foot reflexes such as the toe grasp reflex, which may cause excessive toe clawing, leading to pain and impeding forward advancement of the lower limb over the foot. Inhibition of abnormal tone in the toes allows the foot to become a better weight-bearing surface over which the body may progress during stance (1). Function of toe spreaders/separators is based on the premise that abduction and extension of the toes release intrinsic tone. Tone-reducing AFOs often incorporate total contact principles, with greater contact of the dorsal surface of the foot, to facilitate neutral alignment of the subtalar joint, which is purported to reduce tone in the foot while allowing motion at the ankle joint (70). However, there is little evidence to support the ability of orthoses to reduce tone during ambulation (7,8).

Recently, it has been suggested that triplanar dynamic response orthoses may lead to greater functional improvements than plastic orthoses, through better control of segment alignment and motion (82) (Figure 36.9). These orthoses are made from thermosets, such as graphite composites, to provide sufficient rigidity to support body weight during stance and control forces in all three planes yet allow sufficient flexibility to absorb and return energy. Unfortunately, there is as yet no evidence of their efficacy or applicability to individuals with spasticity and hypertonicity.

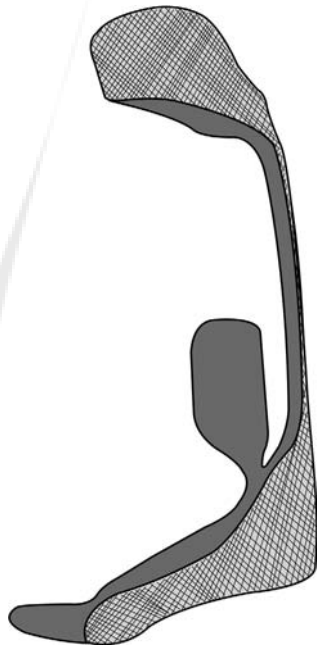

FIGURE 36.9 Graphite composite, triplanar control dynamic response AFO with lateral flange (Dynamic Bracing Solutions, San Diego, CA).

Knee–Ankle–Foot Orthoses

KAFOs are used where a need exists for direct control of the knee joint in addition to the ankle and foot (29) (Figure 36.10). A KAFO is also useful when there is lack of control of the hip extensor muscles (1). All KAFOs provide coronal plane knee stability by default, and the ankle section may be articulated or nonarticulated.

Orthoses that encompass more than one joint, such as KAFOs, are usually bulky and cumbersome, and individuals with weakness, as often occurs in stroke, are unable to tolerate bulky, heavy devices (1). Traditionally, only two basic knee control options were available for use in KAFOs: unlocked or locked. A KAFO with unlocked knee joints provides coronal plane knee stability, with sagittal plane stability of the knee during stance predicated on geometric alignment. This may be achieved with posterior offset knee joints where the mechanical axis of rotation is located posterior to the anatomical axis of rotation, resulting in an external knee extensor moment at the mechanical joints in early

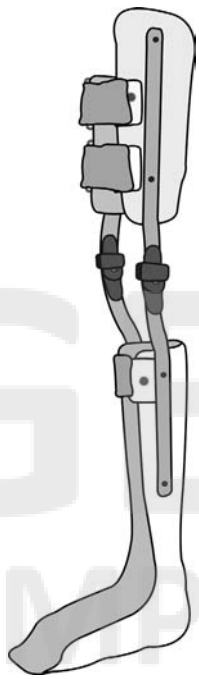

FIGURE 36.10 Hybrid metal and plastic knee–ankle–foot orthosis (KAFO) with drop-lock knee joints.

stance (29). These joints are not entirely reliable, especially on uneven terrain and slopes, and are indicated only where the individual retains adequate hip musculature strength and control, proprioception at the knee, and good balance to ensure stumble recovery should geometric stability not be achieved.

A KAFO with locked knees provides both coronal and sagittal plane control of the knee throughout stance, but also remains locked during swing phase, necessitating compensatory maneuvers during walking to achieve ground clearance of the extended limb during swing. As we progress proximally, immobilization of lower-limb joints increases energy expenditure during functional activities, with immobilization of the knee being particularly detrimental (58). Hence, KAFOs have been used infrequently, owing to their increased weight and energy demands when walking.

Stance-Control KAFOs

Stance-control orthoses incorporate knee joints that automatically stabilize the knee during stance phase but release it during swing phase to allow knee flexion. These relatively new joints, and the availability of strong, lightweight materials, have renewed interest in the potential use of KAFOs in individuals with stroke (12,77,83). It has been suggested that stance-control KAFOs may be particularly useful during the early rehabilitation phase after stroke, as they may facilitate appropriate limb alignment and provide support of the weakened limb during gait training (84). This may decrease the development of abnormal postures, especially proximally, and lead to better long-term functional recovery. Stance-control orthoses may be of benefit both as a temporary poststroke gait-training aid and as an ongoing gait assist for individuals with permanent knee extensor weakness. Different stance-control knee mechanisms are commercially available (e.g., Stance-Control Orthosis™, Horton's Orthotic Lab. Inc., Little Rock, AK; UTX® and Model 9001 E-Knee™, Becker Orthopedic, Troy, MI; UltraSafeStep™, Ultraflex Systems Inc., Pottstown, PA; FreeWalk™ and SensorWalk™, Otto Bock HealthCare, Minneapolis, MN; Swing Phase Lock, Fillauer LLC, Chattanooga, TN), which require different strategies to engage and disengage the knee joint. Hence, not all the available stance-control knee mechanisms may be appropriate for individuals following stroke.

FUNCTIONAL ELECTRICAL STIMULATION

FES is a technique that uses electrical currents to stimulate nerves to activate muscles that have been affected by paralysis secondary to traumatic brain injury, neurologic disorders, spinal cord injuries, and stroke. FES is a long-standing treatment modality that has historically been used therapeutically and in controlled settings. For those individuals who present with upper motor neuron lesions, FES is thought to provide reciprocal and recurrent inhibition that may reduce involuntary stimulation of spastic muscles (85). It is thought that with inhibition and subsequent relaxation of muscles, there is greater opportunity to reduce pain when present and to improve passive range of motion. In recent years, there has been a steady increase in the use of FES, either in conjunction with an orthosis or as an alternative to orthotic management, with an increased emphasis on using FES in a functional capacity (86). FES for functional use has been described using terms such as neuroprosthesis and neuromuscular electrical stimulation (NEMS). The FES/orthosis hybrid design or FES alone has been used with the stroke, cerebral palsy, spinal cord, multiple sclerosis, and traumatic brain injured populations. Although there has been utilization for both the upper and lower limb, the former has tended toward a hybrid design (87) and the latter toward standalone FES use. Common commercial devices for lower-limb application include the Bioness L300 (Bioness Inc., Valencia, CA), Walkaide (Innovative Neurotronics, Austin, TX), and Odstock Dropped Foot Stimulator (ODFS; Department of Medical Physics and Biomedical Engineering, Salisbury District Hospital, Salisbury, Wiltshire, UK). The most common commercial device for the upper limb appears to be the Bioness H200 (Bioness Inc., Valencia, CA), formally referred to as the Handmaster®. Despite this apparent increase in the utilization of FES, the evidence for lower-limb use is limited (86), and that for upper-limb use is even scarcer.

Orthotic Management and FES for the Upper Limb

FES use for the upper limb has primarily focused on wrist/hand function, with particular emphasis on restoring grasping (88). Currently, the most common design is a WHO that incorporates FES. The WHO is able to maintain wrist/hand alignment, whereas the FES stimulates repetitive muscle contractions for either therapeutic or functional use of the hand. Initial training and calibration may require daily use for up to 1 week and, depending on the protocol, 20 to 180 minutes of daily utilization (11,89). Hence, use of this system should include training time and follow-up in the overall treatment plan. This commitment should be conveyed clearly to patients so they can determine for themselves the costs and benefits of utilizing the device.

There is some evidence that the hybrid FES/WHO has short-term benefits while being worn or shortly after being worn by persons with poststroke hemiplegia (88). Reported benefits include increased passive range of motion, reduced edema, diminished hand/wrist impairment, improved overall arm function, and decreased pain. In some instances, although there were no observed benefits, patients chose to continue wearing hybrid devices, suggesting that the patients perceived benefits that were not measured. Investigations of upper-limb FES applications have assessed effectiveness based on motor and sensory recovery, reduced edema, improved passive range of motion, and long-term utilization of hybrid devices. In future, it may be necessary to include more global, patient-oriented assessments (e.g., Goal Attainment Scale) to better determine the benefit of the hybrid devices perceived by individuals with hemiplegia.

Orthotic Management and FES for the Lower Limb

The efficacy of FES use in the lower limb of hemiplegic patients is difficult to define owing to limited evidence and heterogeneity in assessment methods. Studies have explored the physiological effects of FES on voluntary ankle motion; investigated orthotic, carryover, therapeutic, and total effect of FES use; compared FES to AFO use with regard to both effects on gait and perceived value; and evaluated the long-term effects of FES use. A collective understanding of these studies will help the clinician to consider FES as a functional intervention.

When the poststroke patient attempts to voluntarily move the foot and ankle, the physiologic effect of stimulation to the common peroneal nerve during the swing phase of gait is to dorsiflex and, depending on placement of the electrodes, evert the foot (Figure 36.11). With this ability, FES is capable of addressing both the equinus and varus components usually observed in hemiplegic gait. However, FES devices that are exclusively for peroneal nerve stimulation do not provide mediolateral ankle stability, nor do they provide tibial control during the stance phase of gait. Patients who require stability any time between initial contact and terminal stance are likely to require more substantial support. There is evidence to suggest that stimulation of the common peroneal nerve may also lead to inhibition of the plantar flexors (90).

Collective improvement across these areas leading to a change in gait and attributable to FES has been referred to as an *orthotic effect*. The orthotic effect can be described as a change, typically in gait, when the FES is in the "on" position. A number of studies have reported a positive orthotic effect particularly in walking speed and physiological cost index (PCI) (91–93). Another study, using an activity monitor, showed a correlation between use of the FES and gains in walking speed (94). Generally, it has been easier to demonstrate an FES orthotic effect in the chronic stroke population than in more acute presentations where there is the possibility of spontaneous improvement irrespective of the intervention. The orthotic effect, though beneficial, does not describe changes in gait that may remain after the FES is turned off.

The effects on gait observed after the FES is shut off are referred to as the *carryover effect*. This expanded scope of FES capability has led to a growing number of investigations examining the carryover effect (95). Initial observations suggested a short-term carryover effect of FES use that dissipated over time. Subsequent studies have found that the carryover effect may last longer than previously thought, possibly as a result of long-term and repeated FES use (96). Consequently, there has been a shift from the term *carryover effect* to *therapeutic effect* (referring to a patient's presentation before and after FES use). Like other interventions where long-term and repeated therapy constitutes all or a portion of the treatment plan, the therapeutic effect of FES is now being viewed in much the same way. In this same manner, the total effect of the FES now becomes a function of both the orthotic and therapeutic effects.

Thus far, results of studies investigating the therapeutic effects of FES on gait have been less convincing than those demonstrating an orthotic effect (91). In particular, it has been difficult to draw conclusions about the therapeutic effects of FES on walking speed. One study observed improvements in walking speed at 3-, 6-, and 12-month intervals, but also had a simultaneous decline in the original cohort of subjects, suggesting a possible attrition bias (94). In another study, 12 individuals received a single 30-minute FES intervention and then performed ambulation without the FES intervention. Though there was some carryover improvement in standing balance, it was difficult to determine if there was an immediate carryover effect in walking velocity and whether there would be long-term sustainability (97).

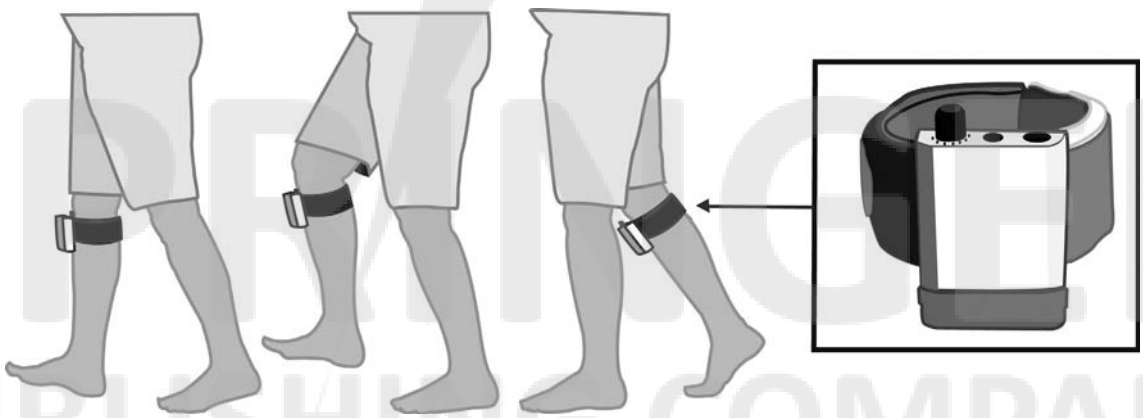

FIGURE 36.11 Example of stand-alone FES device for lower-limb application (Walkaide, Innovative Neurotronics, Austin, TX). The FES device can be adjusted for stimulation to occur to the common peroneal nerve at the time of swing phase for dorsiflexion activation to improve clearance of the foot during swing. In this case, the FES is being used independent of conventional treatment (e.g., AFO).

More recently, there have been investigations comparing the more traditional treatment method (an AFO) to FES intervention. However, small sample sizes and variability in AFO design across subjects and studies make it difficult to draw conclusions about the reported findings. Trends have been observed that may have clinical relevance, but they should be considered with caution. In one study, a subject exhibited improvement in functional ambulation compared to no intervention, but when compared to similar subjects performing the same task with an AFO, functional ambulation tended to be lower (98). In a study by Kottink et al. (99), a randomized control design was used to compare an implantable peroneal nerve stimulator to conventional treatment with an AFO over 26 weeks of use. Neither group showed improvements in walking speed with their respective devices (AFO or FES), nor did they show improvements over time. Finally, a study by Ring et al. (100) comparing FES to AFOs found no appreciable difference during initial application in gait asymmetry index, variability in swing phase duration, and walking speed; however, after four weeks of use, the FES users demonstrated a significant improvement in all areas except for walking speed.

Although quantitative gait data such as walking speed are relevant and important measures, equally important is the patient's perception of function with AFOs compared to FES (101,102). A recent study by Bulley et al. (101) explored the perception poststroke patients had of using an AFO compared to FES. Subjects described greater independence, faster walking, more normal-looking gait, and ease of shoe selection as some of the benefits of FES. Benefits of the AFO included equipment reliability, ease of donning, ease of day-to-day use, and usefulness in emergencies. Drawbacks of FES use included lack of equipment reliability, inability to function in certain situations (e.g., near water), difficulty in donning, and difficulty of wear when traveling. Drawbacks of AFO use included lack of comfort, lack of shoe compatibility, and the fact that it remains in place when not needed, for example, while sitting. Although most subjects preferred the FES, some subjects indicated that they could not rely upon the FES exclusively and still required the use of the AFO for certain tasks. The results of this study are a good reminder for the clinician regarding the limitations of both FES and AFOs; although neither is likely to address all of the patient's needs when used independently, they may do so to a larger extent when used in concert with each other. This is one reason why patient goals and expectations must be clearly defined. It will help determine if utilization of both devices is a better treatment plan than independent use of either design.

In sum, FES as an alternative form of lower-limb orthotic treatment has shown promise during real-time utilization but demonstrated less consistent therapeutic effects. Improvement in walking speed with the FES "on" and patients' positive perception of the FES suggest that it is a feasible treatment option that requires more investigation to determine who would benefit most. Caution should be taken not to prematurely abandon conventional treatment such as the AFO in favor of FES treatment alone. Both options have value for the patient depending on function and task-specific activities. Contraindications and precautions must also be considered, including, but not limited to, the patient's cognition, skin condition, range of motion, use of a pacemaker, and anticipated or current pregnancy (103). Tolerance for FES during daily activities, ability to effectively place electrodes, and ability to maintain the device must also be evaluated. With these considerations in mind, FES offers the medical team an added treatment option that may help to further optimize function for certain individuals with hemiplegia.

RESEARCH FRONTIERS IN THE ORTHOTIC MANAGEMENT OF STROKE

Recent reviews (67,71,104) suggest that, generally, symmetry of gait improves with use of AFOs compared to walking without orthoses. Studies also suggest that nonarticulated AFOs increase weight bearing through the affected limb during walking and standing. AFOs with resistance to plantar flexion, whether articulated or nonarticulated, improve the ankle angle at initial contact and mid swing. There is some indication that nonarticulated or plantar flexion stop AFOs can control knee recurvatum and reduce the external knee extension moment during stance, especially if set in dorsiflexion or anterior tibial inclination. There is also some suggestion that nonarticulated AFOs may control supination of the foot. A few studies have demonstrated that nonarticulated AFOs decrease the energy cost of gait compared to walking without orthoses. Generally, subjects report that AFOs improve their walking and are comfortable when compared to no device, but tend to prefer FES devices in certain circumstances (101).

Although orthoses are commonly used in the management of stroke and empirically have been found to be of benefit, a 2004 consensus conference on the orthotic management of stroke concluded that evidence for the orthotic management of stroke is generally low, both in terms of quality and quantity (12). There exists a need to demonstrate efficacy more objectively, especially within the current medical paradigm of evidence-based practice. For example, there is no evidence in the literature regarding the most appropriate timing of lower-limb orthotic management following stroke; the long-term or carryover effect of lower-limb orthoses has not been demonstrated; and the ability of an AFO to influence range of motion of the hip during gait is unconfirmed by experimental studies on stroke subjects (12). As much of the literature regarding the orthotic management of stroke is based on small numbers of subjects, with the orthoses often poorly described, it has been recommended that well-controlled, multicenter trials involving large numbers of subjects are urgently needed (5).

Although there are still few randomized control trials or studies involving large numbers of subjects, several recent studies have been identified that better define both the characteristics of AFO interventions and the physical presentations of the study subjects, making their findings

more relevant to clinicians (65,73,105–107). As this trend continues, the published literature will better guide clinicians as they create orthotic treatment plans for individual patients. In addition, more studies of orthotic management are utilizing clinical outcome measures such as the 6-minute-walk test (100,108–112), timed-up-and-go (113–117), Berg Balance Scale (114,115), and the modified Emory Functional Ambulation Profile (98,110,118,119), expanding our understanding of the functional effect of orthoses beyond what can be observed in a motion analysis laboratory and providing clinicians with information to which they can more directly compare their patient outcomes. Similarly, insights are being gained into the sensitivity of outcome measures for assessing the effects of an orthosis. For example, Geboers et al. (120) used both the 10-meter-walk test and 6-minute-walk test to evaluate patients with foot drop walking with and without an AFO. The 10-meter-walk test showed no improvement when the AFO was used, but the 6-minute-walk test did. One explanation for these results is that persons with foot drop are able to compensate for gait deficits over short distances but not over extended periods of activity (121). This suggests that gait lab-based studies, with their typically short bursts of walking, may underestimate the effectiveness of AFOs when compared to the functional benefits implied by their widespread clinical use. It also suggests that we may need to consider dosage of orthosis use based on activity level and fatigue, as examples.

Recent literature reviews have shown that the outcome measures used most frequently to evaluate walking ability after stroke are those that assess walking over a short distance at a self-selected walking speed or at a fast pace (122,123). Although informative, such outcome measures provide a relatively limited assessment of the ability of the individual to ambulate in the everyday environment. Outcome measures that assess walking under different conditions, although used sparingly in stroke research, reflect more recent attempts to measure the influence of the environment on mobility (122,124). A core battery of outcome measures appropriate for the evaluation of orthotic management of stroke has been proposed (125). These measures address impairments (muscle activity, joint motion/torques, balance, pain), function (manual dexterity, mobility, walking endurance), falls, and goal attainment. They also span the spectrum from instrumented measures to patient-reported measures. However, most of these outcome measures are generic and do not account for changes in orthotic design and use over time. This may be particularly pertinent to stroke patients who could conceivably progress from using a KAFO in the acute poststroke phase to a nonarticulated AFO and subsequently an articulated or leaf-spring AFO as recovery occurs. The only stroke-specific, performance-based outcome measure that we have identified that attempts to address this issue is the modified Emory Functional Ambulation Profile (126,127). It allows for a weighting factor to be applied to the score to account for changes in orthotic assistance over time.

Another area that has received some attention when it comes to orthotic management of stroke is the effect of AFOs on balance. A recent systematic review suggested that leaf-spring AFOs may have positive effects on balance in adults with stroke-induced hemiplegia, whereas for other types of AFOs, there was some evidence to suggest that balance outcomes were dependent on the design of the device: rigid designs seemed to be beneficial in static balance tasks and more flexible designs superior under dynamic balance conditions (128). However, the descriptions of AFO design presented in the reviewed articles were considered quite poor. This results in a low level of confidence in these conclusions, particularly in the light of more recent concepts regarding the importance of alignment and tuning of AFOs and footwear on function (64), which were not reported. A randomized control trial protocol has been proposed to assess the importance of tuning for orthotic management of stroke (81). In addition, the type of information that should be reported regarding AFO design has been described (129,130).

It has been proposed that improved quality of life and independence are nonbiomechanical effects of orthotic use after stroke (67), suggesting that mobility may affect both biomechanical and nonbiomechanical outcomes. These nonbiomechanical outcomes are rarely reported in the literature.

With regard to the upper limb, evidence as to whether orthoses can improve function and/or impairments remains limited (131). Controversy still exists as to whether static, rigid WHOs prevent deformity or contribute to it; the long-term effects of contracture management, based on either stress–relaxation or creep, are unknown; the optimal protocol for the application of stretch to spastic muscle is unclear; the interaction between orthoses and other therapies remains largely unexplored; and the benefits of hybrid orthoses incorporating FES remain to be defined.

In general, the science of orthotics is immature. Although orthotic technology continues to advance, especially with the application of new materials, microprocessors, and active elements such as motors (132) and pneumatics (133–135), our understanding of how best to apply that technology lags behind. In the past, most orthoses were passive, whereas today there is a growing interest in active orthoses that might, for example, power gait by providing propulsion at push-off (134), assisting knee flexion torque in preswing when the knee is stiff (136), or assisting/resisting knee motion during sit-to-stand, walking, and stair-climbing activities (132). Most active orthoses are currently limited in their clinical application by the size and weight of the devices, in large part as a result of being tethered to the power sources required. One recently developed device, the AlterG Bionic Leg (previously the Tibion Bionic Leg (132)) has overcome some of these obstacles, resulting in a portable, wearable, powered knee orthosis that provides assistance to patient-initiated knee motion. Although promising, use of this device in persons after stroke has to date been reported in only two case studies (137,138). Both studies utilized the device as part of a task-oriented functional training program in chronic subjects and reported improvements in balance (138)

and mobility (137,138) that were retained at one (137) to three months (138) follow-up, suggesting that neural remodeling or reorganization may be possible. Although active devices may be applied to weak limbs in a reasonably safe manner, we need to develop a better understanding of how to safely apply active devices where spasticity and hypertonicity are present and there may be unpredictable resistance to the torque provided by the active orthosis. In addition, active orthoses may not be as effective as anticipated if underlying abnormal neuromechanical coupling exists between lower limb joints (136).

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37

Alternative, Complementary, and Integrative Medicine and Therapy

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Complementary and alternative medicine, commonly referred to as CAM, and most recently as integrative medicine or therapies, is defined as diverse systems, practices, and products not typically considered to be included in conventional medicine (1). In this chapter, CAM is used to represent all therapies in this area. The World Health Organization defines *traditional medicine* as "the sum total of knowledge, skills, and practices based on the theories, beliefs, and experiences indigenous to different cultures that are used to maintain health, as well as to prevent, diagnose, improve or treat physical and mental illnesses" (2).

Many alternative therapies currently practiced in the West have their origins in the ancient medical traditions of Eastern cultures, such as traditional Chinese medicine and the Ayurvedic tradition of India. These ancient approaches treat the body and its health as an integrated system, and illness is seen as an imbalance or disharmony of vital energy and dynamic forces within the whole body. Treatment of illness is thus seldom focused on the symptoms of the illness but on the believed underlying imbalance of subtle energy. Restoring the body to equilibrium or improvement in self-regulation may require a set of integrated interventions that focus on the body, mind, and soul (3). As a result, traditional Chinese medicine has an arsenal of treatments that include not only various forms of acupuncture, but also a vast pharmacopeia of herbs and supplements barely known in Western medicine; various physical movement and physical manipulation techniques such as tuina, a technique similar to chiropractic manipulation; and exercises designed to strengthen the body and to move and balance the subtle energy (chi or qi), including tai chi and qi gong. Many meditation and breathing techniques supplement these physical interventions. The same is the case for Indian medicine, where yoga postures (asanas), Ayurvedic herbs, meditation, sound, and breathing exercises may all be prescribed for a particular disease, all focusing on the restoration of the health of the overall system.

Even though these ancient models often do not seem to have any relationship to modern (Western) concepts of physiology, anatomy, and the ontogeny of disease, many of the techniques that have been generated over the centuries continue to be practiced today and are often considered helpful by practitioners. Interestingly, many of these ancient techniques have parallels in modern therapies, which are sometimes derived from these early traditions and, in other cases, were developed independently of them. Thus, stretching exercises, massage, and other techniques routinely used by rehabilitation therapists are surprisingly similar to the alternative techniques of tuina, yoga, and pranayama (breathing exercises), and so forth. Additionally, recent secondary data analyses of the 2007 National Health Interview Survey of more than 20,000 people indicates that people with functional limitations and people with neurological conditions are more likely to engage in some form of CAM when compared to other adults without such limitations or conditions (4,5).

The use of alternative or nonconventional therapies by individuals to supplement or complement conventional medical treatments has been commonplace for many decades. CAM therapies have historically been used without the knowledge of the patients' health care providers, thus raising the risk of unknown interactions with standard medical treatments. This phenomenon was first brought to the attention of the medical community with the publication of a major national survey published in 1993, along with a follow-up survey confirming the findings seven years later (6,7). Coupled with information from a 2012 systematic review of CAM use (which excluded prayer) by the general public, data support continued and increased use of CAM, with 41% to 63% of older adults using some aspect of CAM (8). These past surveys not only demonstrated the widespread use of CAM, but also indicated that more resources were being spent on these therapies than on conventional medicine (6,7). These findings spurred a major move toward improved understanding of the nature and mechanisms of CAM through the development of a major research agenda initiated by the National Institutes of Health (NIH). The majority of this research is funded and monitored by the National Center for Complementary and Alternative Medicine (NCCAM, http://nccam.nih.gov), a division of the Office of the Director of NIH.

According to NCCAM, there are multiple types of CAM, which may be grouped into the following broad categories:

1. Natural products (i.e., herbal medicine or botanicals, vitamins, minerals, probiotics)
2. Mind and body medicine (i.e., meditation, yoga, acupuncture, guided imagery, tai chi, etc.)
3. Manipulative and body-based practices (i.e., spinal manipulation, massage therapy)
4. Movement and energy therapies (i.e., Pilates, Feldenkrais® method, light therapy, Reiki)
5. Whole medicine systems (i.e., complete systems of theory and practice such as homeopathy or traditional Chinese medicine)

Definitions and additional examples of each of these categories can be found on the NCCAM website (www.nccam.nih.gov). Although many therapies included in CAM are not considered traditional medicine, others may be considered mainstream or alternative, depending on who is doing the categorizing. For example, many supplements and herbal extracts considered alternative in the United States have been used routinely for decades or centuries in European or Eastern medical practice.

The question of what is alternative becomes even more problematic when specifically discussing the field of physical medicine and rehabilitation (PM&R). The modern medical field of PM&R developed as an identifiable discipline during World War II as physicians and therapists utilized a number of complementary treatments that addressed not only the broken body but also the mind, spirit, and soul, with the goal of uplifting and restoring the whole person into a meaningful and productive life, rather than simply focusing on physiological or anatomical healing (9). This can also be seen in occupational and recreational therapies, each of which enjoys a long history of whole body or holistic mind–body therapies and mental health interventions. Occupational, physical, and recreational therapy credit the work of reconstruction aides in World War I for providing the momentum for the development of the professions (10) where the aides focused on treatments to heal the mind and body of soldiers. More recently, yoga, a specific type of CAM, was discussed as an "ancient occupational therapy" and as a holistic modality that may become an aspect of routine daily personal care (11).

Over the years, many complementary treatments involved in rehabilitation have become accepted as standard of care, and the evidence base for these treatments is slowly growing. The holistic nature of this field means that, more than is the case in most medical disciplines, rehabilitation therapists and physicians are willing to explore and utilize potential new therapies that appear to be beneficial even when those same therapies are being subjected to the time-consuming and costly process of evaluation by randomized controlled trials. In fact, many modern and alternative movement and manipulation techniques have emerged from the field of rehabilitation medicine. Examples include such movement and manipulation techniques as Feldenkrais®, Rolfing® or Structural Integration, and Trager® psychophysical integration. Thus, the distinction between complementary/alternative medicine and conventional medical therapy is not always clear in rehabilitation. For example, most conventional category systems defining CAM, including that of the NCCAM, include biofeedback as an example of a mind–body alternative therapy. Biofeedback is typically offered at most New Age and alternative health clinics; however, various forms of biofeedback have been available at many rehabilitation centers for many years. Thus, the status of biofeedback as alternative versus conventional medical therapy is unclear.

The Ottawa Evidence-Based Clinical Practice Guidelines Development Group recently published an extensive and exhaustive review of therapies for poststroke rehabilitation (12). They reviewed a broad range of rehabilitation interventions, both conventional and nontraditional, including biofeedback and constraint-induced therapy, along with other ostensibly alternative therapies such as massage, electrical stimulation, transcutaneous electrical nerve stimulation (TENS), tai chi, and acupuncture. These evidence-based clinical practice guidelines did not refer to any of these therapies as alternative or complementary. Therapies were included because there was research literature providing evidence for or against the effectiveness of the therapeutic intervention. This approach epitomizes the need for evidence-based medicine rather than a focus on alternative versus conventional medicine, as issued by the *JAMA* editors in the first special issue on CAM ever published in that journal (13).

The major premises of this chapter are that the ideas of nontraditional therapies should not be thought of as alternative, and that CAM therapies are not expected to replace conventional therapies in the current standard of care. Rather, the use of CAM therapies is expected to be complementary or integrative, used alongside and absorbed into regular rehabilitation care.

Many of the therapies discussed herein are presented with an explanation of their proposed mechanism(s) of action and evaluated in terms of supporting research evidence for inclusion as an aspect of stroke rehabilitation. The evidence varies in quality, from moderately strong to very weak. The remainder of the chapter is organized around most of the categories proposed by NCCAM, with the exception that the whole medical systems category is not used here; rather, certain specific therapies within those systems are assigned to one of the more specific NCCAM categories.

The chapter concludes with a discussion of strategies for managing therapies that appear promising and safe but for which empirical evidence of efficacy is not yet available.

NATURAL PRODUCTS

Supplements, Herbs, and Homeopathic Remedies

A number of nutritional supplements and herbs have been suggested for the prevention of stroke and related diseases with varying degrees of research evidence. However, there

is little evidence that these compounds can help in stroke recovery, except perhaps in their ability to reduce the likelihood of a recurrence of a stroke (14). With more than 100 clinical trials of allegedly neuroprotective agents, so far none have proven effective as a way to intervene with the cascade of detrimental cellular events that occur with stroke (15,16). However, investigations into the molecular components of Chinese medicine drugs and herbs provide some evidence that many of the drugs and herbs may contain the components necessary for neuronal change (17). Natural agents, such as the antioxidant alpha lipoic acid, certain traditional Asian herbal mixtures, and some homeopathically prepared remedies, have been studied as a means of reducing infarct size. A number of nutrients and herbs have been proposed to assist in treatment of the secondary effects of stroke, such as pressure sores, urinary tract infections, and pneumonia (14,18). Currently, only vitamin D has been found to be useful in preventing poststroke falls (a secondary effect of stroke), although the mechanism is unknown (19). There is evidence that a nutritional supplement that is calorie-dense with high protein and fat for individuals considered to be undernourished may be related to improved outcomes during stroke rehabilitation efforts (20).

A meta-analysis of traditional Chinese medicine drugs was completed in 2007, in which the authors indicated that most published trials of Chinese medicine have been conducted using poor-quality methodologies (21). The authors of the meta-analysis concluded that there was not sufficient or good-quality evidence to support traditional Chinese medicine as a mechanism to prevent death or dependency after stroke. They did state that there is enough evidence to support future research regarding the use of Chinese medicine to manage the secondary effects of stroke. At this time, the evidence is insufficient to recommend herbal and homeopathic treatment options as adjuncts in stroke prevention, treatment, and rehabilitation. Moreover, some of these supplements may have interactions with conventional medications, such as warfarin, anticonvulsants, and so forth. Physicians should inform patients of these concerns and should review the appropriateness of any proposed herbal or nutritional supplement before patients initiate usage. The reader is referred to a more thorough review of these adjunctive treatments, including the more than 100 herbs recommended and used in traditional Eastern medicine for stroke prevention, treatment, and rehabilitation (14,18).

Ginkgo Biloba

The one herbal supplement for which there is a substantial amount of research in neurologic and vascular disorders is an extract of the *Ginkgo biloba* leaf (22). The leaf of the ginkgo tree has been part of the traditional Chinese pharmacopoeia for 5,000 years. It has been shown to increase cerebral blood flow (23), and is therefore commonly used in Chinese medicine in the treatment of stroke. Standardized extracts of the ginkgo leaf are widely used in Asia, Germany, and France and are increasingly being used in the United States.

Ginkgo shows promise in the treatment of some of the most salient and debilitating symptoms associated with stroke, cognitive functioning in particular, and other vascular and neurologic disorders. One example of this evidence reported that 50 patients with subarachnoid hemorrhage who were administered ginkgo extract in a placebo-controlled, double-blind study showed significant improvements in attention and verbal short-term memory (24). Similarly, in another placebo-controlled study of patients with multi-infarct dementia or Alzheimer's disease showed modest, but significant, improvement in cognition on a geriatric assessment scale (25). The evidence for the use of ginkgo has been extensively reviewed by Diamond et al. (22,26), and their conclusions were that the evidence for ginkgo's effectiveness is mixed but encouraging. More recently, however, a systematic review (27) concluded that gingko as a sole herb appears to have no consistent benefit in treatment of acute ischemic stroke; however, its role as part of a more traditional combination of traditional drugs and herbs was not assessed (28). The results of the Cochrane review for stroke indicates that although there is no convincing evidence for the routine use of *Ginkgo biloba*, there are studies that show a relationship between the herb and improvement of patients after an ischemic stroke (27). Discrepancies in the results of these reviews may be related to the stringency of the criteria for inclusion. The clinical applications and precautions for ginkgo use are discussed in detail by Diamond et al. (22). One important caveat is that ginkgo has an anticoagulant effect and should be administered with caution in the presence of warfarin or aspirin and in individuals who have had a hemorrhagic stroke.

Hyperbaric Oxygen Therapy

Hyperbaric oxygen (HBO) therapy is defined as the provision of oxygen at pressures above sea level (1 atmosphere absolute or ATA). This is normally accomplished by enclosing the patient within a pressurized (hyperbaric) chamber. HBO has been primarily used to treat decompression sickness and air embolism, but has been proposed as a treatment for stroke. Advocates note that people with stroke experience a deprivation of oxygen to areas of the brain and suggest that this treatment might enhance neuronal viability by its ability to increase the amount of dissolved oxygen in the blood without changing blood viscosity (29).

The evidence for HBO therapy in chronic stroke is limited and controversial at best. Early, poorly controlled studies and surveys suggested that it might be helpful, but more recent studies have come to the opposite conclusion (30). The treatment parameters remain uncertain, with a range of 1.5 to 2.5 ATM proposed, and some suggest treatment with pressures as high as 3.0 ATM for the initiation of therapy (31).

A recent, small clinical trial (32) randomized a small sample of chronic stroke patients to receive either 60 minutes of HBO in a chamber at 2.5 ATA versus a control treatment of 100% oxygen treatment in an HBO chamber at

1.14 ATA. The small amount of additional pressure in the control group was designed to facilitate blinding patients. Results indicated that a very low pressure of 100% oxygen (1.14 ATM) (intended as a control therapy) was more effective than a treatment at 2.5 ATM. Safety and toxicity have been concerns regarding HBO therapy (33–36). A 2010 review of the evidence concluded that there is no consistent evidence to support use of HBO for acute stroke, but that the potential for clinical benefit cannot be ruled out at this time (30).

Chelation

Chelation is a chemical process in which a substance is used to bind molecules together so that they can be removed from the body. Ethylene diamine tetra-acetic acid (EDTA)-chelation therapy has long been FDA-approved for removing heavy metals (e.g., lead) from the blood; however, its use for other purposes is controversial. It has been advocated for the treatment and prevention of cardiovascular and cerebrovascular disorders, but there are no controlled trials to substantiate its use. In one uncontrolled trial, cerebral arterial occlusion was measured in 57 patients before and after treatment with 10 to 46 sessions of chelation therapy. Eighty-eight percent of the patients improved, with the criteria for improvement not stated, and cerebral arterial stenosis was reported to be reduced from a mean 28% to 10% (37). A retrospective analysis was conducted, in Brazil, of 2870 patients who were treated with chelation therapy between 1983 and 1985 (38). These patients had a variety of vascular and degenerative diseases, with about 18% of the patients diagnosed with cerebrovascular disease or degenerative CNS disease. The investigators reported "marked recovery" in 24% of the patients and "good recovery" in 60%. Animal studies with another chelating agent, deferoxamine, show that the hypoxic-ischemic injury is reduced if deferoxamine is administered soon after the injury (39–41). Currently, there is a large (n = 1708) double-blind, randomized controlled trial of EDTA chelation therapy for people with coronary artery disease being conducted (Trial to Access Chelation Therapy [TACT]) (42). The study is funded in part by the NCCAM and the National Heart, Lung, and Blood Institute. Stroke rates are included as an important primary end point. Preliminary results suggest some benefit in reducing the risk of cardiovascular events, but final results have not been published as of this writing. At present, the evidence of efficacy and safety is insufficient to recommend this treatment for stroke survivors.

MIND AND BODY MEDICINE

Mind–Body Therapies

The mind–body category of NCCAM contains a huge number of diverse interventions. Mind–body interventions, as the name implies, focus their therapeutic efforts on the interrelationship between mental and physical activities. In Eastern models, the two, mind and body, are inextricably intertwined, so physical and cognitive techniques are often discussed together in Eastern treatments of the subject. Techniques in this area can focus primarily on the mind (e.g., hypnosis and meditation), on the body through physical movements (e.g., tai chi and yoga), or on a combination of both (e.g., yoga with meditation). For clarity and to more directly reflect the categories often used in PM&R, we divide these techniques into two sections: mind-focused and movement interventions.

Mind-Focused Therapies

This section includes interventions focused directly on cognitive processes that are intended to favorably affect the whole body.

Optimizing Self-Healing Through Expectations and Beliefs

Virtually all alternative therapies acknowledge the inextricably intertwined nature of the mind and the body. Alternative systems of therapy seldom use only a single intervention; instead, they use multiple interventions that work on various aspects of both the mind and the body. Thus, a traditional Chinese medicine practitioner might use acupuncture, herbs, massage (tuina), and energy healing (qi gong and so forth) in a systematic and integrated treatment of the whole body, including the mind, rather than focusing on a single diagnosis or symptom. Similarly, in Ayurvedic medicine, herbs are a basic part of a treatment, but they are usually combined with physical manipulations (yoga and marma therapy), breathing exercises, mantras or healing sounds, and meditation to quiet the mind and reduce stress. All of these systems of intervention work on both the mind and the body.

In Western medicine, the connection between the mind and the body is also well known and acknowledged as a legitimate way of conceptualizing the way the body maintains a healthy state. Well-defined fields such as behavioral medicine, psychoneuroimmunology, psychiatry, and psychology all recognize and focus on the mind–body connection in health and healing. However, with the advent of powerful surgical and pharmacologic interventions, conventional medicine has tended to push the mind part of the equation into the background, considering it to be a minor, if not irrelevant, component of the healing process. In fact, these belief-based processes have often been considered confounders in clinical research that is designed to look at the pure underlying mechanisms and healing ability of a medical intervention, free of any artifacts that might make the treatment look better or worse than it really was. The unwanted effects of these beliefs and expectations have come to be called *placebo*, from the Latin for "I please," in effect implying that patients are mindlessly following their doctor's suggestions. Rigorous, placebo-controlled, clinical research protocols have become the only true test of the underlying effectiveness of a treatment because they control, not only for the placebo effect, but also for placebo-like effects such as natural healing and other artifacts in the healing process.

Recently, some biomedical researchers have begun to look at the placebo effect more closely, not merely as a confounding phenomenon that occurs in research designs, but also as a possible source of healing per se (43–45). In an extensive review of the literature on the placebo effect, Walach and Jonas (45) have suggested that the placebo process should really be called something that reflects the fact that it is a "meaning attribution" process. They provide suggestions, based on the literature, for enhancing the process whereby positive meaning is given to a clinical situation. From a therapeutic point of view, the placebo response can best be defined as the effect that is caused by the meaning of a therapeutic intervention for a particular patient and context (45). Notice that this "meaning response" definition acknowledges that humans are not deterministic machines mechanically reacting to external causes such as drugs, physical therapy, and so forth; rather, we respond in part as a result of our interpretation of what is happening to us, including the meaning attached to a particular treatment and the manner in which the health care giver presents it. To the extent that a patient responds to the extracausal components of the intervention itself, it must be considered to be a real effect. If the environmental cues send a negative message about the therapy (technically referred to as a *nocebo*), we should expect to see a poorer result from the treatment. Similarly, if the cues are positive and supportive, the pure effects of the therapy can be expected to be enhanced. And the changes in treatment effectiveness are not simply because of willfulness or weak-mindedness on the part of the patient; they are real effects that emerge from the patient's attribution of meaning to the situation.

Health care providers who are developing and integrating CAM approaches to medicine, involving both conventional and nonconventional therapies, have begun to stress the importance of this mental component of the healing process. They are encouraging its use in the clinic and even conducting research designed specifically to assess the extent of and effectiveness of various placebo-inducing factors. It is also being argued that the term *placebo* should no longer be used to characterize this phenomenon, because it has the negative connotation of weak-willed compliance to an authority figure (43). The suggestive component of this process not only includes the bedside manner of the caregivers, but also includes the physical environment itself. More and more clinics are utilizing a healing environment approach to their space. Walls and equipment are in warm colors. Soothing music is available in the waiting room as well as in the clinical suite. Invasive and complex-looking equipment is placed as unobtrusively as possible, and so forth. Research on the effectiveness of these techniques is still in very early stages, but the importance of harnessing this meaning aspect of the placebo effect must be recognized (43,45–47).

A useful list of ways to enhance the healing effects of a therapeutic intervention based on research literature on placebo has been presented by Walach and Jonas (45). Based on their literature review, they propose a number of ways to enhance the meaning attribution process in a clinical setting, which is presented here in Table 37.1.

Even though not all of these interventions may be easily applicable to a rehabilitation setting, they should suggest, by generalization, the types of things a clinician can do and say that will encourage the patient and facilitate the healing

TABLE 37.1 Ways a Health Care Provider Can Optimize the Meaning Attribution Process in the Doctor–Patient Relationship

- Always work with—not against—patient's expectations.
- If patients' expectations are unhealthy or harmful, work to change them first before jumping from intervention to intervention.
- Talking can induce a response toward cure. Rapport between doctor and patient is an important vehicle for suggesting therapeutic effects and enhancing expectations.
- One of the greatest skills of a doctor—and a topic often left out of the debate around evidence-based medicine—is individualization. It is in the subtle changes to therapy and how they are delivered by a skilled healer that the meaning response is harnessed to its fullest.
- Raising hope and alleviating anxiety in a credible way is one of the most therapeutic acts in general.
- It has been shown empirically that a simple act, such as giving a clear diagnosis and prognosis, improves outcome.
- A frequent assumption is that only specific causal effects count, like those produced by drugs or surgery. Other effects also count.
- Giving placebos is not identical to using the meaning response therapeutically. One need not give sugar pills. However, in some cases, the use of nonactive or minimally active drugs might be a better option than continuous medication with toxic, but effective, therapies.
- Therapeutic rituals might be helpful in eliciting the meaning response. It may be useful to help patients develop their own rituals, like taking a drug after a morning bath, in a special room, before or with prayer, or having it administered by a friend.

Source: From Ref. (124). Johansson BB, Haker E, von Arbin M, et al. Acupuncture and transcutaneous nerve stimulation in stroke rehabilitation: a randomized, controlled trial. *Stroke*. 2001;32(3):707–713.

process. A whole body of research is emerging in which the effects of these interventions are being tested in rigorous research designs (43,44). In the meantime, clinicians should take to heart the fact that the mind is a major component of healing and, over time, can facilitate or thwart the effects of even the most powerful physically focused intervention.

Meditation

There is little to no evidence for the use of meditation or mindfulness-based stress reduction after stroke. There is limited evidence that mindfulness-based stress-reduction intervention, including meditation, may improve poststroke fatigue (48). Recent meditation literature completed in adults without stroke has demonstrated neural changes after meditation; neuroimaging was used to identify increased cortical thickness and brain connectivity (49–52). Such neural changes may be associated with improved motor, cognitive, and emotional recovery for people who have sustained a stroke.

With regard to stroke prevention, the most robust finding from the extensive research literature on meditation is the success of meditation for reducing hypertension (53–57). Currently, a large randomized clinical trial is underway, the hypertension analysis of stress reduction using mindfulness meditation and yoga (HARMONY) study, to study mindfulness meditation (and yoga) as a modality to control hypertension for individuals with high blood pressure (58). Given the success of meditation for reducing hypertension and the fact that hypertension is a primary predisposing factor for stroke and recurrence of stroke (59), it seems reasonable to conclude that meditation may be effective in reduction of risk of recurrent stroke.

Biofeedback

Biofeedback is a therapeutic technique originally developed for muscle relaxation, but it has also been used recently in a number of other ways as well. It is a good example of a family of techniques that remains on the boundary between alternative and mainstream medicine and therapy, despite a substantial body of research evidence, including several meta-analyses (60–62). However, a more recent Cochrane review did not find treatment benefit for biofeedback when added to therapy to improve motor function after stroke, but the authors indicate that the included studies were small and of poor design (63).

The Ottawa Panel on Evidence-Based Clinical Practice Guidelines Development Group reviewed and recommended several forms of electromyographic biofeedback (EMG-BFB). Their guidelines support the use of EMG-BFB for upper and lower extremities at all stages of stroke recovery (12). The Ottawa Panel concluded that there is strong support for audio and video feedback training for unilateral neglect reduction in subacute stroke and general facilitation EMG-BFB training for upper and lower extremities, including rhythmic positional training in chronic stroke. They concluded that EMG-BFB should be included as an intervention for poststroke patients who have a high level of motor return and where gait and standing are the focuses of rehabilitation. More details on the specifics of the use of EMG-BFB in stroke rehabilitation can be found in the Ottawa Panel report (12).

Positive, but less conclusive, research evidence for other uses of BFB in stroke recovery has been reported and should be considered when other interventions are not successful (63). For example, BFB may be helpful in controlling urinary incontinence (64–66). It appears to assist with some aspects of the rehabilitation of hemiparesis and mobility and gait recovery (67,68) and may be useful in the rehabilitation of swallowing in patients with dysphagia (69–71). Interestingly, Nelson identifies biofeedback as a modality that has mixed success, but notes that it may have a positive impact with improvements in self-confidence, change in locus of control, and ability to instantly integrate feedback on motor and mental activity (64). It may be that the change in motor function is less important than the perceived improvements and improved self-confidence to complete a movement or task.

A newer form of feedback is EEG-based feedback, or neurofeedback (64). In this approach, electrodes monitor the EEG activity at one or more scalp locations, and a computer displays information about the brain's activity to the patient. Then, operant conditioning combined with various cognitive strategies or functional tasks is used to train the patient to alter his or her own EEG activity in the desired direction. Given the relationship between EEG activity in particular frequency bands over specific cortical locations and metabolic rates of various cortical structures (72), this approach has been hypothesized to allow the therapist and patient to alter cortical metabolism and thereby influence neural activity and neuroplasticity in various regions of the brain (73,74). Neurofeedback has been hypothesized to alter or accelerate the processes of functional reorganization of the cortex following stroke, thereby enhancing or accelerating functional recovery. Aside from two case reports in chronic stroke survivors suggesting improved cognitive functioning (75,76), this technique remains untested in stroke patients, and its efficacy remains speculative at this time.

Interactive Metronome Therapy

Another novel technique for cognitive rehabilitation following stroke is Interactive Metronome Therapy (64). This technology uses operant conditioning of an individual's motor planning, sequencing, timing, and attention by having him or her engage in simple, repetitive motor tasks such as clapping the hands or tapping the feet in time with a set beat. The system provides both visual and auditory feedback to indicate how far off beat each repetition of the task is (in milliseconds) and whether the repetition was early (before the beat) or late (after the beat) to allow the individual to alter the rate of movement on a beat-by-beat basis. The tempo of the beat is adjustable. Thus, in the course of just over a second, the individual receives audio and visual feedback about his or her last response, tracks the next beat, adjusts his or her behavior accordingly, and makes the next response. This deceptively simple task is cognitively demanding, and

many patients find it frustrating and confusing in the beginning of their treatment. The research on Interactive Metronome technology has focused largely on the remediation of attention deficit disorder in children (77,78). At this time, there is no published research evidence for its efficacy in stroke rehabilitation; only that it may be feasible to add to occupational therapy (79) and may improve upper-extremity function and perceived stroke recovery (80).

Mental Practice/Motor Imagery

Mental practice, or motor imagery, is a technique by which physical skills are mentally rehearsed in a safe, repetitive manner. Mental practice increases motor skill learning and performance in elderly individuals (81,82), and the same neural and muscular structures are activated when movements are mentally practiced as during physical practice of the same skills (83–85). Other similarities between mental practice and physical practice include:

1. The time taken to mentally and physically perform movements is highly similar (86).
2. During mental practice, the speed/accuracy trade-off is maintained (87).
3. Mental practice produces similar autonomic events as physical practice of the same skills (88).

Pilot data suggest that the addition of mental practice to motor therapy may actually yield greater motor improvement than conventional motor therapy in subacute (89–91) and chronic stroke (92–97). Of interest, a randomized placebo-controlled trial for people with chronic stroke demonstrated significantly different improvements for individuals who received mental practice plus 30 minutes of therapy than those only receiving 30 minutes of therapy (98). Subjects who received mental practice showed less physical arm impairment, increased arm function, and new ability to engage in valued activities. A 2006 review of the literature indicates that mental practice may be beneficial after stroke, but that further research is required (99).

Movement Therapies

A number of movement-based therapies, such as balance training and dance therapy, are utilized in physical rehabilitation, and a few can be thought of as alternative. Because of the limited mobility of many stroke patients, however, the application of these approaches is limited and often must be modified and simplified to safely accommodate their capabilities. Nevertheless, there is some evidence, often with nonstroke elderly patients, suggesting that these approaches should be considered and developed for future clinical use. Three movement therapies are briefly discussed here: tai chi, qi gong, and yoga.

Tai Chi and Qi Gong

Tai chi and the closely related qi gong are whole body movement approaches based on traditional Chinese medicine that use gentle, rhythmic, and ritualized movements of the arms and legs. Tai chi is associated with and has emerged from the martial arts; qi gong, although using similar movements, generally refers to the use of breathing as well as stylized movements for healing purposes. Qi gong can also refer to a form of subtle energy healing in which subtle energy or chi is emitted from a master into another person for healing purposes. In this chapter, qi gong refers to the stylized movements of a person with the purpose of moving the chi within his or her own body.

Tai chi has been used with success in improving balance and reducing falls and fear of falling in fall-prone elderly subjects (100–102), and appears to be safe for people with chronic disease and disabilities (100,102). Research for tai chi after stroke is growing, as evidenced by a published review in 2012 (103). At the time of the review, five randomized, controlled trials of tai chi for stroke were available and included. Results of the review show an improvement in multiple variables after tai chi was introduced to people with stroke, including improvement in quality of life, balance, and mental health. At this time, more research on this promising technique is warranted.

Yoga

Yoga is a philosophical system that originated in India approximately 5000 years ago and was primarily intended as a means of increasing self-awareness. The term *yoga* means "union," or yoke referring to the universal self, and includes any practice designed to enhance this self-awareness. Thus, meditation, study of the Scriptures, pure devotion to God, repetition of a mantra, selfless service, physical postures, and many other practices are all forms of yoga. In the West, however, the term *yoga* usually refers to Hatha yoga, considered the foundation of all other yoga practices, and encompasses a number of systems focusing on the physical body, using postures (asanas), diaphragmatic breathing (pranayama), and meditation (dhyana). Although not well understood, there is evidence to suggest that the combination of postures and breathing is most beneficial (104) and more therapeutic than traditional exercise (105–109). Yoga postures are designed to prepare the body for maximizing self-awareness. One advantage of yoga is that many poses can be performed in sitting or supine positions, so they may be safer and easier to perform for people with limited mobility.

The U.S. Department of Health and Human Services recently stated that "yoga is often recommended as a form of total-solution exercise for older adults, although there is little scientific evidence to support this recommendation" (110). There is a real need to further explore yoga as a viable aspect of rehabilitation therapies among populations with different diagnoses.

Although there are numerous studies on the effect of yoga on hypertension and cardiovascular physiology, which have some relevance to stroke prevention, a 2007 systematic review of the literature found no controlled trials of yoga for stroke rehabilitation (111). However, at the time, only one case study had been completed (112). Since then, two small

case series (111,112), one qualitative study (113), and a randomized pilot study (114) have been reported.

One case series involved four chronic (six months to eight years after stroke) patients with hemiparesis who completed biweekly yoga sessions for eight weeks (112). Study participants reported improvement in several outcome measures (Berg Balance Scale, Timed Movement Battery, and Stroke Impact Scale domains of physical, cognitive, emotional, and social participation). The yoga therapy program included a number of classical seated, supine, and standing yoga postures, a short period of breathing exercises (pranayama), and a short meditation period.

Lynton et al. presented the results of a small pilot study involving yoga in chronic stroke patients (111). The 3 participants in this study attended yoga classes twice a week for 12 weeks and underwent pre- and postassessments using the O'Connor Tweezer Dexterity test, a timed test in which the participant places pins in a peg board with tweezers, and the Boston Aphasia Exam for speech. Each of the three subjects improved in dexterity (the O'Connor Tweezer Dexterity Test) and speech (Boston Diagnostic Aphasia Exam) scores. A qualitative study indicates a perceived improvement in strength, ROM, and gait and an acceptance of a "different body" after yoga (113).

These studies indicate that people with stroke can physically and cognitively engage in and enjoy the physical, psychological, and emotional benefits from yoga, yet it is unknown how these benefits generalize to the chronic stroke population. In spite of the minimal published evidence on the utility of this treatment, a number of clinical rehabilitation programs do offer yoga as an option to patients, given its favorable safety profile and favorable anecdotal patient reports. Most recently, Schmid et al. (114) completed a randomized pilot study of yoga versus usual care for people with chronic stroke. Results indicated that people with chronic stroke were able to complete eight weeks of seated, standing, and floor postures and could engage in the physical postures, breathing, and meditation of a modified yoga program (Table 37.2). The study was not powered to see differences between groups, but those randomized to the yoga intervention benefited from significant improvements in balance, balance self-efficacy, and quality of life. Results were more impressive for those individuals who "completed the intervention" by completing at least 5 of the 16 sessions; in addition to improved balance, they also had increased self-efficacy and quality of life. The small sample size makes it impossible to draw definite conclusions, but the positive trends in these studies suggest that further research examining the usefulness of yoga in stroke recovery is warranted.

Acupuncture

Acupuncture has been used for more than 2000 years to treat stroke in China and other parts of Asia. According to traditional Oriental medical theory, upon which acupuncture is based, the body contains a system of energy channels called *meridians*. These meridians are not physical vessels that can be identified by anatomical dissection; rather, they are hypothetical pathways through which energy flows. The energy that flows through these meridians is considered a life force and is referred to as *qi* or *chi* (both spellings are pronounced "chee"). Illness is viewed as an imbalance in the flow of qi throughout the body. Acupuncture and related traditional Chinese medicine therapies are all designed to alter the flow of qi and to return the body to a state of health and balanced qi. Numerous variations have evolved over the centuries, including the relatively recent use of electrical stimulation of needles at some acupuncture points during treatment sessions. Other (nontraditional Chinese medicine) potential mechanisms by which acupuncture might be effective for certain conditions have been proposed as alternatives to traditional Chinese medicine theories (115).

A modest amount of research on the effectiveness of acupuncture in stroke recovery has appeared in the Chinese research literature for several decades. Unfortunately, most of this early research does not meet current standards of clinical research methodology, so it is of limited utility in evaluating the effectiveness of acupuncture. Beginning in the early 1990s, research with improved rigor began to appear, with variable findings regarding the efficacy of acupuncture to facilitate stroke recovery (116). The evidence in favor of therapeutic efficacy for stroke recovery was sufficiently strong to warrant a conclusion by the 1997 NIH Consensus Development Conference on Acupuncture (117) that there was limited and encouraging evidence for the relationship between acupuncture and stroke recovery, although not sufficient to recommend its use as a medical procedure.

In the extensive meta-analysis by Sze et al. (118,119), the authors concluded that acupuncture is associated with a weak to moderate effect on motor recovery and activities of daily living, but the authors dismiss the relevance of these findings, attributing this effect to a true placebo effect rather than an effect specific to acupuncture. However, a review and reanalysis of these studies was conducted (120,121); after accounting for methodological flaws in several of the clinical trials, this reanalysis concluded that the evidence may support the efficacy of acupuncture. Many of the clinical trials of acupuncture do not statistically analyze the data as improvement (change) scores, but rather as absolute performance levels at follow-up. The use of change scores helps correct for baseline differences among subjects, an important issue given that baseline functional ability has been shown to be a key predictor of functional outcome after stroke. A Cochrane review from 2006 and (edited in 2009) maintains the lack of clear evidence for acupuncture as an aspect of stroke rehabilitation, but does recommend additional trials due to the current published data (116).

There is some evidence that the anatomy and severity of a stroke play an important role in the responsiveness to acupuncture therapy and perhaps other treatment modalities as well. Naeser et al. (122) studied CT scan findings for 20 stroke survivors treated with acupuncture and found that efficacy correlated with stroke location and extent. Subjects who responded to acupuncture were found to have less than

TABLE 37.2 Modified Yoga in Seated, Standing, and Supine Postures

WEEK 1	WEEKS 2–3	WEEKS 4–8
Entire practice is seated with seated relaxation	Seated and standing practices with a seated relaxation	Seated, standing, and supine on floor poses with supine/floor relaxation
		
		

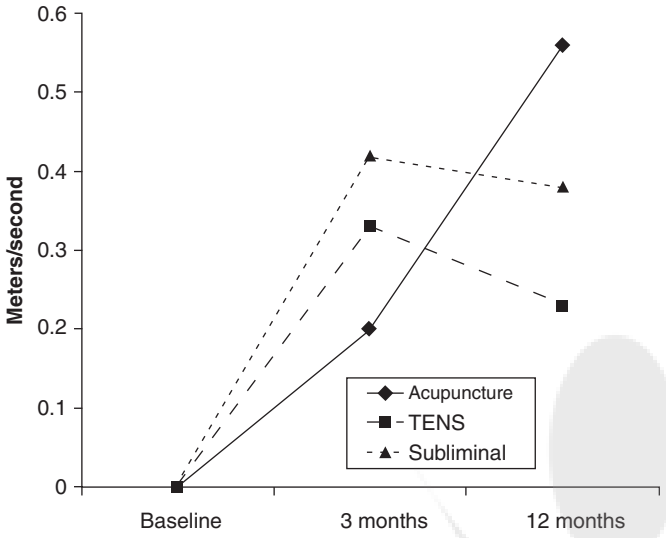

FIGURE 37.1 Walking speed as a function of acupuncture condition.

Source: From Ref. (124). Johansson BB, Haker E, von Arbin M, et al. Acupuncture and transcutaneous nerve stimulation in stroke rehabilitation: a randomized, controlled trial. *Stroke*. 2001;32(3):707–713.

one-half of pyramidal tracts and periventricular white matter infarcted on the CT scan. This preliminary study suggests that stroke anatomy and severity should be included when characterizing participants in acupuncture studies in stroke survivors. The possibility of both floor and ceiling effects for acupuncture therapy should also be further explored to determine if patients with excessively severe or very mild strokes are unable to benefit from this treatment. Failure to consider this possibility poses a risk of diluting clinically meaningful effects in the moderately affected population.

The systematic reviews of acupuncture have focused on motor recovery and global measures of functional outcome, but several other aspects of recovery have been prioritized in specific studies. People who received acupuncture after stroke have also demonstrated improved ability to maintain postural control in the presence of perturbation (123) and improved walking (124,125) (see Figure 37.1). Other research has shown that acupuncture may be a viable treatment option for dysphagia in people with stroke; using video fluoroscopic swallowing study (VFSS) as an assessment tool, it was found that people with stroke who received acupuncture had fewer episodes of choking while eating or drinking (126,127).

The evidence for the efficacy of acupuncture after stroke is still best described as mixed, and definitive conclusions for or against the efficacy of this technique seem premature. In the absence of any specific medical contraindications, acupuncture generally seems safe and well tolerated by people who have sustained a stroke.

MANIPULATIVE AND BODY-BASED PRACTICES

Manipulative and pressure-based therapies encompass any of a number of techniques that involve touching the body with an external object, such as massage therapy, or a penetrating needle, as in acupuncture. Manipulative therapies are used in the treatment of a number of medical and physical conditions and are also used as a general technique for relaxing the body and generating a feeling of well-being in otherwise healthy individuals. Many fundamental therapies, such as massage, myofascial adjustments, or osteopathic manipulation, have numerous variations, with different names based on the particular variations in the application of the fundamental technique.

Massage and Acupressure

Acupressure is a form of manual therapy that is based on the same traditional Chinese medicine theory underlying acupuncture. Based on this meridian system, acupressure, like acupuncture, aims to balance the flow of qi and is used either preventatively or as a means of healing an illness. Acupuncture involves the insertion of needles in specific points along the meridians; acupressure, instead, uses the fingers to press these points. Because the same points are used in acupuncture as in acupressure, there is a general assumption that both techniques should have similar effects, although nonpenetrating acupressure might be expected to show milder effects. Practitioners suggest that acupressure might be appropriate for situations where acupuncture seems desirable but the subject or patient is not willing to submit to needle insertion or acupuncture was unacceptably painful.

Many different types of Oriental bodywork therapies use acupressure. Among the most widely used in the United States are:

- Shiatsu (literally translated as "finger pressure" in Japanese)
- Jin shin jyutsu ("the art of circulation awakening")
- Jin shin do ("the way of the compassionate spirit")

What is common to all of the different acupressure systems is the use of sequenced applications of pressure to the meridian points (or *acupoints*) in order to tonify (acupuncture technique for strengthening the body) or sedate them (128,129). Fundamental differences between the different forms of acupressure relate to the amount of pressure applied to the points, length of application, the intent of treatment (e.g., overall relaxation or balance versus treating a specific condition), and philosophy (e.g., the extent to which the treatment approach is integrated with other methods, such as Western manual manipulation techniques, dietary or herbal methods, or psychology) (128). Only a few studies have examined acupressure after stroke. In a small, poorly controlled study, Hogg (130) found that acupressure was more effective on several outcome measures than a control treatment consisting of light laying-on of hands (therapeutic touch). In a Korean study, the use of acupressure was tested in a small randomized trial (131). Individuals who received acupressure in addition to usual care enjoyed significantly improved upper-extremity function, activities of daily living, and depression compared to the usual care control group. Thus, at this time, continued interest and additional research are warranted.

Marma Therapy

Marma therapy is a massage-based therapy originating in Indian Ayurvedic medicine. It uses energy "chakras" and special energy points, or Marma points, with vigorous pressure to "unblock the channels of energies" and to promote healing (132). In stroke, the pressure would typically be applied primarily to the affected side. There are 107 Marma points where flesh, veins, arteries, tendons, bones, and joints meet (132). The points are related to the yogic system of channels through which prana flows (nadis) rather than to the acupuncture meridian system. The effectiveness of Marma therapy is supposed to be related to the sensitivity of these points. Marma points are therefore selected on the basis of their sensitivity; the therapy is reduced as function returns (132).

What appears to be the first controlled study of Marma therapy for stroke is a small (n = 30), nonrandomized, controlled pilot trial on stroke patients in an acute stroke unit (132). Outcomes of Marma therapy (three 45-minute sessions plus standard rehabilitation) were compared to outcomes of standard rehabilitation only. Although no statistically significant effect was detected on the Barthel index at 12 weeks after treatment, scores showed greater improvement for the Marma group at both 6 and 12 weeks after treatment. The authors have indicated that even though the recruitment to the study was challenging, the Marma treatment was believed to be both beneficial and acceptable by patients (132). Despite its methodological limitations, this study demonstrates promise for this therapy and a larger, randomized, controlled trial seems appropriate. Similarly, further formal study of related Ayurvedic and yoga-based interventions is needed.

MOVEMENT AND ENERGY THERAPIES

According to the NCCAM definition of *energy medicine*, this category includes any form of stimulation with external energy, such as electricity, as well as the more controversial forms of subtle energy, such as chi, Reiki, and so forth. The latter forms of energy are controversial because they cannot be detected with currently existing technology, hence the NNCAM's use of the term *putative* for these forms of energy. Because there is so little evidence for the subtle-energy forms of therapy, except where observable interventions are used to influence this energy (as in tai chi), they are not discussed further here.

Electrical Stimulation

Various forms of electrical stimulation have been used in treating specific medical problems associated with stroke. TENS is used to stimulate nerves in an effort to control pain, and therapeutic electrical stimulation is often used to stimulate paretic muscles in an effort to induce recovery of muscle function. The conventional applications of these techniques are covered in detail in Chapter 21.

Electroacupuncture is another type of electrical stimulation used in stroke survivors. Unfortunately, the use of electricity with acupuncture in these studies is quite variable (different needle sites, length of time the needle is maintained, etc.) and inconsistent from study to study, so few conclusions can be drawn regarding the direct effects of the electrical stimulation independent of the effects caused by acupuncture per se. These studies were included in the general discussion of acupuncture earlier.

At least one study in which acupuncture is the primary focus used a form of TENS as the control condition (124). In this study, surface electrodes were applied to acupuncture points, and either a strong current (TENS) or an extremely low, undetectable current (sham TENS) was applied to acupuncture points, so the effectiveness of TENS relative to sham TENS, as well as (electro)acupuncture, could be estimated. No difference between acupuncture-point TENS and sham TENS was seen for functional and motor recovery, though, on reanalysis, electroacupuncture appeared more effective than either in improving functional independence or walking speed (121). In a study by Wong (133), *electrical acupuncture* was defined as the application of electricity via surface electrodes over acupuncture points. In other words, it was a nonconventional form of TENS. Subjects with this form of treatment, combined with rehabilitation, did better on several neurologic and functional outcomes when compared to a rehabilitation-only control group. Additionally, when electroacupuncture was compared to acupuncture, it appears that the electroacupuncture group enjoyed significantly more improvement in the management of stroke-related spastic paralysis (134). Electroacupuncture and tuina manipulations for poststroke shoulder pain led to improved outcomes when compared to typical rehabilitation (135). When combined with typical rehabilitation, increased electroacupuncture hertz was associated with greater improvements in poststroke gait and motor assessments (136). Based on these studies, the evidence for what could be called electroacupuncture, or acupuncture with TENS, appears encouraging enough to warrant further research.

CONCLUSION

The therapies presented in this chapter are by no means an exhaustive listing. The research-based evidence for the therapies discussed here varies from minimal to moderately positive. Many other CAM therapies have and will be proposed in the future, often with little empiric or theoretical basis for their use. Even though many of these therapies may be innocuous, ultimately the criterion for incorporating any therapy into routine treatment (mainstream or nonconventional) must be the existence of research, showing evidence of safety and efficacy. Some maintain that this fundamental requirement will eventually erase the distinction between conventional and alternative medicine (13). Unfortunately, this evidence base is likely to be long in coming.

Even though the same evidence-basing procedures must be applied to all therapies, whether traditional or nontraditional, it is important to recognize that many alternative therapies have a low risk of adverse reactions. In the absence of clear evidence of efficacy, but with a low risk of harm,

many patients and their caregivers are willing to accept CAM therapies to treat symptoms that are otherwise not yet amenable to proven therapies.

Most CAM therapies will be used in conjunction with other rehabilitation therapy, and the most judicious use of alternative or complementary therapies will generally be as an adjunct to well-established conventional therapies that are considered to be standard of care. In some cases, alternative therapies can be explored when other therapies appear to have run the course of their effectiveness. In many cases, the use of CAM therapies is initiated by patients; clinicians must understand the need of patients to try alternative options and determine how to deal with such requests. Communication with patients, including an honest appraisal of the evidence base for both conventional and CAM therapies, is the best approach to safe and appropriate use of these therapies in clinical practice.

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38

Seating, Assistive Technology, and Equipment

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Assistive technology (AT) plays a significant role in the lives of individuals with disabilities to help maintain, increase, or improve the functional activities of daily living (ADLs) within the home and community. Appropriate selection and application of technology has a great potential not only to contribute to, but also to improve the quality of life of the individual.

This chapter provides a brief overview of the range of AT available and applicable to individuals who have experienced physical impairments as a result of a severe stroke. An important step to ensure appropriate selection of AT is to start with an AT team that consists of qualified AT professionals who have a keen interest in including and encouraging active participation of the end user in the AT evaluation and selection process, as described in the AT service delivery model. Sections covered in this chapter include AT interventions in wheelchair seating and mobility, electronic aids for daily living, augmentative and alternative communication (AAC), adaptive driving, and wheelchair transportation safety, as they may be applied and fit into the individual's stroke recovery and rehabilitation process.

AT SERVICE DELIVERY MODEL

A successful AT service delivery model requires specialized knowledge in the design and application of AT, as it has tremendous potential for a positive impact on the community integration of people with disabilities. The specialized knowledge starts out with the AT assessment team that consists of physiatrists, occupational and/or physical therapists, speech–language therapists with specialty training/certification, rehabilitation engineering technologists, and qualified equipment suppliers. Other professionals may also be consulted depending on the needs and goals of the client. Rehabilitation counselors, nurses, personal care assistants, and other similar professionals can also make important contributions to the AT service delivery team.

To assure that specialized knowledge is present within the AT assessment team, the Rehabilitation Engineering and Assistive Technology Society of North America (RESNA) (www.resna.org) offers a credentialing program in AT to clinicians and suppliers. RESNA offers three levels of credentials, as outlined in the following paragraphs: assistive technology professional (ATP), the seating and mobility specialist (SMS), and rehabilitation engineering technologist (RET).

Through the ATP credential provided to suppliers and clinicians, RESNA recognizes "demonstrated competence in analyzing the needs of consumers with disabilities, assisting in the selection of appropriate assistive technology for the consumer's needs, and providing training in the use of the selected device(s)" (1). To attain the ATP credential, an individual must demonstrate compensated employment in the field of AT and pass an examination that consists of fundamental elements and case-based scenarios.

To identify clinicians who specialize in seating and mobility service provision, RESNA created the SMS credential. RESNA's justification of the creation of the SMS is as follows: "[W]hile the ATP is a broad-based exam covering all major areas of assistive technology, the SMS exam is focused specifically on seating, positioning, and mobility. The program is intended for clinicians, suppliers, engineers and others involved in seating and mobility service provision."

For engineers and technicians who have been supporting AT clinics, RESNA created the RET credential. The RET credential first requires an individual to hold an engineering or technology degree. After a suitable period of clinical AT service delivery experience, individuals are eligible to sit for the ATP examination and the supplemental RET examination. However, at the time this chapter was updated, RESNA has stated that "RET certification is active for current certificates but is under review and is not currently available to new applicants." These credentials help consumers to identify individuals who have acquired specialized knowledge of AT and are committed to providing high-quality services.

The design and application of the AT service delivery starts out with the introduction of the client to the AT assessment team and empowerment of the client to be an active decision-making member of that team.

A proper assessment begins with an initial interview that involves listening and paying attention to the client's needs, concerns, and goals for a device. It is important to understand

the medical variables—assessed by the physiatrist and shared with the team on how underlying medical conditions may impact the prescription of a AT device—as well as the physical and functional variables assessed by the therapists on how physical capacities and limitations affect mobility and instrumental ADLs. It is important to know how the client performs tasks, where the deficits are, and how AT can compensate for deficits to augment task performance. The user is given an opportunity to try the equipment to determine how he or she best performs and assesses this. Transportation variables are also important to consider if transporting the wheelchair and seating system are essential goals. The person who will be stowing the device should get an opportunity to try doing so before the final prescription being written.

The AT team members will explain the outcomes, reasons, and facts upon which they based the final recommendation of the device to the client. However, the final decision on the mobility device lies with the client, the family, and/or caregivers.

The assessment and service delivery process is completed during delivery of the new device to the client, and the therapist signs off on the correctness of the final fitting and operation of the new AT device.

FIGURE 38.1 Example of an Ergo contoured seating system.

SEATING/MOBILITY

Seating

AT for seating and positioning for a person after a stroke can vary according to the individual's needs. Several seating challenges can occur following a cerebrovascular accident (CVA). These challenges are secondary to but not limited to two main factors:

1. Poor trunk balance and muscle tone caused by hemiplegia
2. Increased extensor tone more notably evident following a left CVA with right-sided involvement

Several residuals from the stroke can affect the person's ability to complete many daily tasks that he or she was able to perform prior to the stroke. These residuals include impairments of motor skills, cognition, and vision. It is important that the individual requiring the use of a mobility device become more functionally independent with his or her ADL needs while seated in the wheelchair. A key to functional seating involves stabilizing the pelvis. A rule of thumb to remember with seating is that pelvic stability leads to enhanced upper trunk stability.

In fact, stabilizing the pelvis is the first step in improving upper trunk mobility, thus increasing ability to perform ADL skills. There are several seat cushions available in the market, which include solid and contoured bases (Figures 38.1 and 38.2). If pressure management is an issue, seat cushions can be comprised of air, gel, or simply just a soft foam. Knowing your patient's skin integrity is crucial to cushion selection.

A contoured seat base can be utilized for the individual with hemiplegia. The contour of the base will aid in maintaining the pelvis, hips, and lower extremities in neutral alignment. The degree of the contour will depend on the amount of support that the individual needs to maintain the position. An anti-thrust cushion will prevent the individual with extensor tone from sliding forward on the seat (Figure 38.3). The anti-thrust cushion is higher in the front, thus providing a shelf that makes it difficult for the individual to overcome. Placing

FIGURE 38.2 Example of a contour molded cushion with gel-filled inserts.

FIGURE 38.3 Example of anti-thrust cushion.

a seat dump (a structure where, the front of the seat frame is higher than the back) in the frame of the wheelchair can provide the same effect as the cushion.

Thigh guides placed along the lateral aspect of the upper portion of the lower extremity will provide lower-extremity support and alignment (Figure 38.4). The thigh guide will prevent external rotation and abduction of the hip joint.

Adductor pads can be placed lateral to the knee joint to provide support and prevent adduction, thus improving neutral alignment. An abductor pad for lower-extremity alignment will prevent abduction and internal rotation of the hip. The abductor is placed between the knees. This can be an external pad that is removable, or it can be incorporated into the contoured seat base. A solid seat provides a static surface on which the cushion can be placed. This support prevents the cushion from contouring to the surface it is placed upon. A pelvic belt will also assist in maintaining the pelvis in position. The belt can be a standard two-point or a four-point. The point value refers to numbers of attachment to the frame. Four points of attachment provide greater contact, thus controlling and supporting the pelvis.

Lower-extremity alignment and support are critical in maintaining pelvic stability. It is necessary for the individual to achieve full foot contact and placement on the footplates. Without foot support, the individual will slide and shift on the seat. The hanger angle of the wheelchair frame is an important part of achieving foot placement. A range-of-motion assessment will provide information needed to determine the appropriate legrest hanger configuration. When using elevating legrests, the individual should maintain foot contact as well as knee extension throughout the elevation process. Angle-adjustable footplates can be adjusted to assure foot contact in the event of decreased ankle range of motion or ankle instability at neutral posturing.

Stability of the upper trunk can be achieved by utilizing a variety of back supports. Back support can be provided through the use of a solid or flat surface, a contoured (mild, moderate, or deep) surface, or upholstery (Figures 38.5–38.7). The decision on the type of back support to be utilized depends largely upon the individual's trunk balance. A large variety of back supports not mentioned is also available and is more specific for spinal deformities.

FIGURE 38.4 Example of thigh guide placement.

FIGURE 38.5 Flat solid back.

FIGURE 38.6 Moderate contoured back.

A solid back support provides static stability. The solid support allows for greater wheel strikes when propelling, as the upper extremities have full range of movement without contact of an external source. A lateral support can be utilized with the solid back to prevent the individual from leaning sideways when sitting or traveling.

The contoured back support provides lateral stability for the upper trunk. The amount of contour depends on the amount of support the individual requires to remain upright. Adjustable tension back upholstery can provide upper-trunk stability without the need to utilize a back support

FIGURE 38.7 Deep contoured back.

FIGURE 38.8 Example of adjustable tension back upholstery.

(Figure 38.8). This will aid in keeping the overall weight of the wheelchair down for the individual who is a self-propeller.

Lateral trunk supports attached to the side frame of the wheelchair provide stability and support of the upper trunk. The sizes of the supports vary and should be ordered according to the individual's size. Placement of the support is also crucial; it should not be placed directly under the axilla because it may cause nerve impingement.

Support of the affected upper extremity for the individual with hemiplegia is also important. Assortments of arm troughs are available on the market. The arm trough will provide full contact and support of the distal portion of the upper extremity, thus preventing it from falling from the armrest (Figure 38.9). The palmar portion of the arm trough can be provided in a variety of shapes, depending on the individual's hand positioning needs. The arm troughs are attached to the frame of the armrest. Height-adjustable armrests are necessary, as they assure adequate shoulder placement and support. A subluxation is often evident with hemiparesis, so proper height adjustment is needed to assure the shoulder joint is placed properly in the socket. A lap tray can also be utilized for upper-extremity support. The tray can be a full design or half design.

FIGURE 38.9 Example of seating system with arm trough with custom palmer support and lateral trunk supports.

FIGURE 38.10 Example of tilt-in-space seating system.

Other seating features that can be incorporated into the frame of the wheelchair are tilt-in-space and recline. Tilt-in-space can be utilized for the individual who is unable to sit upright against gravity. The tilt-in-space provides a gravity-decreased plane, thus improving sitting (Figure 38.10). Tilt-in-space can also provide pressure relief for the individual who is unable to independently change position and shift the weight for effective pressure relief maneuvers. When utilizing a tilt-in-space seating system, it is recommended to add a headrest for cervical support and stability. Headrests also come in a large variety of shapes and sizes, and selection is based on comfort and functional support.

The reclining-back wheelchair can first be utilized in the event that the individual has systemic issues that may prevent him or her from sitting upright. Overall, the use of a reclining-back wheelchair is typically not beneficial to the individual with hemiplegia. Reclining the back opens the hip angle, thus decreasing the stability of the pelvis.

The lack of control of the pelvis can lead to poor support and alignment of the upper and lower trunk. Tilt-in-space is the preferred alternative to meet an individual's seating and positioning needs.

This section was completed as an attempt to provide a basic insight into the specific seating and positioning needs for persons after CVA. For more in-depth reading on this topic, please refer to the reference list at the end of this chapter.

Mobility

Use of wheelchairs, including both manual and electrically powered, could be a transient or long-term need for individuals after CVA. Therefore, as with any other piece of AT equipment, the wheelchair selection, customization, and delivery process after CVA has to be an individually tailored procedure. Also, utilization of wheelchairs could significantly alter limitations that could result after CVA, which could be based on changes in physical functioning and use of alternative mobility aids, especially during the first year after CVA (2). Periodic assessments before wheelchair prescription are key, and should include physical, sensory, cognitive, perceptual, behavioral, and environmental assessment along with identification of other barriers for use of a wheeled mobility device. Recent literature suggests use of Wheelchair Skills Test (WST) and Wheelchair Collision Test (WCT) as screening measures specifically designed for individuals after CVA for identifying problems related to use of wheeled mobility devices, which could also serve as a guideline for customization of the prescribed device (3,4).

Manual Wheelchairs

For individuals after CVA, manual wheelchair (MWC) propulsion can become very tiresome because of several factors, such as primary use of one upper/lower extremity for propulsion, limited coordination between the available extremities, and problems with visual-perceptual abilities. Despite

FIGURE 38.11 Attendant-propelled with tilt-in-space (Quickie IRIS).

these difficulties, MWCs have been considered a primary aid for independent mobility for this population (5).

Attendant-Propelled

This type of MWC is typically used as a dependent mobility option for individuals who are not able to functionally self-propel any type of MWC because of physical and/or cognitive limitations (Figure 38.11). An attendant-propelled MWC frame usually comes equipped with a tilt/recline combination seating system for gravity-assisted postural support. Also, in the early post-CVA stages, attendant-propelled wheelchairs could be a safer option, as self-propulsion could result in dislocation of joints of extremities with flaccid muscle tone. The previous notion was that self-propulsion in early stages after stroke could result in increased abnormal muscle tone, resulting in further physical disability. However, recent studies have indicated no such detrimental effect of self-propulsion wheeled mobility on physical disability in early post-CVA stages (6).

Manual Self-Propelled

The traditional self-propelled MWC can be classified into five basic categories for medical justification purposes:

- Standard wheelchairs
- Standard hemi (low seat)
- Lightweight
- High-strength lightweight
- Ultralightweight wheelchairs

The hemi wheelchairs have low seat-to-floor height, with provisions for modifications that enable a person after CVA to be able to use a wheelchair with one side of his or her body (upper and/or lower extremity). Self-propelled MWCs can fall in the following three categories.

Pushrim-Activated Propelled

Even though this is the most commonly used interface, it could result in repetitive strain injuries (RSI), which, coupled with preexisting conditions of muscle weakness, reduced physical capacity, pain, and fatigue, could make MWC propulsion significantly inefficient. Pushrim-activated power-assisted wheelchairs (PAPAWs) have recently become an alternative option to MWCs to reduce the risk of RSI and maintain physical conditioning of the users (Figure 38.12). Studies investigating individuals with spinal cord injury reported effectiveness of PAPAWs in improving mechanical efficiency of propulsion by significantly reducing energy expenditure, stroke frequency, upper-extremity range of motion, and power requirement for wheelchair propulsion (7). A PAPAW should be considered as a therapeutic intervention for addressing learned nonuse, as the individual

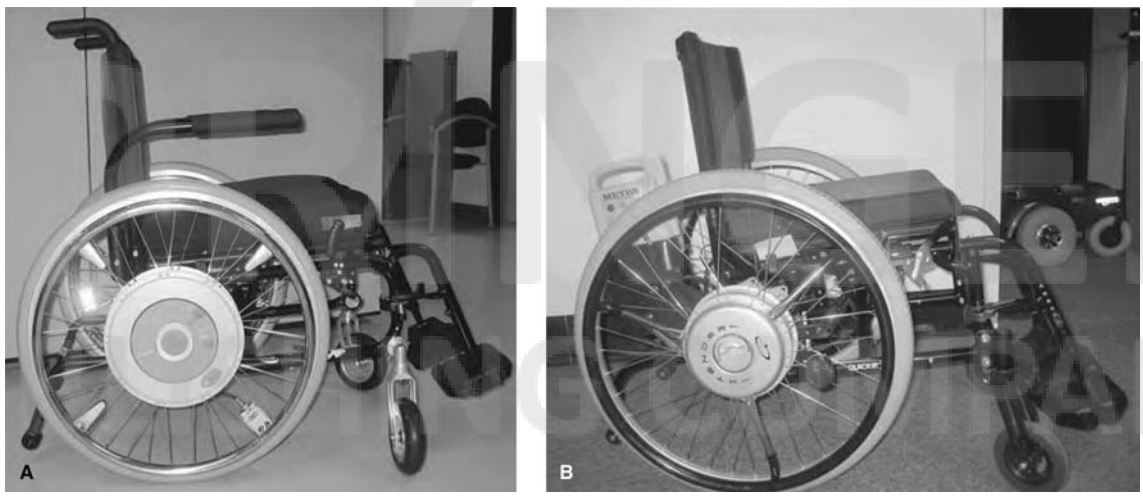

FIGURE 38.12 (A) PAPAW (e.motion); (B) PAPAW (Quickie Xtender).

FIGURE 38.13 Lever drive system.

wheels of the PAPAW system may be programmed separately to enhance and encourage function of the affective side during self-propulsion.

Lever Drive

Lever drive mechanisms, which may be attached to the MWC on either one or both sides, indirectly transfer push or pull forces that are applied to the rod/lever system to the wheels (Figure 38.13). This mechanism facilitates use of the shoulder and elbow muscle group and reduces tiring effects on wrist and hand muscles. Also, this form of propulsion method was reported to be energy efficient, inducing less physical restraint as compared to unilateral/bilateral pushrim use (8).

Foot-Propelled

This form of propulsion method has been reported to be physiologically efficient, resulting in faster speed of propulsion as compared with the traditional mode of propulsion after CVA using one side of the body (hand and foot; 9). However, assessment of the client is a prerequisite before prescribing the system. The assessment must include seat-to-floor height to allow for heel strike and toe pulling, appropriate seat depth to allow for knee flexion, a stable back and seat support, and high friction surfaces for seat and shoe (10).

Power Wheelchairs

One concern, and sometimes a limiting factor for prescription of power wheelchairs (PWCs), after CVA is a visual-perception deficit known as *unilateral neglect* (UN), which can be defined as neglect of one side of the environment during any task performance. UN raises safety concerns for individuals with right-side affected CVA to use power mobility safely and independently (11).

Computer-assisted training was reported to be effective in reducing unsafe driving behavior that may cause incidents and improving ability to complete a real-world wheelchair obstacle course for individuals with UN (12). Similarly, use of a virtual reality (VR) environment is suggested as one of the intervention techniques for improving safety with an application to provide wheeled mobility training for individuals with CVA and UN (13). PWCs can be classified in three major categories according to the Centers for Medicare and Medicaid (CMS) Healthcare Common Procedure Coding System (HCPCS).

Standard Power Wheelchair

Standard PWCs do not have any option for customized programmability and/or customized seating and postural support (Figure 38.14). These low-cost and very basic PWCs are commonly prescribed for individuals diagnosed with CVA for anticipated use in low-active indoor environments. A study conducted by Pearlman et al. (14) revealed that these chairs do not meet the American National Standards Institute (ANSI) and RESNA standard requirements testing, as they are unstable and have limited durability. Caution is advised when prescribing this type of power wheelchair.

Programmable Power Wheelchair

These PWCs provide options for customization of control parameters for speed adjustment, tremor damping, acceleration control, and braking. This type of PWC can be equipped with customized power seat options and is therefore preferred for individuals with CVA (Figure 38.15).

FIGURE 38.14 Example of a standard power wheelchair.

FIGURE 38.15 Example of a programmable power wheelchair.

Lightweight, Portable Power Wheelchair

Lightweight, portable PWCs are base-equipped with basic seating designed for ease of transportation (Figure 38.16). This type of PWC should be considered only for end users with very limited and specific mobility needs.

Customized, Motorized Power Wheelchair

Customized, motorized PWCs are base-equipped along with a provision of other seating options like elevating seat and footrest, tilt and recline, lateral tilt, and standing frame. These PWCs are typically equipped with high-performance motors, the batteries needed to support increased weight capacities, and higher-performance power seating systems. Precise and sound medical justification is needed when prescribing this type of PWC. Typically, this type of PWC is not frequently recommended for an individual diagnosed with CVA who weighs less than 300 pounds and has average body structure.

Justification of an appropriate PWC that can meet all requirements of the end user and is a safe option in terms of durability and ability to withstand repeated use is a complicated process, in spite of previous research indicating higher durability and cost-effectiveness of customizable PWCs as compared to standard PWCs (14). Besides the CMS classification system, PWCs can be divided into three main categories

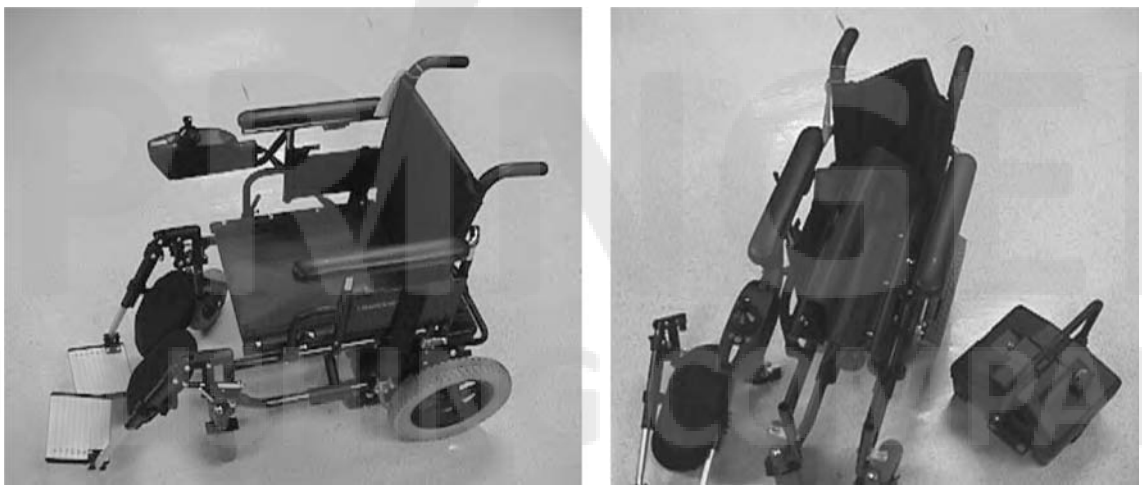

FIGURE 38.16 Example of a portable power wheelchair.

FIGURE 38.17 Three categories based on the presence of drive wheels in relation to seat of user: (A) front-wheel drive (FWD), (B) mid-wheel drive (MWD), and (C) rear-wheel drive (RWD).

based on the presence of drive wheels in relation to the seat of the user (Figure 38.17):

Front-wheel drive (FWD)
Mid-wheel drive (MWD)
Rear-wheel drive (RWD)

For FWD, the drive wheels are located in the front of the seat, and it is effective over uneven ground and rough terrains. The main disadvantage of FWD is the fish-tailing effect, where the PWC tends to sway laterally while going up and down ramps. MWDs are the most efficient PWC for indoor use with availability of limited space because their turning radius is small. However, MWDs sometimes pose problems when traversing uneven ground or rough terrains. RWDs are considered to be the fastest PWC, and they can provide good stability on most surfaces. However, they require a good amount of space for turning and could be unsafe while going up a ramp (15). Decisions regarding types of PWC are based on several factors, especially frequency of usage and environment of use.

ELECTRONIC AIDS FOR DAILY LIVING

Electronic aids for daily living (EADLs) are devices used to access, operate, and control electrical appliances. EADLs can be used in a home, school, or workplace. The primary purpose of an EADL is to enable a person to independently perform daily functions that he or she could not otherwise accomplish. Typical functions that an EADL enables people to perform include alerting caregivers of needs, using the telephone, changing bed positions, managing lights and room temperature, opening and securing doors, operating TV/stereo equipment and operating remote/security video cameras. Other names for EADLs are environmental control systems (ECSs) and environmental control units (ECUs) (16). Examples of EADL devices are shown in Figure 38.18.

Persons who use and benefit most from such devices are those with severe physical limitations that affect mobility and the upper extremities. Individuals with the diagnosis of quadriplegia, muscular atrophy, muscular dystrophy,

Pilot One
Courtesy of AbleNet

Relax II
Courtesy of AbleNet

Possum Primo
Courtesy of AbleNet

GEWA PROG
Courtesy of ZYGO-USA

SAJE Roomate Plus
Courtesy of SAJE Technology

Quartet Simplicity II
Courtesy of Quarter Technology, Inc.

Angel FX
Courtesy of Angle ECU

Pocket Mate
Courtesy of SAJE Technology

Possum Jive!
Courtesy of AbleNet

REACH
Courtesy of Break Boundaries

FIGURE 38.18 Electronic aid for daily living (EADL) device examples.

cerebral palsy, multiple sclerosis, and amyotrophic lateral sclerosis (ALS) are often aided by the use of an EADL. Persons with fewer physical limitations, such as paraplegia, amputations, or a CVA, can also benefit from such devices, but often are not considered candidates for the typical funding sources. In fact, this technology has been limited largely because of funding barriers (7,17,18). However, age appropriateness for vocational potential, skill base, and demonstration of need can increase the funding possibilities.

EADLs are controlled through a switch input, touchscreen, or voice recognition or can be integrated with other controls such as alternate computer access, wheelchair controls, and augmentative communication devices. Using

integrated controls to operate an EADL is helpful and often necessary when a person has a limited number of switch/control sites available.

Continuum of Devices

EADL devices have been categorized in different ways including: (a) inputs received, (b) complexity of the system, and (c) control provided. Often, devices do not fall neatly into these categories, and as new or different products appear on the market, the categorization process becomes less defined. Therefore, EADL devices can be considered as a continuum of inputs, system complexity, and control provided.

Inputs

Inputs are the mechanisms that activate the system. Inputs can include one or more of the following: (a) single switch; (b) dual switch; (c) direct select; (d) voice; (e) indeterminate system; and/or (f) automatic. A single switch either limits the user to one function control, such as turning a light on/off, or requires the system to scan through a menu of choices. When using a single switch to scan through menu choices, the user's speed is limited to the scanning speed set by the device. A dual switch provides more control by allowing the user to regulate the scanning speed before making a selection. Direct select allows the user to select from a menu of choices and reduces or eliminates the need for scanning to the desired item. Voice recognition provides direct control of functions by using predefined voice commands. Intermediate systems include speech generating devices (SGDs), wheelchair controls, and alternate computer access. For example, if a person is using powered mobility, she or he can enter a mode to send a switching signal to the EADL. Alternately, some wheelchair controllers can directly send infrared, Bluetooth, or radio frequencies directly from the wheelchair to the device a user would like to control. Some portions of an EADL system can be controlled automatically, such as turning on lights for a given space by sensing motion, or starting a sump pump when moisture is detected.

Complexity

Complexity of an EADL system incorporates (a) the number and types of inputs/outputs available, (b) the user interface, and (c) the functional depth.

Inputs/Outputs. As discussed, there are a number of possible inputs. An EADL can vary from accepting a single input and providing a single control output to accepting multiple types of inputs and providing multiple control outputs. The control outputs most typically include X-10, Insteon®, radio frequency (RF), infrared (IR), Bluetooth, and direct connection. They are discussed under "control provided."

User Interface. The user interface of an EADL can vary greatly. The device may provide either a static or a dynamic interface and usually provides visual and/or audible feedback. Static interfaces do not change. A common example of a static interface is a TV remote: the labels and buttons remain in the same position. With a TV remote, the feedback provided to the user is the consequence of the button push—that is, the volume is increased or the channel is changed. Often, EADL devices that scan have static labels or icons. When using static labels, a light beside the label may brighten when that option is available. If static icons are used, the icon often lights up when the option is available. Dynamic interfaces, in contrast, present information that varies according to the previously selected item. For example, an EADL device may present the options of using the phone, operating the TV, or controlling lights. In this example, once the user selects the phone option, the interface choices provided will change from phone, TV, and light to specific phone functions such as answer, hang-up, or dial. Dynamic interfaces can provide more information and be less confusing; they are generally found on more complex devices.

Visual feedback can be a blinking light, highlighted or colored text/picture, or changing text/picture. With some systems, the entire display can change to indicate the context, such as showing a phone or room layout with the items that can be controlled. Likewise, audible feedback can range from a simple beep to unique sounds to voice prompts and confirmations. Some devices even provide instructional assistance.

Functional Depth. The functional depth of a device is related to its sophistication. The functional depth is noted in areas such as the level of functionality provided, the ease of setup, the amount of programming available to the user, the ability for the user to switch input methods, macro abilities, and wireless capabilities. For example, two devices may be able to operate a phone. However, one may have to use an IR-controlled phone whereas the other may be able to operate a standard landline phone. The EADL that uses the IR phone will require the person to be directly in front of the phone (line of sight) and may require him or her to use the phone on speaker. Furthermore, the options for using the phone may be limited to answer, hang up, and dial from a pool of preprogrammed speed dials. Alternatively, a more sophisticated EADL may allow the user to control the phone from another room, enjoy a private conversation, allow preprogrammed speed dials such as "Mom," "bank," "Jim," and so on; these systems may also enable the user to spontaneously dial numbers and input phone cards, bank numbers, and so on. Some even provide an automated answering function.

Another example of functional depth can be seen in X-10 control. X-10 is discussed in the "Control provided" section. X-10 can provide on/off control of 16 devices on 16 different house codes for a total of 256 control signals. Some EADLs can only be set by the user to use one house code at a time. This limits the control signals to 16. Therefore, because one X-10 signal is used to turn a device on, and another to turn it off, only eight devices can functionally be controlled. Some very basic EADLs can only control a few X-10 devices.

A more sophisticated device can take advantage of all 16 house codes, allowing 16 signals per code.

In terms of IR control, basic EADL devices may allow the user to control a limited number of functions such as TV on/off, volume up/down, and channel up/down. An EADL that has more functional depth will provide the user with many more functions that are often provided by a standard IR remote.

Control Provided

Common types of electrical appliances controlled by EADL are telephones, lights, door openers, door locks, fans, drapes, blinds, beds, audiovisual equipment, home climate controls, call systems, and security cameras (19). The control provided by the EADL is related to the possible outputs previously listed: X-10, Insteon®, RF, IR, Bluetooth, and direct connection.

X-10 is a RF signal that is carried over the existing home wiring to turn devices on/off. X-10 is inexpensive, has been available for many years, and requires no special wiring. Insteon® (www.insteon.net) is similar to X-10, but in addition to placing the signal on the home wiring, it also produces an RF signal that travels through the air. This provides redundancy in the signal and is therefore a more reliable way to control a device. RF allows control in all directions and through walls. However, it is susceptible to interference from other RF devices. IR is able to control a wide array of functions, and an EADL device can often "learn" the IR codes, thus making them easy to program. The main limitation of IR is that it must be in line of sight of the device that is being controlled. Bluetooth is a wireless means of transmitting a signal, but the maximum range is limited to about 30 feet. Directly connecting a device to an EADL ensures that the signal will reach its target; this is often used with bed controls, telephones, or specialized equipment.

EADL Evaluation Considerations

When considering an EADL for someone, many personal factors must be considered (Figure 38.19). Personal factors include accessibility needs, preferences, cognitive and physical abilities, comfort with using technology, desire to use technology, degenerative conditions, voice quality, and voice changes. Factors to address when considering equipment include the places where the device will be used, the layout and size of each area, the devices to be controlled, the electrical condition of the controlled environment, mounting to bed/chair, switch type, required integration with existing AT equipment, and particular EADL limitations and benefits. Funding factors include cost and the goals/requirements of the funding agency.

Costs

The basic cost of full EADL systems can range from $700 to $6000. A completely installed system with door openers and other options can cost $2000 to $15,000. Typically, the only funding available for EADL systems comes from vocational

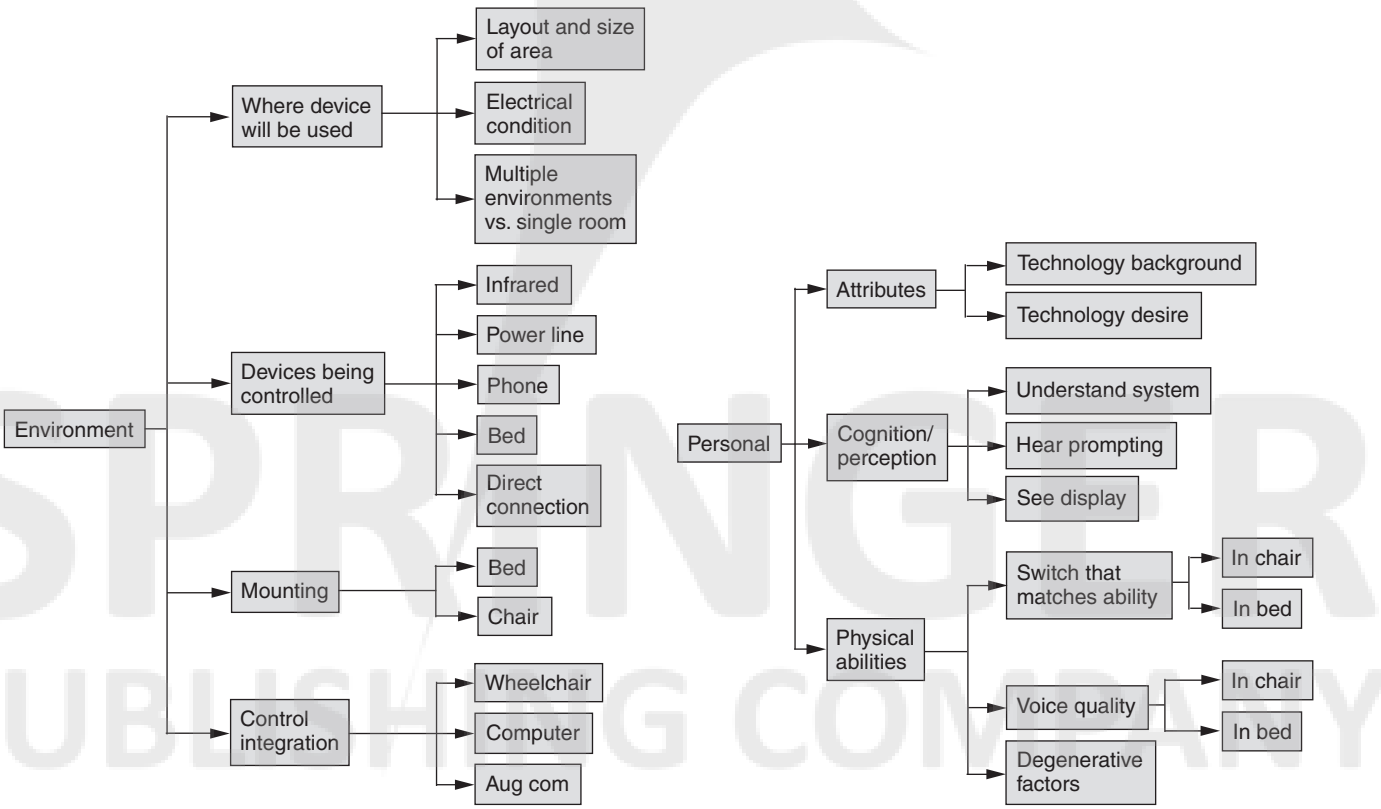

FIGURE 38.19 EADL evaluation considerations.

rehabilitation agencies, the Veterans Administration, worker's compensation, civil and nonprofit organizations, and philanthropists. Medical insurance does not cover EADLs.

Lower-Cost Alternatives

Persons diagnosed with a CVA often have function on one side of the body. Such persons may find it helpful to consider lower-end home automation options. Specifically, a large-button, universal remote can assist by decreasing needed hand dexterity and making it easier to see the buttons. A remote control that combines IR features with X-10 capabilities can lessen the need to get up to turn on lights or open or lock doors, and provides a means to signal assistance from someone in another room. Switch-activated telephones and cell phones are also available. These devices can give a person more security and independence. For persons whose speech is significantly affected, switch-activated telephones that call and play a prerecorded message can be considered.

AUGMENTATIVE AND ALTERNATIVE COMMUNICATION

The process of achieving communication success for individuals who have had a stroke and could benefit from AAC may be perceived as an insurmountable challenge by their families and those providing clinical services. Yet, the goal of AAC intervention is to optimize the communication of individuals with significant communication disorders (18). AAC AT provides a viable rehabilitation solution to assist individuals who cannot speak to regain various degrees of function and improve communication performance and outcomes.

Individuals recovering from stroke who are candidates for AAC may have a motor speech disorder, language impairment, or a combination of both speech and cognitive–linguistic considerations that affect body structure and function, daily activities, and full participation in life experiences (20). These considerations, as identified using the World Health Organization's (WHO) International Classification of Functioning, Disability and Health (ICF), present issues that influence the selection and intervention of AAC AT (21). In addition, candidates for AAC will have immediate short-term needs for technology as well as possible long-term use beyond rehabilitation. Regardless of the duration of use for an individual, the AAC AT must be considered based on how language is represented and generated using the system before specific technologies or devices are considered. These primary language considerations include whether the AAC system provides for spontaneous novel utterance generation (SNUG), prestored messages, or both, and how core and extended vocabulary is stored and accessed on the system (22). Several AAC systems may be considered, trialed, and recommended over the course of rehabilitation and a lifetime. How the systems handle these language considerations and transitions and maintain consistency when change occurs is important to achieving long-term effective communication performance and desired outcomes.

Graphic symbols are used on AAC AT to construct messages. AAC language representation methods (LRMs) refer to the ways that symbols are used to generate communication. The three commonly used LRMs in AAC have been identified and described as alphabet-based methods, single-meaning pictures, and multiple-meaning symbols (23). Understanding the characteristics of each method is important when taking into consideration the specific characteristics and degree of a possible cognitive–linguistic impairment. In addition, people with aphasia may have impaired resource capacity and resource allocation abilities that will influence their use of AAC interventions (24). Therefore, language considerations (cognitive–linguistic functioning) should take priority in selecting AAC AT to match technology features to how language is best represented for an individual. Many AAC systems provide multiple methods to access vocabulary and generate messages. Research has shown that the communication performance for the different methods varies significantly (25). Consequently, selecting the LRMs based on the client's communication abilities, needs, and potential for improvement is critical for achieving the best possible performance.

A thorough appreciation of AAC LRMs is needed to evaluate how LRMs may be accessed using the range of aided AAC technology and types of AAC display technology recommended for individuals with acquired communication disabilities. High-performance technology solutions can then be identified as nondedicated or dedicated AAC systems. Nondedicated systems include computers, iPADs, tablets, PDAs, and other mass-market hardware with software applications designed to support communication. For example, Lingraphica® is software run on a laptop computer that is designed specifically for persons with aphasia (Figure 38.20). The voice output used with computers is

FIGURE 38.20 A laptop computer designed specifically for persons with aphasia.

TABLE 38.1 Components of Dedicated AAC Technology (Hill©)

LANGUAGE REQUIREMENTS	CONTROL INTERFACE (HARDWARE)	HARDWARE COMPONENTS	SELECTION METHODS	ACCESSORIES	ADDITIONAL CONSIDERATIONS
Alphabet-based methods Single-meaning pictures Semantic compaction Multiple methods	**Touchscreen** Visual scenes Page or activity-based displays Core/activity row display **Static display** Keyboard Pictorial overlay **Hybrid system** Static keyboard and touchscreen	**Speech outputs** Digitized Synthesized Combination **Auditory outputs** **Visual outputs** **Electronic outputs** **Data logging** **Memory capacity**	**Direct selection** Keyboard Headpointing Eye gaze Neuro-controls **Scanning** 1-switch 2-switch Joystick Neuro-controls **Morse Code**	Mounting systems Carrying case Peripherals (switches, headsticks, and joystick)	Technical support Training Repair services Warranties Portability and weight

synthesized speech (text-to-speech), and a variety of male, female voices and accents/languages are available. Dedicated systems are designed specifically for the purpose of communication and can be classified into low, light, and high-performance technology. The range of aided technology increases as availability of power, voice output, electronics, and computer components become part of the system. Table 38.1 shows the complex nature of decision making for selecting AAC technology once a comprehensive assessment of speech, language, communication, vision, hearing, physical abilities, and client preferences, values, and expectations has been conducted by the speech–language pathologist and AAC/AT team (26).

The display technology used to generate messages can be a static keyboard or touchscreen that comes in various sizes and thus influences the number of possible selections on the display. The display configuration supports any of the chosen LRMs or multiple LRMs. The appearance of the display can vary in the number, arrangement, shape, color, size, and organization of the keys. The applications used with individuals with acquired communication disorders include visual scenes, various grid organizational patterns, and a core and activity row pattern. Single-meaning picture or multimeaning icons may be used on visual scenes and grids or page-based displays, whereas alphabet-based methods are configured on a grid display. The core and activity row pattern is used exclusively with Semantic Compaction™ for one-hit access as a single-meaning picture method or with sequencing (27). Most AAC manufacturers provide a range of devices that offer one or more display configurations on a system. For example, visual scenes may be used for one communication activity, such as retelling a story, whereas a core/activity row would be used for another level of participation, such as requesting, commenting, or questioning (28). A careful exploration of the features and components of systems is critical to understanding how the technology may support language/communication functioning and intervention goals.

An important aspect of successful AAC intervention is the considerable training and practice required to regain skills and/or become a more efficient and effective communicator (29) after a stroke causes a severe communication disorder. Today's technology includes tools and features to monitor performance and outcomes for AAC intervention. Many AAC systems have built-in language activity monitoring (LAM) to collect data on the use of an AAC system (30). Any AAC system under consideration can be compared with other possible options for making the most informed choice. LAM data can be analyzed using the Performance Report Tool (PeRT) to generate a report of quantitative summary measures of communication (31). Clinical data on the number of symbols and/or words used, frequency of methods used to generate utterances, and frequency of vocabulary use provide insights for intervention. Outcome measures based on the type of activity and participation, along with preferred use, that indicate strong user satisfaction with AAC intervention have been reported (32).

Because communication is so important to the life experience of people who use AAC and have had strokes, significant clinical effort should be focused to optimize performance. Identifying the tertiary components of AAC AT services that are important to a person with a disability can maximize the potential use of an AAC system (Table 38.1). AAC systems can be mounted on wheelchairs or positioned for access anywhere in the home or office. AAC AT can function as a keyboard emulator to provide access to computers and enhance access to email and the Internet. AAC systems with IR technology can support environment controls and enhance independence. LAM tools can support telerehabilitation services for persons recovering in remote areas and with other transportation and health issues (33). Internet resources and support organizations specific to AAC, such as the AAC Institute (www.aacinstitute.org), provide the most current information to practitioners, family members, and consumers to support the complex questions about AAC AT.

ADAPTIVE DRIVING

One of the many important goals in the rehabilitation recovery process after a stroke is the ability to return to independent living in one's community. Community mobility, specifically driving, can contribute to a person's quality of life. Transportation into the community allows access to activities outside the confinement of one's home. Individuals who are no longer able to drive are more likely to report worsening depressive symptoms (34). Many stroke survivors express an interest in returning to driving during their rehabilitation process. It has been reported that 30% of stroke survivors who drove prior to their stroke are said to resume driving after their stroke (35).

Stroke can cause physical-motor, cognitive, visual, and psychological impairments that can impact a person's driving performance. A Certified Driving Rehabilitation Specialist (CDRS) can provide a comprehensive driving evaluation to assess the extent of the neurologic impairments and determine the ability of a person to operate a vehicle safely after a stroke (36). A typical comprehensive driving evaluation consists of a clinical assessment and on-road assessment. The clinical assessment evaluates the basic skills necessary for driving, such as vision, perception, cognition, physical functioning, and knowledge of driving. This aspect of the process can help to identify strengths or deficit areas related to driving. Actual driving skills then can be assessed in a vehicle with consideration of information gathered from the clinical assessment. The vehicle can be modified with adaptive equipment that the person may need to use for improved independent operation of the vehicle.

After completion of the driving evaluation, education and training may be indicated with or without the use of adaptive equipment. Adaptive equipment can be recommended by a CDRS to compensate for the loss of functional skills after a stroke. Adaptive equipment for the individual's vehicle is prescribed after completion of a comprehensive driving evaluation and training program and only after it is determined that the person will be able to develop competency to drive with the prescribed equipment.

A steering device, such as a spinner knob, can be attached to the steering wheel to allow a person to steer with one hand (Figure 38.21). A left-sided accelerator can be used if a person is unable to use his or her right foot to operate the gas or brake pedal (Figure 38.22). A turn signal crossover (Figure 38.23) shows the relocation of the turn signal indicator from the left side of the steering wheel to the right side. This allows a person without the use of his or her left hand to access the turn sig-

FIGURE 38.21 Spinner knob attached to the steering wheel.

Courtesy of Howell Ventures Ltd.

FIGURE 38.22 Left foot accelerator with gas pedal guard.

Courtesy of Howell Ventures Ltd.

nal using only his or her right hand. Other secondary vehicle controls, such as windshield wipers, lights, and horn, can be relocated onto the steering wheel next to the steering device or at any other location within the vehicle. This can be done so that the driver is able to access all vehicle controls quickly and accurately with his or her dominant hand. If sitting balance is impaired and the person tends to lose his or her balance as the vehicle goes around a curve in the road, a chest harness may be indicated. This affords additional trunk control beyond what a seat belt provides, but it does not replace the use of the seat belt. A strap or other modifications can be used for seat belt retrieval if the person is unable to grasp or reach his or her seat belt. A parking brake extension can be attached to a floor-mounted parking or emergency brake pedal (Figure 38.24). Using this type of device, the person without the use of his or her left foot then can apply the parking brake using his or her hand. Partial loss of visual fields or the presence of scotomas can sometimes be compensated for by the use of specially placed mirrors. As with all adaptive equipment, specialized education and training are required to assure correct placement and proper use of the additional mirrors (37).

FIGURE 38.23 Right side turn signal.

Courtesy of Mobility Products and Design.

FIGURE 38.24 Parking brake extension.

Courtesy of Mobility Products and Design.

The ability to drive depends on a set of visual, perceptual, cognitive, and psychological skills. Impairment in any or all of these areas will affect the individual's driving performance. These deficit areas can be more challenging and difficult to compensate for, as compared to the physical impairment areas, especially when driving a vehicle in an ever-changing dynamic environment.

Common driving behaviors that may be observed in an individual after a stroke and would require additional training and education for remedial purposes include (38):

- Difficulty in maintaining a centered lane position or drifting across the lane lines into other lanes
- Poor speed modulation (driving either too fast or too slow)
- Poor judgment of distances (positioning too close to other vehicles)
- Delayed response or reaction time
- Poor decision-making skills
- Difficulty in completing lane changes, merges, and blending with traffic
- Poor anticipation of other drivers or pedestrians
- Missing of traffic signs and signals
- Near misses, close calls, and frequent blowing of horns by other drivers directed at the driver

Unfortunately, not all functional deficits caused by a stroke can be easily compensated for by means of adaptive equipment or dedicated training. Severe cognitive impairments, uncontrolled spasticity, and significant visual field loss (e.g., visual homonymous hemianopsia or unilateral visual attention deficits) are examples of problems that may permanently prevent a person from driving a vehicle after a stroke. When it is determined that an individual is no longer

FIGURE 38.25 Turning automotive seat and wheelchair lift.

Courtesy of Bruno Independent Living Aids, Inc.

able to drive, suggestions and materials should be provided for alternative means of transportation. The individual's family and friends are encouraged to support the no-driving recommendation and assist the stroke survivor with ongoing access to the community (36).

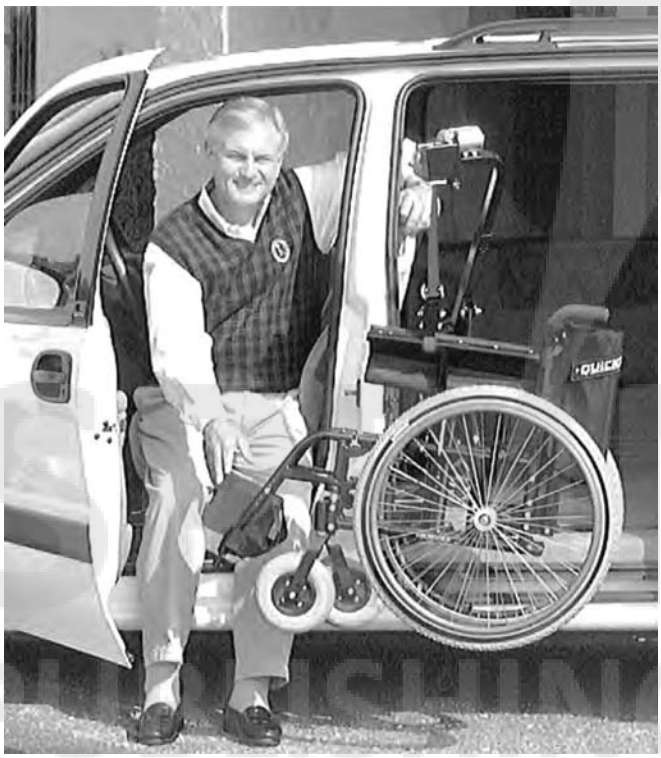

FIGURE 38.26 Wheelchair lift-side door application.

Courtesy of Bruno Independent Living Aids, Inc.

A variety of adaptive equipment and vehicle modifications can be used for vehicle ingress and egress. Persons with impaired hand function can use automatic car door openers (also known as keyless entry), built-up key holders, or key turners. Power-based seats can be installed in the car seat to allow a driver or passenger to transfer from a wheelchair to the vehicle seat. These power-based seats have options that allow the car seat to swivel out, glide out of the vehicle, and then lower to a desired level for ease in transfers. Wheelchair lifts (Figures 38.25 and 38.26) are available to load and unload mobility equipment, such as MWCs, PWCs, or scooters, into the vehicle without significant vehicle modifications. A car topper is another type of lift that attaches to the top of a sedan-type vehicle and can lift and store a MWC. Wheelchair or scooter users may require a vehicle ramp or lift to either get into their vehicle or lift their mobility device into the vehicle. These major vehicle modifications are typically prescribed by a CDRS and installed by a mobility equipment dealer. It is critical that, prior to prescribing and installing the adaptive equipment in the vehicle, compatibility between the individual, mechanical device, and vehicle is assured. Obviously, this must be done before the vehicle is modified.

WHEELCHAIR TRANSPORTATION SAFETY

Individuals recovering from a stroke may travel in a motor vehicle to seek medical care and continue to participate in family and community activities. It is safest to ride seated in a vehicle seat using the vehicle's seat belt system that complies with federal safety standards. However, an individual relying on a wheelchair for mobility may not be able to safely transfer to a vehicle seat. If transferring is not feasible, the

person must ride while seated in the wheelchair. When this occurs, it is very important to ensure the safety of the wheelchair-seated occupant by using after-market safety systems that meet voluntary standards (39).

To ensure the safety of the wheelchair-seated occupant during vehicle transportation, the entire wheelchair transportation safety system must be considered. This system includes three main components: the wheelchair, the wheelchair securement, and the occupant restraint. This section address selecting crashworthy wheelchairs and wheelchair securement equipment, securing the wheelchair, and properly restraining the occupant.

The Wheelchair

It is best to have a wheelchair that has been designed and tested for use as a seat in a motor vehicle. This means that the wheelchair has been designed to withstand forces generated in a crash, provides the occupant with effective support during impact loading so that the occupant's restraint belts remain properly positioned, considers access and fit of the vehicle occupant restraints, and provides attachment points to secure the wheelchair to the vehicle. Such wheelchairs comply with voluntary standard ANSI/RESNA WC19 or ISO 7176-19 and are referred to as WC19, transit, or transit option wheelchairs (40,41). These wheelchairs have four, crash-tested, and clearly labeled securement points for attachment of tie-down/securement straps or hooks (Figure 38.27). If a WC19 wheelchair is not an option, a wheelchair with an accessible frame to allow securement straps to be attached to nonremovable frame junctions is the next best choice. It is best to keep the wheelchair back at an angle of no more than 30 degrees to the vertical. Hard wheelchair trays should be removed and secured elsewhere during travel. Medical and other equipment should be secured to the wheelchair or vehicle to prevent it from breaking free and causing injury in an accident.

Wheelchair Securement

The wheelchair must not add to the forces on an occupant during emergency maneuvers or an accident. Therefore, the wheelchair must be secured using a means independent of restraining the occupant. For example, the same strap should not be used to restrain the occupant and secure the wheelchair. The securement system must be designed to attach to the wheelchair frame, prevent excessive movement or tipping during driving events, and withstand crash forces.

The wheelchair should be positioned facing forward in the vehicle and secured using a system that has been crash-tested and complies with the voluntary standard ANSI/RESNA WC18 or ISO 10542 (42,43). The system should be installed according to the manufacturer's instructions by a reputable vehicle modifier. The most common type of securement is the four-point tie-down system (Figure 38.28) (44). This system consists of four tie-down straps that anchor to the vehicle floor and four points on the wheelchair (two front and two rear). The end fittings that attach to the wheelchair can be hooks or loops that wrap around the wheelchair frame or designated securement attachment points. Although this system can be used with a wide variety of

FIGURE 38.27 WC19-compliant wheelchair securement point with required label.

FIGURE 38.28 Example of a four-point tie-down system used to secure a wheelchair.

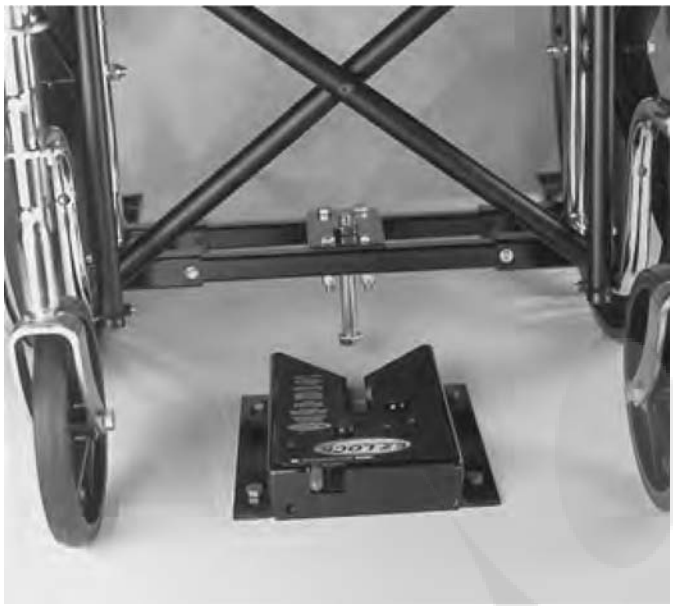

FIGURE 38.29 Example of a docking-type wheelchair securement system.

Courtesy of EZ Lock Incorporated.

wheelchairs and does not require additional hardware to be placed on the wheelchair, it does require an attendant or caregiver to secure and release the wheelchair.

If the wheelchair is not a WC19 wheelchair with four designated securement points to attach the four tie-down straps, the straps should be attached to the welded junctions of the wheelchair frame. The attachment points should be as close to the seat surface as possible to improve the stability of the wheelchair and result in rear tie-down strap angles preferably between 30 and 45 degrees to the horizontal. Tie-down straps should not be attached to removable or adjustable components of the wheelchair, such as armrests, footrests, or wheels. The four straps should be tightened to remove any slack.

Wheelchairs can also be secured using automatic docking systems. This type of securement utilizes a wheelchair adaptor (i.e., special hardware mounted on the wheelchair), which engages with a docking station or receptacle mounted to the vehicle floor or sidewall. The advantages of wheelchair docking technology have been demonstrated by proprietary systems that have been used for independent securement of wheelchairs in private vehicles for many years (Figure 38.29). These systems offer increased independence for the wheelchair user and reduced attendant intervention (38). They also remove the need for human judgment, resulting in more consistent and proper use of the systems. However, they require that a unique proprietary adaptor be retrofitted to the wheelchair; this may add unwanted weight, affect ground clearance if mounted underneath, or add to the overall length if mounted in the rear. Docking systems also tend to cost more to purchase and maintain than the traditional four-point tie-down system. Docking systems should also have been crash-tested to meet voluntary safety standards and should have been successfully crash-tested with the specific wheelchair model being used.

Occupant Restraint

In addition to wheelchair securement, a crash-tested occupant restraint system is necessary to prevent occupant ejection from the vehicle or contact with the interior structure of the vehicle. Postural supports are not designed to withstand crash forces and are often not positioned correctly for effective restraint in a crash. Both pelvic and shoulder restraints are needed to safely limit the excursion of the head, chest, and pelvis (39,43). The pelvic belt should be placed across the front of the pelvis near the upper thighs, not over the abdomen, at an angle between 45 and 75 degrees to the horizontal when viewed from the side. To allow proper placement on the pelvis, the pelvic belt should not be routed around armrests. This can often be avoided by inserting the lap belt under the armrest or between the armrest and the seatback. The shoulder belt should cross the middle of the shoulder and the center of the chest and connect to the lap belt near the hip. The shoulder belt should be anchored to the vehicle above and behind the occupant's shoulder to allow proper contact with the shoulder and chest. A WC19-compliant wheelchair has the option of a crash-tested pelvic belt that is anchored to the wheelchair, increasing the ease of achieving proper fit. This crash-tested pelvic belt will have labeling to indicate that it complies with ANSI/RESNA WC19. A vehicle-mounted shoulder belt should be attached to the pelvic belt to provide complete protection. A headrest positioned directly behind and in close proximity to the head can help protect the head and neck in rear impact. Space around the wheelchair rider should be as clear as possible to reduce the chance of injury from contact with items in the vehicle's interior during travel or a crash.

RESEARCH FRONTIERS—FUTURE TECHNOLOGIES

People with reduced functional capabilities who are aging into or with disability have become a large and growing segment of the world population. Recent advancements in technology such as computation, robotics, machine learning, communication, and miniaturization of sensors bring us closer to a futuristic vision of compassionate intelligent devices and technology-embedded environments. Even though many intelligent systems have been developed, most of them are for manufacturing, military, space exploration, and entertainment. Their use for improving health-related quality of life has been treated as a specialized and minor area. AT, for example, has fallen into the cracks between medical and intelligent-system technologies. The missing element is a basic understanding of how to relate human functions (physiological, physical, and cognitive) to the design of intelligent devices and systems that aid and interact with people.

A dilemma faced by clinicians is reconciling the fact that observations of patients only occur during (infrequent) face-to-face meetings in a clinic or laboratory, whereas what is really needed are assessments that reflect the patient's

capabilities in the real world, where distractions are present and multitasking performance is often required. As such, there is a need for ecologically valid tests that can provide information about a patient's ability to function in a real-life environment. One way to obtain ecologically valid measures is through the use of ubiquitous computing.

People with cognitive impairments often have difficulty with executive functions and prospective memory, including such tasks as organizing a schedule, initiating activities, and remembering to perform the appropriate task at the correct time. External cueing systems can assist people with cognitive disabilities by reminding them to perform a task at the appropriate time or providing guidance through a task. Such systems can range from low-tech paper-and-pencil solutions to mainstream voice recorders and PDAs, to specialized software designed for people with cognitive impairments. Despite attempts at using simple reminders (timers, pressure monitors, and PDA reminders/surveys), user's guides (handouts and note cards), and consumer booklets developed to promote clinical practice guidelines, users do not seem to follow clinicians' instructions. Novel approaches are emerging that use machine learning and artificial intelligence for real-time coaching of the person with disabilities, both for long-term monitoring of the person's use of the equipment and for providing hard information for clinicians to use to augment their education of people with disabilities. This research is patient-centered and is likely to allow clinicians and people with disabilities to take more proactive roles in the ways technology can enhance their lives, for example, by avoiding detrimental health effects of prolonged seated postures.

One problem with current technology is that effectively combining manipulation and mobility assistance with perception and decision making wherever a person goes is quite difficult. When end users were consulted, they reported they wanted a zero gap in mobility and manipulation between them and an unimpaired person. A primary challenge is to overcome the shortcomings and unmet needs with a device that provides coordinated mobility and manipulation. Some of the new functionalities required are to detect and/or predict user intent, provide coordinated movement between a power base and multiple manipulators, include natural and intuitive user interfaces and control modes, and incorporate real-world navigation and docking assistance. To make interaction easier, a wide range of natural and intuitive interfaces that reduce the time to complete tasks and produce fluid, human-like motions are needed.

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VII

STROKE CARE SYSTEMS AND OUTCOMES

39

Stroke-Specific Functional Assessment Instruments

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The manifestations of stroke are heterogeneous and depend on many factors, including the size of the lesion, the affected brain region, and the patient's premorbid status. Although no two stroke patients are exactly the same, the ultimate goal of treatment for stroke survivors is to diminish sequelae of the disease and help patients return to community life. Functional assessments evaluate a patient's abilities beyond the primary affected cerebral functions related to movement, cognition, and language.

As evidence-based practice and initiatives to improve the quality of health care have grown worldwide, recognition of the need to measure functional status in all health care settings has also increased (1). There are many instruments that have been used in clinical practice and research to assess functional outcomes in patients who have suffered a stroke (2,3). Some are designed for general use (usually called generic instruments), and others are designed for use specifically in patients with a stroke (called condition-specific functional instruments). The most commonly used generic instruments in stroke are the functional independence measure (FIM) and the Barthel index (BI) to assess basic daily activities, and the Short Form-36 (SF-36) to assess health-related quality of life. The use of these generic measures in stroke has been extensively reviewed elsewhere (4–7). The focus in this chapter is on reviewing condition-specific instruments that have been designed for use with patients who have suffered a stroke.

Functional status instruments vary widely in the scope of functional content included in the instrument. Some focus on the assessment of specific body movements or discrete functional tasks, even as others assess a patient's ability to accomplish self-care activities. Another group of measures addresses more broadly defined concepts of quality of life. The selection of an appropriate functional assessment measure is a complex process, and many factors must be considered, including the scope of the instrument, the purpose for which it was developed, the administration and scaling methods used, and the psychometric properties, as well as its feasibility in a particular context.

The aim of this chapter, therefore, is to provide readers with a conceptual framework for reviewing functional assessment instruments, introduce the range of condition-specific functional status instruments that are available to use with patients who have suffered a stroke, review some of the key criteria to guide selection among the variety of available instruments that might best meet a user's specific needs, and highlight some newer methodological techniques available to improve the assessment of function with patients who have experienced a stroke.

WHAT IS FUNCTIONAL ASSESSMENT?

Before selecting a functional assessment measure, it is necessary to have a clear understanding and definition of the concept being assessed and the range of functional content to be considered for a particular application. Currently, there is no clear and commonly accepted definition of functional status or a clear delineation between instruments that assess function and those that assess other health concepts. As work to define and quantify health concepts has evolved, many different types of instruments designed to assess overlapping health and functional concepts have been developed. These include instruments that purport to assess disability, function, activities of daily living, activity performance, advanced activities, physical performance, health, health status, quality of life, and health-related quality of life. In the past, there was no consensus on how these terms should be used or measured (8).

The World Health Organization's (WHO) International Classification of Functioning, Disability, and Health (ICF) tried to address this concern by providing the field with a useful conceptual framework for considering the definition and scope of functional assessment in stroke rehabilitation (9). In 2001, the WHO released the ICF to provide researchers and clinicians with a biopsychosocial view of health states from a biological, personal, and social perspective. Over the past decade, the application of the ICF has grown in the field of stroke rehabilitation because the model provides a universal language to facilitate communication and a comprehensive structure to cover the rehabilitation care of stroke (10–12). The ICF organizes concepts in two parts. The first deals with function and disability, and the second deals with contextual factors. The function and disability domains of the ICF, expressed in either neutral or negative

terms, are described from the perspective of body systems, the individual, and society. *Body functions and structures* are defined as physiological functions of body systems or anatomical elements such as organs, limbs, and their components. Hemiparesis is an example of a common impairment in a body function following the onset of a stroke. *Activity*, in contrast, is defined as the execution of specific tasks or actions by an individual. An example of the activity concept is a person's ability to walk independently or transfer from bed to chair. Finally, *participation* is described as encompassing one's involvement in life situations, such as the ability to return to one's former occupation following a stroke. The ICF organizes the areas of activity and participation into several domains that include the following:

- Learning and applying knowledge
- General tasks and demands
- Communication
- Mobility
- Self-care
- Domestic life
- Interpersonal interactions and relationships
- Major life areas
- Community, social, and civic life

Health-related quality of life includes aspects of all three ICF dimensions, but it is a distinct concept that usually includes domains that assess social functioning, emotional well-being, and life satisfaction, as well as physical functioning. We focus on stroke-specific measures of activity, participation, or health-related quality of life in this chapter.

The two contextual elements of the ICF are *environmental factors* and *personal factors*. Environmental factors are all aspects of the external or extrinsic world that form the physical, social, and attitudinal circumstances in which people live and conduct their lives. Personal factors include gender, race, age, lifestyle, habits, social background, and other individual characteristics or experiences that are not classified elsewhere in the ICF. Even though these contextual factors may act as facilitators or barriers as they affect functioning and disability, they are not directly included within a functional assessment instrument.

Purpose of Functional Assessment

A patient's functional status can be assessed for several different purposes that have bearing on the criteria that should be considered when choosing an assessment instrument. For this chapter, we focus on two distinct purposes to which functional assessment instruments are typically applied. The first can be characterized as discrimination. Discriminative functional instruments are designed to differentiate among patients at a point in time. At the level of a group of patients, a discriminative functional assessment can be done for the purpose of describing a patient population or for selection purposes in recruiting patients for a study; at an individual patient level, discriminative assessment can be done to set patient treatment goals or to gauge a patient's prognostic potential. Alternatively, a functional assessment can be used for evaluative purposes. In this situation, the assessment instrument has to be adequate to measure meaningful change in function over time. At the group level, this type of index can be used to evaluate hypotheses pertaining to the impact of therapeutic interventions on function when applied in clinical studies. At the individual patient level, evaluative instruments can be used to monitor change in a patient's functional status or to modify treatment approach during an episode of care.

Key Psychometric Properties

In addition to considering the scope of the functional content needed in a functional assessment, a user should consider the psychometric quality of the functional assessment instrument for the purpose to which it will be put, be it discrimination or evaluation. For discriminative instruments, standards of validity and reliability must be achieved. For the purpose of evaluation, the additional criterion of responsiveness must also be considered.

Validity

Validity concerns the degree to which the functional assessment instrument actually measures what it is intended to measure. There are several approaches to examining an instrument's validity. If the score represents the specific theoretical domain or universe of content, the assessment has content validity. For example, a questionnaire on quality of life should contain items that are related to the concept of quality of life but not gait control. If the score is in accordance with an established functional measurement administrated at the same time, the assessment has concurrent validity. For example, a new self-care measure should be highly correlated to the BI, an established measure of this concept. If the functional score can predict a future criterion score, the assessment has predictive validity. For example, results of a patient's functional assessment at hospital admission may predict functional outcome at discharge.

Reliability

Reliability of an assessment is the extent to which repeated measurements yield the same outcome. The concepts of validity and reliability are related. An instrument with poor reliability will have diminished validity as well because it gives different outcomes at each measurement. However, it is possible that a highly reliable instrument still cannot measure the intended concept well and thus have poor validity.

Reliability assessment can include how consistent the result of an instrument is if readministered over time by the same person (test–retest) and/or if administered by different people (inter-rater reliability). Similar results should be obtained regardless of who administers the assessment. For example, scores should be nearly the same when the assessment is administered by a therapist or a nurse. Internal

consistency reliability reflects how consistent items are under the same category in an assessment. For example, items that measure self-care activities should have a higher correlation with each other than with items that measure instrumental activities of daily living (IADLs).

Responsiveness

Choosing a functional assessment with suitable responsiveness is a crucial criterion if the intended application is evaluative. A functional assessment with good responsiveness is sensitive to clinically meaningful change over time within a patient and the change is responsive to intervention effects (13). Good reliability and validity do not guarantee that an assessment also has good responsiveness. Responsiveness can be seen as a form of longitudinal validity, meaning that a functional instrument should be able to detect changes in function in patients whose function actually changes and no or small changes in persons whose function remains stable over time (13).

Additional Factors to Consider

Validation in Stroke Population

When evaluating the psychometric properties of a stroke functional assessment instrument, it is important to consider the population in which the psychometric testing was performed. A generic instrument should be tested in a stroke population before it is used in research or clinical practice. For stroke-specific instruments, the similarity of the validation population to the target population must be considered. Ideally, the psychometric testing will have been performed in a representative sample of stroke patients that has a broad range of important characteristics. If a more restrictive sample of stroke patients was used, it is important to consider whether the type of stroke, severity of stroke, degree of functional limitation, and the timing of the assessment after stroke are adequately similar between the two groups.

Feasibility

Many factors affect the feasibility of using a particular instrument. The setting of use and the subjects' severity of stroke will influence the amount of time that can be spent doing the assessment and the number of items that can be used. Even if a functional instrument is ideal in other ways, if an assessment requires special training, takes an excessive amount of time to administer, or has a complex scoring procedure, it increases the burden for health care professionals and may rarely be used.

Mode of Assessment

Many functional assessments rely on self-reported functional abilities rather than observed direct performance by an assessor. Some instruments are designed to rely primarily on the patient's self-report, whereas others rely on caregivers or family members. The focus of self-report assessments is on the activities that people regularly perform in their own environment.

Use of Proxy Reports of Function

It is sometimes necessary to rely on proxy reports of function if a patient has a problem in communication because of affected cognition and language, and, as a result, an interview with the patient is not possible. In contrast, when a patient does not have severe loss in cognition and functional level, the use of proxy reports of function may not be needed. A high agreement on basic and IADLs was found between patients' self-report and proxies' report in this case (14,15). Proxy reports might be more suitable when trying to obtain data from patients with severe functional problems. One study has found that a proxy was more likely to complete a mail survey if the patient had more functional limitations (16).

Because the source of information can influence reliability and validity of the functional assessment, it is important to clarify whether the score obtained from a proxy provides the same information as that obtained from the patient's own self-report, especially with patients who experience cognitive and communicative problems. When a proxy is used to provide a functional assessment, the agreement between the proxy and patient should have been assessed.

Self-Report Versus Direct Performance

An alternative approach to self-report functional assessments is to observe participants directly while they perform a series of set functional tasks. Direct performance tests can be a useful alternative when patients have communication or cognitive problems that limit their ability to report their function. In addition, the direct performance tests can provide an accurate assessment of a person's capacity to do specific functional tasks, including tasks that he or she might not regularly undertake as part of his or her daily activities. Many studies have shown that direct performance measures provide similar but slightly different outcomes than self-report assessments (17). This is probably because direct performance tests are evaluating what a person is capable of doing under set conditions, and self-report assessments ask people what they actually do in their own environment.

Overview of Stroke-Specific Functional Assessments

This section of the chapter describes the most commonly used stroke-specific measures of activity, participation, and health-related quality of life. For each measure, we summarize the instrument's background, scope, purpose, and psychometric properties. Table 39.5 (provided at the end of the chapter) summarizes the intended purpose, ICF conceptual domains covered, mode of administration, and psychometric properties of the nine stroke-specific functional assessments reviewed.

American Heart Association Stroke Outcome Classification

The American Heart Association Stroke Outcome Classification (AHA.SOC) was developed by a multidisciplinary panel to measure the full range of deficits following a stroke (18). The global classification identifies the severity and extent of neurologic impairments as well as the level of independence according to basic ADLs (BADLs) and IADLs. Therefore, the instrument covers all the three domains in the ICF: body structures and functions, activities, and participation. The primary purpose of the instrument is to serve as a standardized and comprehensive classification system to document the impairments and disability resulting from a stroke. A secondary aim is to gauge the effect of treatment.

The AHA.SOC contains three scales. The first scale, AHA.SOC-Domain, classifies the extent of neurologic impairments in six domains: motor, sensory, vision, affect, cognition, and language. The scale ranges from 0 (0 domains impaired) to 3 (more than two domains impaired). The second scale, AHA.SOC-Severity, classifies the severity of neurologic impairments into one of three levels: A (no/minimal neurologic deficit because of stroke in any domain), B (mild/moderate deficit because of stroke in one or more domains), and C (severe deficit due to stroke in one or more domains). The third scale, AHA.SOC-Function, classifies the dependency in BADLs and IADLs. The scale ranges from I (independent in BADLs and IADLs and tasks required of roles that patient had before the stroke) to V (completely dependent in BADLs in more than five areas and IADLs). The classification score is meant to document the limitations resulting from the most recent episode of stroke. It is recommended that clinicians use clinical examinations and standardized assessments to support their rating decisions for each scale (18). Time to complete the classification was not reported, but it may depend on the completion of standardized assessments.

Concurrent validity was assessed by correlations with the modified Rankin Scale (r = 0.70), the BI (r = –0.87), Lawton IADL Scale (r = –0.85), and physical function in SF-36 (r = –0.70) (19). The inter-rater reliability is good for the number of impaired neurologic domains classification (k = 0.56) and excellent for the severity of impairment classification (k = 0.76) and for the functional disability classification (k = 0.77) (18). It can discriminate ADL-related disabilities after one, three, and six months after a stroke (19).

The AHA.SOC is a comprehensive clinical assessment of impairment, severity, and function after a stroke and a useful tool to classify stroke severity. Although the classification covers all the three conceptual domains in the ICF, the AHA.SOC-Function assesses BADLs and IADLs together and shows no clear division between activities and participation. Administration of AHA.SOC may require experienced health care professionals to obtain required information and to decide the rating. It is recommended that the classification not be completed unless related standardized assessments are available.

Modified Rankin Scale and Oxford Handicap Scale

Rankin initially described functional recovery of a group of stroke patients on a five-level scale (20). The scale later was used as a global disability measure. To avoid ambiguity, the scale was revised to have six levels and clearer wording to differentiate levels one and two (21). The scale was renamed the modified Rankin Scale and has become a popular outcome measure for stroke clinical trials (22,23). The instrument was changed a third time by changing the word *disability* to *handicap*, and the term *lifestyle* was incorporated to expand the scale to measure handicap. This version is referred to as the Oxford Handicap Scale. Both scales are classification instruments to discriminate functional levels of patients. The modified Rankin Scale covers the conceptual domain of activities whereas the Oxford Handicap Scale covers activities and participation.

Administration relies on professional judgment. Both scales have six grades ranging from 0 (no symptoms) to 5 (severe disability; bedridden, incontinent and requiring constant nursing care and attention in the modified Rankin Scale; or severe handicap-totally dependent patient requiring constant attention night and day in the Oxford Handicap Scale) (21,24). Time to complete the scale varies, depending on how familiar the clinician is with the patient. The structured interview takes approximately 15 minutes (25).

Concurrent validity of the modified Rankin Scale was determined by comparing this scale with the BI (26). Concurrent validity of the Oxford Handicap Scale was assessed by a regression with multiple functional health indicators, including the BI and subscales of the Sickness Impact Profiles (SIP) (27). The results showed that the Oxford Handicap Scale is a global functional health index but with a focus on physical disability (27). The inter-rater reliability of the modified Rankin Scale is moderate for raters with similar professional backgrounds (k = 0.56) but low for raters with different backgrounds (k = 0.25) (21). A structured interview was suggested to improve its inter-rater reliability (28). However, the effect of this approach is not well supported (29). The inter-rater reliability of the Oxford Handicap Scale showed moderate agreement (k = 0.42) (24). The test–retest reliability was only available for the modified Rankin Scale (k = 0.81) (28). The modified Rankin Scale was less responsive to change when compared with the BI and the FIM in a group of stroke patients who received a rehabilitation service (30). For a comprehensive review of psychometric properties of the modified Rankin Scale, please see elsewhere (31).

The modified Rankin Scale and the Oxford Handicap Scale are simple outcome measures designed for use with patients after stroke. The broadly defined scale categories may be time efficient and adequate to classify patients in a clinical setting, but appear less psychometrically adequate for evaluating change. The Oxford Handicap Scale captures the domain of participation restrictions following a stroke, but is not designed for use with inpatients because it measures lifestyle issues that are not relevant while a patient is in the hospital. The lack of standardized criteria for administering both scales reduces the reliability of the scales.

TABLE 39.1 Chedoke-McMaster Stroke Assessment Disability Inventory

Gross Motor Function Index
1. Supine to side lying on strong side
2. Supine to side lying on weak side
3. Side lying to long sitting through strong side
4. Side lying to sitting on side of the bed through strong side
5. Side lying to sitting on side of the bed through weak side
6. Standing
7. Transfer to and from bed toward strong side
8. Transfer to and from bed toward weak side
9. Transfer up and down from floor and chair
10. Transfer up and down from floor and standing

Walking Index
11. Walking indoors
12. Walking outdoors, over rough ground, ramps, and curbs
13. Walking outdoors several blocks
14. Stairs
15. Age and sex appropriate walking distance (in meters) for 2 minutes (2-point bonus)

Scoring key from the Functional Independence Measure, Uniform Data System for Medical Rehabilitation, State University of New York at Buffalo

Independence (no helper)
7. Complete independence (timely, safely)
6. Modified independence (device)

Modified dependence (helper)
5. Supervision
4. Minimal assist (subject = 75%)
3. Moderate assist (subject = 50%)

Complete dependence (helper)
2. Maximal assist (subject = 25%)
1. Total assist (subject = 0%)

Chedoke-McMaster Stroke Assessment

The Chedoke-McMaster Stroke Assessment includes two outcome domains: a physical impairment inventory and an activity inventory (previously called a *disability inventory*) (32). The physical impairment inventory is a discriminative measure that is based on the body structures and functions conceptual domain in the ICF. The activity inventory is an evaluative measure that assesses change in mobility function, which is part of the activities conceptual domain in the ICF (Table 39.1).

The Chedoke-McMaster Stroke Assessment is a direct performance exam. Time to complete the assessment is approximately 1 hour. Administration and scoring rules are provided in a users' manual (33).

The physical impairment inventory has six dimensions: shoulder pain, postural control, the arm, the hand, the leg, and the foot. Each dimension is measured using a seven-point ordinal scale corresponding to the stage of motor recovery. The activity inventory has two subscales: gross motor function and walking. There are 10 items measuring rolling, sitting, transferring, and standing in the gross motor function subscale and 5 items measuring walking indoors, outdoors, stairs, and distance in the walking subscale. The activity inventory is suggested to be used with the Uniform Data System for Medical Rehabilitation, which includes the FIM (32). Scoring for each item is on a seven-point Likert scale based on the assistance needed, except for the last item, a 2-minute walk test. A higher score indicates more independence. The maximum score of the activity inventory is 100.

Concurrent validity of the physical impairment inventory was assessed with correlation with the Fugl-Meyer Test ($\gamma = 0.95$), and the activity inventory with the FIM ($\gamma = 0.79$) (32). All the reliabilities were estimated with intraclass correlation coefficient (ICC) (32). The internal consistency of the six dimensions in the physical impairment inventory ranges from 0.93 to 0.98. The inter-rater reliability of the physical impairment inventory is 0.97, and of the activity inventory is 0.99. The test–retest reliability of the activity inventory is 0.98. Variance ratio was used to assess the responsiveness between admission and discharge of a group of stroke patients (32). The Chedoke-McMaster Stroke Assessment was 1.92 times more responsive when compared with the FIM.

The Chedoke-McMaster Stroke Assessment is a stroke-specific instrument that has demonstrated high levels of validity and reliability. The two-inventory design can facilitate measurement of treatment effects because it provides a way to classify stroke survivors into homogeneous subgroups based on motor recovery. However, the scope of the activity inventory may be too narrow if administered alone, because it only measures mobility function. To fully assess functional domains commonly affected after a stroke—for example, self-care and communication—supplemental assessments are necessary.

Frenchay Activities Index

The Frenchay Activities Index (FAI) is a 15-item questionnaire that assesses activities performed inside and outside the home, including 1 mobility, 7 IADLs, and 7 indoor or outdoor social/role activities (34,35). The instrument covers activities and participation domains in the ICF. The FAI is designed as an evaluative instrument, which intends to obtain information on the premorbid lifestyle and up to three to six months after a stroke to help determine rehabilitation goals and record progress in activities (34,35).

The FAI measures three domains: domestic (preparing main meals and washing clothes), leisure/work (reading books and gainful work), and outdoor activities (local shopping and outings/car rides). Administration can be done through self-report of patients and/or relatives (36). The questionnaire takes less than 10 minutes to complete, which makes it feasible to use in a clinic. Scoring is based on a four-point Likert frequency scale ranging from never (1) to the highest frequency (4). The use of a frequency scale is assumed to reduce the subjective judgment of quality of an activity (35).

Concurrent validity was assessed by examining correlations with the BI ($\gamma = 0.66$) and subscales of the SIP scale (γ range is from –0.14 to –0.73) (35,36). A more recent study showed moderate correlations with the stroke impact scale (SIS) and the motor activity

log (Spearman's rho range: 0.3–0.6) (37). The FAI has excellent inter-rater reliability ($\gamma > 0.80$) (35,38). The test–retest reliability over one week in most items is excellent (kappa range: 0.25–1.00) (39). There is a high agreement between patients and their proxies on the FAI (ICC = 0.87 for the total FAI; ICC = 0.85 for the domestic domain; ICC = 0.63 for work/leisure domain; ICC = 0.87 for outdoor activities domain) (40). The FAI has been shown to detect change in patients who received a three-week stroke motor intervention (standardized response mean = 0.5) (37).

The FAI allows health care professionals to understand premorbid lifestyle of patients, so rehabilitation goals can be set to fit individual needs. Although items in the three domains cover concepts of activity and participation in the ICF, the two concepts are merged in the three domains. The FAI has been validated in older patients; the coverage of activities may be not sufficient for younger age groups, who have different social roles and task demands (41). For example, a young female patient may have to fulfill a mother's role and carry out caring activities that are not covered by the FAI. Moreover, items of leisure activities lack diversity to capture the experiences of younger patients who may have different hobbies, which could further affect the responsiveness in this population.

Hamrin Activity Index

The Hamrin Activity Index (AI) was specifically designed for a study to measure an activity program for patients with stroke in nursing care in Sweden (42). The AI is an evaluative instrument. The instrument includes 16 items in 3 domains: mental capacity, motor activity, and ADL function. These items cover the conceptual domains of body structures and functions and activities in the ICF.

Administration involves a structured interview with the patients and relatives (42). It may take up to one hour to have the assessment done properly. The mental capacity domain includes four subscales: degree of consciousness; orientation in time, space, and person; ability to communicate verbally; and psychological activities. The maximum score of this domain is 32, with a higher score indicating a better capacity. The motor activity domain measures functions of the four extremities with six subscales: right arm, right hand, right leg, left arm, left hand, and left leg. Scoring is from a functional point of view in relation to ADL performance, such as functional grip. The maximum score is 24, with a higher score indicating higher functioning. The ADL function domain includes six subscales: ambulation, personal hygiene, dressing, feeding, and continence with two items, emptying function of bladder and bowels. Scoring is based on the assistance needed to complete the activity. The maximum score is 36, with a higher score indicating more independence.

The concurrent validity was tested through a correlation with the Rankin disability scale, but the value of correlation was not reported (42). Similarly, the internal consistency was assessed but not reported (42). No inter-rater reliability was specifically assessed because mainly one researcher conducted the interviews in the activity intervention study (42). The instrument did not demonstrate responsiveness in patients 3 and 12 months after stroke (43).

One feature of AI is that it measures the patient's ability to communicate verbally, which may be affected by the disease. However, the application of the scale to patients with communication or language deficits has not been tested. Moreover, motor activity only focuses on unilateral motor function, whereas most daily activities require coordination between right and left extremities to complete. The application of this instrument can be limited given that AI was created within a research context to evaluate specific outcome domains of an intervention program. In addition, psychometric properties should be carefully assessed before applying this instrument.

Nottingham Extended ADL Scale

The Nottingham Extended ADL Scale was initially developed by clinicians and researchers in Nottingham, United Kingdom, to assess functional status in stroke patients after returning home (44). It is a questionnaire that includes 22 activities in 4 categories—mobility, kitchen, domestic, and leisure; therefore, it covers the conceptual domains of activities and participation in the ICF (see Table 39.2). The questionnaire is easy to understand and can be self-administered. Patients are asked whether they do the activity, rather than *if* they can do it, on four levels of responses: not at all, with help, on my own with difficultly, on my own. The original scoring of the scale is coded as dichotomous [0, 0, 1, and 1] to indicate whether a patient is dependent [0] or independent [1] (44). This scoring is recommended (personal communication), although researchers have applied a 4-point Likert scale to correspond to the four levels of responses [0, 1, 2, and 3] (45,46).

The concurrent validity was established with correlations to the BI, Nottingham Health Profile, Geriatric Depression Score, and the London Stroke Satisfaction Score (Spearman's rho range: –0.70–0.84) (47). Each category of the Nottingham Extended ADL Scale—mobility, kitchen, domestic, and leisure activities—showed acceptable values on Guttman scaling, which means each formed a unidimensional, hierarchical scale (48). Although the test–retest reliability over 2 weeks in all items ranges from "poor" to "excellent" (kappa range: 0.29–1.00), the kappa value is greater than 0.75 in 19 items (44). The scale is also sensitive to change within 1 year after stroke (effect size range: 0.04–1.40) (47).

The Nottingham Extended ADL Scale measures daily activities beyond self-care activities and is designed to be used as a postal assessment (44). The scale has the potential to reduce data collection burden and research expense in rehabilitation studies that track stroke patients' recovery in the community. Although a sum score of the four categories indicates an overall functional level of a stroke patient, the sum score might be questionable because the scale has not been shown to be a unidimensional measure of ADLs (49). For this reason, the category scores may be used to evaluate patients' functional change over time.

TABLE 39.2 Nottingham Extended ADL Scale

The following questions are about everyday activities. Please answer by ticking ONE box for each question. Please record what you have ACTUALLY done in the past few weeks.

DID YOU.	NOT AT ALL	WITH HELP	ON YOUR OWN WITH DIFFICULTY	ON YOUR OWN
1. Walk around outside?				
2. Climb stairs?				
3. Get in and out of a car?				
4. Walk over uneven ground?				
5. Cross roads?				
6. Travel on public transport?				
7. Manage to feed yourself?				
8. Manage to make yourself a hot drink?				
9. Take hot drinks from one room to another?				
10. Do the washing up?				
11. Make yourself a hot snack?				
12. Manage your own money when out?				
13. Wash small items of clothing?				
14. Do your own housework?				
15. Do your own shopping?				
16. Do a full clothes wash?				
17. Read newspapers or books?				
18. Use the telephone?				
19. Write letters?				
20. Go out socially?				
21. Manage your own garden?				
22. Drive a car?				

Rivermead ADL Scale

The Rivermead ADL scale was designed to evaluate ADLs for stroke patients in the United Kingdom (50). Activities selected in the scale were considered important for people's daily life. It is an evaluative instrument that records the functional progress of stroke patients. The instrument measures a patient's ability to perform specific tasks, so it reflects the conceptual domain of activities in the ICF.

The Rivermead ADL scale is a task performance exam. The administrator follows a standardized procedure, and patients are required to demonstrate each task. The evaluation is terminated after three consecutive failed items. The instrument includes 16 ADLs and 15 IADLs and uses a hierarchical scaling: the order of the items reveals increasing difficulty. Scoring is based on three levels:

- 1 = Independent with or without aid
- 0v = Independent but verbal assistance is required
- 0 = Dependent

The administration time varies from 30 to 60 minutes.

The validity of the Rivermead ADL scale was established through Guttman scaling. The results showed the existence of a valid cumulative and unidimensional Guttman scale with acceptable reproducibility (coefficients ≥ 0.89) and scalability (coefficients ≥ 0.79) (51). The inter-rater reliability ($\gamma = 0.89$), and the test–retest reliability are excellent ($\gamma = 0.95$) (50). Whether the scale is responsive to clinically meaningful change is unknown.

The application of hierarchical scaling is one advantage of the Rivermead ADL scale. The total score not only reflects the functional limitation, but it also shows the actual items that the patient can do. Although the standardized procedure and direct physical performance increases the instrument's reliability, substantial time may be required for proper training and administration. Its responsiveness remains unknown. Some activities in the scale may be culturally sensitive, and a cross-cultural comparison should be conducted before applying the instrument to the U.S. population.

Stroke-Specific Quality of Life Scale

Domains and items for the Stroke-Specific Quality of Life Scale (SS-QOL) were developed from interviews with patients with ischemic stroke (52). It is an evaluative instrument for stroke-specific, health-related quality of life (Table 39.3).

The SS-QOL is a self-report measure that is interview administered. Time to complete the interview is not reported. Twelve domains in the scale cover areas that may be affected by a stroke: energy, family roles, language, mobility, mood, personality, self-care, social roles, thinking, upper-extremity function, vision, and work/productivity. Concepts underlying the SS-QOL can be linked to body function, activities and participants, and environmental factors of the ICF (53). All items are rated on a five-point Likert scale, with higher scores indicating desirable outcomes.

The concurrent validity was initially assessed by comparing SS-QOL scores with established measures for each domain (52). Patients with language and cognitive deficits were excluded from this validation study, and, as a result, there was inadequate variation in the scores for the language, thinking, and social role domains to allow the assessment of their validity. A study later applied confirmatory factor analysis to validate the SS-QOL and found acceptable factor loadings (greater than 0.40) on items in each domain (54). The

TABLE 39.3 Stroke-Specific Quality of Life Scale

DURING THE PAST WEEK:

		COULDN'T DO IT AT ALL	A LOT OF TROUBLE	SOME TROUBLE	A LITTLE TROUBLE	NO TROUBLE AT ALL
SC1.	Did you have trouble preparing food?	1	2	3	4	5
SC2.	Did you have trouble eating, for example, cutting food or swallowing?	1	2	3	4	5
SC4.	Did you have trouble getting dressed, for example, putting on socks or shoes, buttoning buttons, or zipping?	1	2	3	4	5
SC5.	Did you have trouble taking a bath or shower?	1	2	3	4	5
SC8.	Did you have trouble using the toilet?	1	2	3	4	5
V1.	Did you have trouble seeing the television well enough to enjoy a show?	1	2	3	4	5
V2.	Did you have trouble reaching for things because of poor eyesight?	1	2	3	4	5
V3.	Did you have trouble seeing things off to one side?	1	2	3	4	5
L2.	Did you have trouble speaking, for example, get stuck, stutter, stammer, or slur your words?	1	2	3	4	5
L3.	Did you have trouble speaking clearly enough to use the telephone?	1	2	3	4	5

DURING THE PAST WEEK:

		COULDN'T DO IT AT ALL	A LOT OF TROUBLE	SOME TROUBLE	A LITTLE TROUBLE	NO TROUBLE AT ALL
L5.	Did other people have trouble understanding what you said?	1	2	3	4	5
L6.	Did you have trouble finding the word you wanted to say?	1	2	3	4	5
L7.	Did you need to repeat yourself so others could understand you?	1	2	3	4	5
M1.	Did you have trouble walking? (If you can't walk, circle 1 and go to question M7)	1	2	3	4	5
M4.	Did you lose your balance when bending over or reaching for something?	1	2	3	4	5
M6.	Did you have trouble climbing stairs?	1	2	3	4	5
M7.	Did you have trouble with needing to stop and rest when walking or using a wheelchair?	1	2	3	4	5
SR5.	I didn't see as many of my friends as I would like.	1	2	3	4	5
SR6.	I had sex less often than I would like.	1	2	3	4	5
SR7.	My physical condition interfered with my social life.	1	2	3	4	5

(*continued*)

TABLE 39.3 Stroke-Specific Quality of Life Scale (*continued*)

DURING THE PAST WEEK:

		STRONGLY AGREE	MODERATELY AGREE	NEITHER AGREE NOR DISAGREE	MODERATELY DISAGREE	STRONGLY DISAGREE
MD6.	I felt withdrawn from other people.	1	2	3	4	5
MD7.	I had little confidence in myself.	1	2	3	4	5
MD8.	I was not interested in food.	1	2	3	4	5
E2.	I felt tired most of the time.	1	2	3	4	5
E3.	I had to stop and rest often during the day.	1	2	3	4	5
E4.	I was too tired to do what I wanted to do.	1	2	3	4	5

Now, we would like to ask how you feel you are doing today in some general areas compared to how you were before your stroke. Put an "X" in the box to show whether each area is a lot worse, a little worse, or the same as before your stroke. Please remember to compare how you are doing today with how you were before your stroke happened.

	A LOT WORSE THAN BEFORE MY STROKE	SOMEWHAT WORSE THAN BEFORE MY STROKE	A LITTLE WORSE THAN BEFORE MY STROKE	THE SAME AS BEFORE MY STROKE
1. E. My energy level is . . .				
2. L. My speech is . . .				
3. M. My walking is . . .				
4. V. My vision is . . .				
5. UE. The use of my arms or hands is . . .				
6. T. My thinking is . . .				
7. MD. My mood is . . .				
8. P. My personality is . . .				
9. W. I do my jobs at home or at work.				
10. SC. I can take care of myself.				
11. FR. I do things for my family.				
12. SR. I do things for my friends.				
13. Overall, my quality of life is . . .				

SS-QOL also demonstrated excellent internal consistency in all domains (Cronbach alpha range 0.79–0.96) (54). No test–retest or inter-rater reliabilities are available. The responsiveness was evaluated on patients one and three months after an ischemic stroke. Most of the domains were shown to have moderate responsiveness (standardized effect sizes greater than 0.4) (52)

One advantage of SS-QOL is that it is a comprehensive measure of stroke. For example, it assesses language function, which has been ignored by most functional assessments. Because SS-QOL is a condition-specific quality-of-life measure, it is related more to the overall health-related quality of life in stroke patients than generic QOL measures (55). However, the scoring procedure can be confusing, as one domain may use two response set keys. The Likert response scale for each key is inconsistent with others, that is, in one scale, 5 may indicate "no help needed" or may indicate "strongly disagree." Consequently, the domain sum score may be difficult to interpret. In addition, this is a lengthy questionnaire and, therefore, might be inefficient to use in some settings. SS-QOL was validated mainly using direct self-reports of patients with ischemic stroke, although validation in patients with aneurysmal subarachnoid hemorrhage has been reported (56). Caution is needed in applying it to different populations or if proxies are used.

Stroke Adapted Sickness Impact Profile

The Stroke Adapted Sickness Impact Profile (SA-SIP30) is adapted from the 136-item SIP to measure quality of life after stroke (57). The scale eliminates the disadvantage of length in the SIP by excluding irrelevant and unreliable items. It is an evaluative instrument and covers body structures and functions, activities, and participation in the ICF.

Administration is via a structured interview with the patient. The SA-SIP30 includes 30 yes/no items in eight domains: body care and movement, ambulation, mobility,

household management, social interaction, communication, emotional behavior, and alertness behavior (57). The first four domains assess a physical dimension, and the other four assess a psychosocial dimension. Items are weighted for scoring with a lower score indicating a more desirable outcome. Time to complete the questionnaire is less than 30 minutes.

Validity was compared with the 136-item SIP ($\gamma_s = 0.96$), as well as with the BI ($\gamma_s = 0.50$) and the Rankin Scale ($\gamma_s = 0.68$) (57). The internal consistency was moderate to good ($\alpha > 0.68$) (58). No test–retest and inter-rater reliabilities were specifically reported for the SA-SIP30. Responsiveness was assessed on patients at 6 and 12 months and showed moderate effect sizes (effect size = 0.6) (58,59).

SA-SIP30 is a time-efficient quality-of-life measure for stroke patients. However, the scale has few psychosocial items and has a tendency to measure physical functioning rather than health-related quality of life (60). The scale has not been validated in patients with cognitive or language impairments or with proxy reporting.

Stroke Impact Scale

The SIS was developed from the perspective and input of stroke patients, caregivers, and health professionals with stroke expertise (61). It is a comprehensive evaluative instrument that tries to capture the heterogeneous consequences after a stroke. It covers all three conceptual domains in the ICF (Table 39.4).

It is a self-report measure administered through a structured interview with a patient and includes 59 items in 8 domains: strength, hand function, ADLs/IADLs, mobility, communication, emotion, memory and thinking, and social participation. SIS scoring uses a five-point Likert scale, with a higher score indicating higher function. Time to complete is approximately 15 to 20 minutes. If the patient has trouble following a three-step command because of cognitive impairment or aphasia, a proxy can be used to complete the interview (62). The instrument can also be administered via telephone interview and mail survey, which increases the feasibility for use to follow up functional recovery in a community setting (63).

Validity was assessed through correlations with established measures (61). The correlation coefficients are from 0.82 to 0.84 for items in the mobility and ADLs/IADLs domains. The correlation coefficients are from 0.44 to 0.58 for items in the memory and communication domains. The correlation coefficient is 0.70 for items in the participation domain. The internal consistencies of the eight domains range from 0.7 to 0.92 (ICCs) (61). Rasch analysis also demonstrated that most items in each domain are unidimensional, and five misfit items identified by the analysis were dropped from the latest version of SIS (62). The sensitivity

TABLE 39.4 Stroke Impact Scale (Version 3.0)

The purpose of this questionnaire is to evaluate how stroke has impacted your health and life. We want to know from your point of view how stroke has affected you. We will ask you questions about impairments and disabilities caused by your stroke, as well as how stroke has affected your quality of life. Finally, we will ask you to rate how much you think you have recovered from your stroke. These questions are about the physical problems that may have occurred as a result of your stroke.

1. IN THE PAST WEEK, HOW WOULD YOU RATE THE STRENGTH OF YOUR . . .	A LOT OF STRENGTH	QUITE A BIT OF STRENGTH	SOME STRENGTH	A LITTLE STRENGTH	NO STRENGTH AT ALL
a. Arm that was most affected by your stroke?	5	4	3	2	1
b. Grip of your hand that was most affected by your stroke?	5	4	3	2	1
c. Leg that was most affected by your stroke?	5	4	3	2	1
d. Foot/ankle that was most affected by your stroke?	5	4	3	2	1

These questions are about your memory and thinking.

2. IN THE PAST WEEK, HOW DIFFICULT WAS IT FOR YOU TO . . .	NOT DIFFICULT AT ALL	A LITTLE DIFFICULT	SOMEWHAT DIFFICULT	VERY DIFFICULT	EXTREMELY DIFFICULT
a. Remember things that people just told you?	5	4	3	2	1
b. Remember things that happened the day before?	5	4	3	2	1
c. Remember to do things (keep scheduled appointments or take medication)?	5	4	3	2	1
d. Remember the day of the week?	5	4	3	2	1
e. Concentrate?	5	4	3	2	1
f. Think quickly?	5	4	3	2	1
g. Solve everyday problems?	5	4	3	2	1

These questions are about how you feel, about changes in your mood, and about your ability to control your emotions since your stroke.

(*continued*)

TABLE 39.4 Stroke Impact Scale (Version 3.0) (*continued*)

3. IN THE PAST WEEK, HOW OFTEN DID YOU . . .	NONE OF THE TIME	A LITTLE OF THE TIME	SOME OF THE TIME	MOST OF THE TIME	ALL OF THE TIME
a. Feel sad?	5	4	3	2	1
b. Feel that there is nobody you are close to?	5	4	3	2	1
c. Feel that you are a burden to others?	5	4	3	2	1
d. Feel that you have nothing to look forward to?	5	4	3	2	1
e. Blame yourself for mistakes that you made?	5	4	3	2	1
f. Enjoy things as much as ever?	5	4	3	2	1
g. Feel quite nervous?	5	4	3	2	1
h. Feel that life is worth living?	5	4	3	2	1
i. Smile and laugh at least once a day?	5	4	3	2	1

The following questions are about your ability to communicate with other people, as well as your ability to understand what you read and what you hear in a conversation.

4. IN THE PAST WEEK, HOW DIFFICULT WAS IT TO . . .	NOT DIFFICULT AT ALL	A LITTLE DIFFICULT	SOMEWHAT DIFFICULT	VERY DIFFICULT	EXTREMELY DIFFICULT
a. Say the name of someone who was in front of you?	5	4	3	2	1
b. Understand what was being said to you in a conversation?	5	4	3	2	1
c. Reply to questions?	5	4	3	2	1
d. Correctly name objects?	5	4	3	2	1
e. Participate in a conversation with a group of people?	5	4	3	2	1
f. Have a conversation on the telephone?	5	4	3	2	1
g. Call another person on the telephone, including selecting the correct phone number and dialing?	5	4	3	2	1

The following questions ask about activities you might do during a typical day.

5. IN THE PAST TWO WEEKS, HOW DIFFICULT WAS IT TO . . .	NOT DIFFICULT AT ALL	A LITTLE DIFFICULT	SOMEWHAT DIFFICULT	VERY DIFFICULT	COULD NOT DO AT ALL
a. Cut your food with a knife and fork?	5	4	3	2	1
b. Dress the top part of your body?	5	4	3	2	1
c. Bathe yourself?	5	4	3	2	1
d. Clip your toenails?	5	4	3	2	1
e. Get to the toilet on time?	5	4	3	2	1
f. Control your bladder (not have an accident)?	5	4	3	2	1
g. Control your bowels (not have an accident)?	5	4	3	2	1
h. Do light household tasks/chores (dust, make a bed, take out garbage, and do the dishes)?	5	4	3	2	1
i. Go shopping?	5	4	3	2	1
j. Do heavy household chores (vacuum, laundry, or yard work)?	5	4	3	2	1

The following questions are about your ability to be mobile at home and in the community.

6. IN THE PAST TWO WEEKS, HOW DIFFICULT WAS IT TO . . .	NOT DIFFICULT AT ALL	A LITTLE DIFFICULT	SOMEWHAT DIFFICULT	VERY DIFFICULT	COULD NOT DO AT ALL
a. Climb one flight of stairs?	5	4	3	2	1
b. Climb several flights of stairs?	5	4	3	2	1
c. Get in and out of a car?	5	4	3	2	1

(*continued*)

TABLE 39.4 Stroke Impact Scale (Version 3.0) (*continued*)

7. IN THE PAST TWO WEEKS, HOW DIFFICULT WAS IT TO USE YOUR HAND THAT WAS MOST AFFECTED BY YOUR STROKE TO . . .	NOT DIFFICULT AT ALL	A LITTLE DIFFICULT	SOMEWHAT DIFFICULT	VERY DIFFICULT	COULD NOT DO AT ALL
a. Carry heavy objects (a bag of groceries)?	5	4	3	2	1
b. Turn a doorknob?	5	4	3	2	1
c. Open a can or jar?	5	4	3	2	1
d. Tie a shoelace?	5	4	3	2	1
e. Pick up a dime?	5	4	3	2	1

The following questions are about how stroke has affected your ability to participate in the activities that you usually do, things that are meaningful to you and help you to find purpose in life.

8. DURING THE PAST FOUR WEEKS, HOW MUCH OF THE TIME HAVE YOU BEEN LIMITED IN . . .	NONE OF THE TIME	A LITTLE OF THE TIME	SOME OF THE TIME	MOST OF THE TIME	ALL OF THE TIME
a. Your work (paid, voluntary, or other)	5	4	3	2	1
b. Your social activities?	5	4	3	2	1
c. Quiet recreation (crafts, reading)?	5	4	3	2	1
d. Active recreation (sports, outings, travel)?	5	4	3	2	1
e. Your role as a family member and/or friend?	5	4	3	2	1
f. Your participation in spiritual or religious activities?	5	4	3	2	1
g. Your ability to control your life as you wish?	5	4	3	2	1
h. Your ability to help others?	5	4	3	2	1

9. STROKE RECOVERY

On a scale of 0 to 100, with 100 representing full recovery and 0 representing no recovery, how much have you recovered from your stroke?

_____ 100 Full Recovery
_____ 90
_____ 80
_____ 70
_____ 60
_____ 50
_____ 40
_____ 30
_____ 20
_____ 10
_____.

to change of the SIS depends on the patient's stage of stroke severity. The scale has been shown to detect change from 1 to 3 months and 1 to 6 months for minor and moderate stroke ($t > 1.73$), and from 3 to 6 months for people with moderate stroke who have higher functioning ($t > 2.14$) (61).

The SIS has demonstrated good test–retest reliability through telephone interview (ICCs range from 0.75–0.95) and mail survey mode (ICCs range from 0.68–0.98) in a sample of veterans (63). SIS has demonstrated a moderate level of agreement between the proxy and patient (ICCs range from 0.50–0.83), especially in the domains that are related to physical function (strength, hand function, ADLs/IADLs, and mobility) (64). These four domains can be combined as one physical domain score. A short version (SIS-16), in which items are selected from these four domains, has demonstrated less ceiling effect for patients with mild stroke than the BI (65).

To our knowledge, SIS is the first stroke-specific instrument validated in a large and diverse group of stroke survivors, including ischemic and hemorrhagic stroke, from multiple clinical sites in the United States and Canada. Test content is comprehensive, and the scale can differentiate among patients with various functional states because of its broad range of item difficulty (62). The scale can be widely applied because it has been validated for use by mail or telephone and when

a proxy respondent is required. Another advantage is that the short version of SIS-16 can be an alternative to traditional ADL scales.

Research Frontiers: Future Directions for Functional Assessment

The Precision Versus Feasibility Dilemma

As the review of instruments in the earlier text demonstrates, we have greatly improved the breadth of functional status measurement used in the stroke field and the broader health care arena (66,67). However, even those functional outcome instruments with excellent breadth still have problems of inadequate depth of measurement (68). Thus, although we now have the capability to quantify many different functional dimensions, most instruments are relatively crude and imprecise, which particularly restricts their utility as evaluative instruments designed to monitor clinically relevant change in function in the clinic, quality improvement, and/or research. Those instruments that do provide more depth of measurement along with breadth are quite lengthy and are thus impractical to use in most settings and for most applications.

Contemporary test development techniques, relatively new to the health care arena, provide the field with innovative means of solving this measurement dilemma and open the way to more responsive instruments to monitor change in function. Although these newer measurement techniques have yet to be applied to the development of a stroke-specific functional status instrument, this is an active area of research.

Contemporary Methods to Improve Functional Assessment

We believe two contemporary measurement techniques—item response theory (IRT) and computer-adaptive testing (CAT)—have the ability to overcome many limitations in traditional functional status instruments and have the potential to transform how functional assessment is done within rehabilitation. Although these advances have been used in educational testing for many decades, they have only begun to be applied to functional outcome assessment in rehabilitation and other arenas of health care in the past decade.

Item Response Theory Techniques

IRT methods examine the associations between individuals' response to a series of items designed to measure a specific concept such as functional status (69). Data collected from samples of rehabilitation patients are fit statistically to an underlying IRT model that best explains the covariance among item responses (70,71). IRT measurement models are a class of statistical procedures used to develop measurement scales. The measurement scales are comprised of items with a known relationship between item responses and positions on an underlying functional domain, called an *item characteristic curve*. The form of the relationships is typically nonlinear. Using this approach, probabilities of patients scoring a particular response on an item at various functional ability levels can be modeled. Persons with more functional ability have higher probabilities of responding positively to functional items than persons with lower functional abilities. These probability estimates are used to determine the individual's most likely position along the functional dimension. When assumptions of a particular IRT model are met, estimates of a person's functional ability do not strictly depend on a particular fixed set of items. This scaling feature allows one to compare persons along a functional outcome dimension even if they have not completed the identical set of functional items. Because items and functional outcome scores are defined on the same scale, items can be optimally selected to provide good estimates of each domain of function at any level of the scale. This feature of IRT creates important flexibility in administering tests in a dynamic and tailored approach for each individual. See Hambleton (1989) for a more detailed explanation of IRT methods (72).

IRT is currently being applied in rehabilitation to develop new measures, improve existing measures, investigate group differences in item and scale functioning, equate different instruments, and, as we highlight, develop efficient test applications, such as CATs.

To apply IRT to functional outcome assessment, an appropriate item pool of functional tasks or activities must be assembled. An *item pool* is a collection of outcome items that represent a range of levels of a particular outcome domain. Item pools used in IRT analyses are developed by equating outcome items from different sources so they can be meaningfully compared on a common underlying scale. IRT methods open the door to understanding the linkages among items used to assess a common functional outcome domain and, in this way, serve as the psychometric foundation underlying CAT (73–75).

The quality of life in neurological disorders instrument, known as Neuro-QOL, was recently created in a major initiative sponsored by the National Institute of Neurological Disorders and Stroke. This is the first comprehensive measurement system for health-related quality of life (HRQoL) that has focused on people with neurological disorders and uses modern IRT-based methods to create CATs and short forms that are brief enough to be used in a variety of settings (76). Although this instrument is not stroke-specific, in that it was developed for people who have one of many major neurological conditions, throughout the development process the input of stroke expert clinicians and stroke survivors and their caregivers was obtained, and the instrument has been tested in people with stroke. The Neuro-QOL has developed 14 generic item banks and 8 targeted scales to assess HRQoL in 5 adult and 2 pediatric conditions. The development of the Neuro-QOL is ongoing, and the content of the instrument is expected to evolve to include more health domains. The instrument content is freely available at the Neuro-QOL website: http://www.neuroqol.org.

CAT Methodology

CAT programs use a simple form of artificial intelligence that selects questions tailored to the test-taker, and thereby shortens or lengthens the test to achieve the level of precision desired

TABLE 39.5 Stroke-Specific Functional Assessment Instruments

NAME		AMERICAN HEART ASSOC.	MODIFIED RANKIN SCALE	CHEDOKE-MCMASTER SCALE	FRENCHAY ACTIVITIES INDEX	HAMRIN ACTIVITY INDEX	NOTTINGHAM EXTENDED ADL SCALE	RIVERMEAD ADL SCALE	STROKE SPECIFIC QOL	STROKE ADAPTED SIP	STROKE IMPACT SCALE
Intended purpose	Classification	✓	✓	✓							
	Evaluation of change	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
ICF domains	Body structures and functions	✓		✓		✓			✓	✓	✓
	Activities	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
	Participation	✓			✓		✓		✓	✓	✓
Mode of administration	Patient interview/report				✓	✓	✓		✓	✓	✓
	Professional judgment	✓	✓								
	Physical performance			✓				✓			
	Validity	*	*	*	*	*	*	*	*	*	*
Psychometric properties	Test–retest reliability		*	*	*		*	*			*
	Interrater reliability	*	*	*	*			*			
	Responsiveness		*	*	*	*	*		*	*	*

Note: * = Related psychometric property was assessed and reported. Please see text for detailed review.

by a user. Functional status CAT applications rely on extensive item pools constructed for each outcome area. They contain items that consistently scale along each functional domain from low to high proficiency and include rules guiding starting, stopping, and scoring procedures. CAT methodology uses a computer interface for the patient/clinician report that is tailored to a patient's unique functional ability level. The basic notion of a CAT test is to mimic what an experienced clinician does. A clinician learns most when he or she directs questions at the patient's approximate level of proficiency. Administering functional items that represent tasks that are either too easy or too hard for the patient provides little information. In contrast to traditional, fixed-form functional tests that ask the same questions of everyone, regardless of how the respondent answers, CAT instruments, like a skilled clinician, tailor their assessment by asking only the most informative questions based on a person's response to previous questions.

A CAT is programmed to first present an item from the midrange of an IRT-defined item pool and then direct subsequent functional items to the level based on the patient's (or clinician's) previous responses without asking unnecessary questions. The selection of an item in the midrange is arbitrary, and the CAT can be set to select an initial item based on other information entered about the patient, such as age, diagnosis, or severity of his or her condition. By having comprehensive item banks available in each functional outcome domain of interest, the selection of additional items after the initial one can be based on responses to the previous items. This allows for fewer items to be administered while gaining precise information regarding an individual's placement along an outcome continuum.

We will illustrate how the CAT works using a functional activity scale developed in our research group (77). In this functional activity scale, we assume that the midpoint of the scale is 50, and this serves as the initial (default) score estimate prior to CAT administration. For this example, we used data collected in a prospective rehabilitation outcome study (78). We set the CAT precision stopping rule as a 95% CI less than 3.0. The case is an individual who suffered a stroke and is now receiving rehabilitation therapy in a community-based outpatient center.

The initial item administered is, "How much difficulty do you have coming to sit at the side of a bed?" A response of "a little difficulty" yields a score estimate of 38.2 with a large confidence interval.

A second question is administered, based on the estimate from the first response, "How much difficulty do you have carrying a suitcase?" The person responds, "No difficulty." A new score estimate is then calculated (44.4 ± 9.2), and the CAT program checks to see if the stop rule has been satisfied. Because the stop rule in this case is a confidence interval of less than 5, a third item is administered.

To the third item, "How much difficulty do you have running to catch a bus?" the person responds, "A little difficulty." A new score estimate is calculated (44 ± 6). The stop rule has not yet been satisfied, so a fourth item is administered.

The item, "How much difficulty do you have doing heavy housework?," is given to the person, and the answer is "a little difficulty," with a new score estimate of 44.2 ± 3. Because this meets the stop rule, no additional items are administered, and a final score estimate based on four items is 44.2 with a confidence interval of ±3. In this case, the four items administered were able to reproduce closely the score of 43.8 that was obtained by the administration of all 101 items in the full item pool. The number of items administered can be increased to achieve the desired level of precision.

Though intuitively appealing on its surface, to be truly innovative and useful in rehabilitation, functional status CATs must be shown to meet several standards for acceptability for clinical and research applications. These include:

1. Acceptable score accuracy in comparison to the entire item pool
2. Adequate score precision for group and individual assessments
3. Sufficient content breadth for application across a wide array of care settings
4. Adequate responsiveness for monitoring clinically relevant change
5. Feasibility with respect to user burden and administration cost for widespread use. This is an active area of research investigation within rehabilitation.

SUMMARY

Functional assessment is now an essential part of stroke research and clinical practice. The selection of the most appropriate instrument is a complex process that requires careful consideration. Health professionals, researchers, and others who utilize functional assessments must carefully evaluate the existing instruments to determine which one is most appropriate to meet their needs. The field of functional assessment has progressed so that there are now many stroke-specific functional assessments to choose from (Table 39.5). Potential users should consider the scope of the instrument, the purpose for which it has been developed, the administration and scaling methods used, and the psychometric properties of the instrument, as well as its feasibility in a particular context.

Even though the breadth of content in functional status instruments used in the stroke field and the broader health care arena has improved in recent decades, existing instruments still have problems with the balance between feasibility and breadth as well as depth of coverage. Fortunately, new methodologies such as IRT and CAT provide a way to overcome these problems. These methods have already been applied to the Neuro-QOL instrument, which has been developed for people with neurological problems and validated in people with stroke. It is anticipated that these methods will be applied to more stroke-specific measures in the future and yield further improvements in our ability to accurately and efficiently measure functional status in a wide range of people following a stroke.

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40

Predictive Factors for Recovery

Robert W. Teasell and Norhayati Hussein

Stroke often results in significant neurologic deficits leading to loss of function or independence, the consequences of which can be devastating to both patients and families. Fortunately, patients demonstrate significant recovery following stroke, although the degree to which individuals recover after stroke is highly variable. Most stroke recovery occurs during the first three to six months following a stroke (1–3). The course of recovery decelerates as a function of time and is generally a predictable phenomenon.

Even though a number of processes have been identified as contributing to neurologic recovery following a stroke, the role of each is not completely understood. Recovery from stroke has long been attributed to the resolution of edema and return of circulation within the ischemic penumbra, prompting skeptics to speculate that rehabilitation has limited influence on stroke recovery (4). However, it is now well recognized that recovery can be a prolonged process, extending well past the resolution period of acute physiological and structural changes occurring as a result of the stroke. Results from animal and clinical studies have shown that the cerebral cortex undergoes functional and structural reorganization for weeks and months following a stroke, with compensatory changes extending up to six months in more severe strokes (5). Physiological factors that account for stroke recovery include resolution of poststroke edema, reperfusion of the ischemic penumbra, resolution of diaschisis, and cortical reorganization in response to learning and rehabilitation training.

NEUROPHYSIOLOGICAL FACTORS IN STROKE RECOVERY

Resolution of Poststroke Edema

In the early period following a stroke, edema surrounding the ischemic or infarcted area may disrupt local neuronal functioning. A portion of the early recovery following a stroke may be attributable to resolution of edema (6) (Figure 40.1). As the edema subsides, neurons that have become inactive but remain structurally intact begin to function again. This process takes place relatively early in the course of recovery; however, it can extend for as long as eight weeks after stroke (7). Greater edema is associated with cerebral hemorrhage, which may take longer to subside and may partially explain why patients with hemorrhagic strokes tend to enter rehabilitation later than those with ischemic strokes and yet achieve similar outcomes by the time of discharge (8).

Reperfusion of the Ischemic Penumbra

A focal ischemic lesion of the brain consists of a core area of infarcted tissue, caused by loss of arterial perfusion, that is surrounded by a region of reduced blood flow or perfusion, known as the *ischemic penumbra* (9,10) (Figure 40.2). The penumbra is at risk for infarction, but is still salvageable. Reperfusion of this area early on following a stroke permits ischemic and nonfunctioning, but still viable, neurons to regain function with subsequent clinical recovery.

Resolution of Diaschisis

Diaschisis is a reversible state of low reactivity or depressed function as a consequence of a sudden interruption or loss of excitation in regions of the brain remote from, but connected to, the site of cerebral damage. Nudo et al. (11) noted that diaschisis occurs early after injury and is an inhibition or suppression of the surrounding cortex or distant areas of cortex with a connection to the damaged area (11). This reversibility may be partially a consequence of resolution of edema, which may account for a portion of the spontaneous recovery. Neuronal function may return following the resolution of diaschisis, particularly as the affected area of the brain demonstrates recovery and connections are restored.

Cortical Reorganization

Rehabilitation helps to facilitate cortical reorganization, an important contributor to the recovery process and one that is influenced by rehabilitation. Neuroplasticity following a

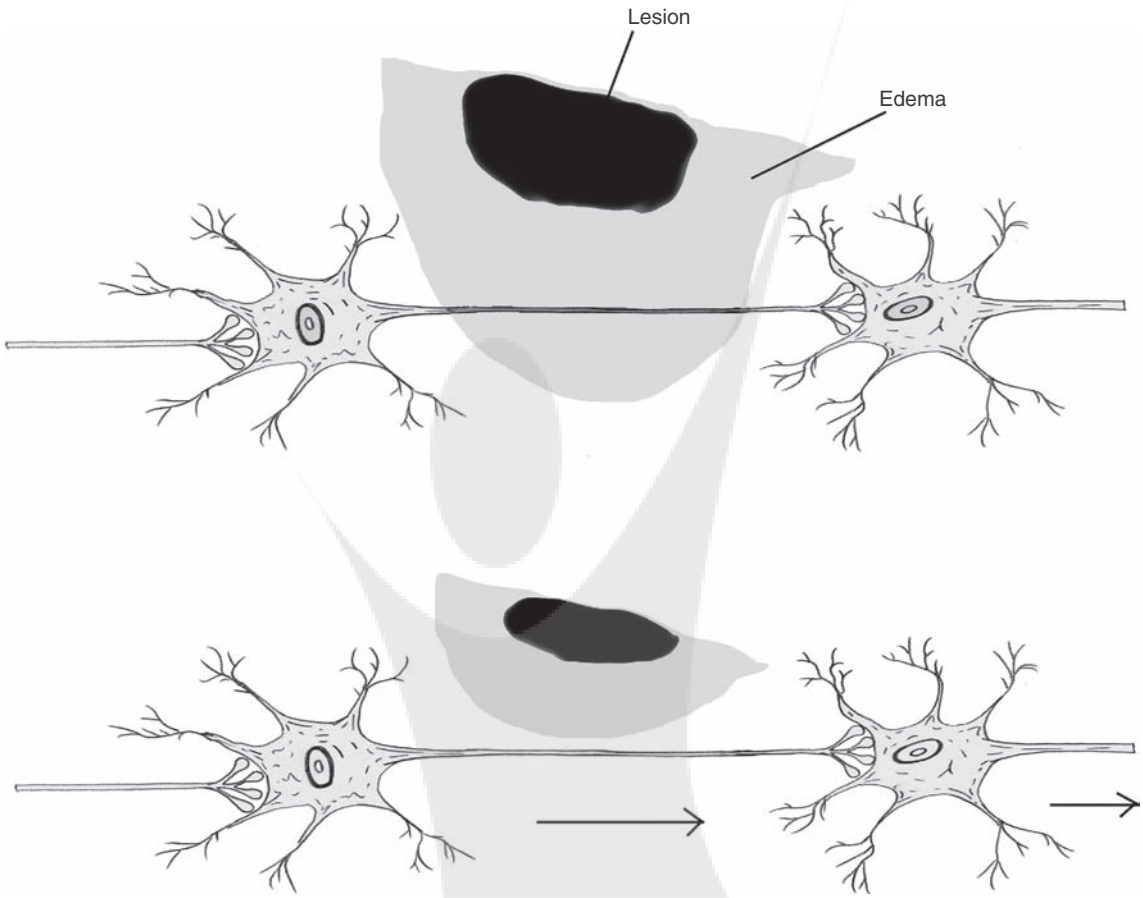

FIGURE 40.1 Resolution of poststroke edema.

stroke, after damage to the motor cortex, is based on three main concepts (12):

1. In normal (nonstroke) brains, acquisition of skilled movements is associated with predictable functional changes within the motor cortex.
2. Injury to the motor cortex from stroke results in functional changes in the remaining cortical tissue.
3. After a cortical stroke, these two observations interact so that reacquisition of motor skills is associated with functional neurologic reorganization occurring in the undamaged cortex (12).

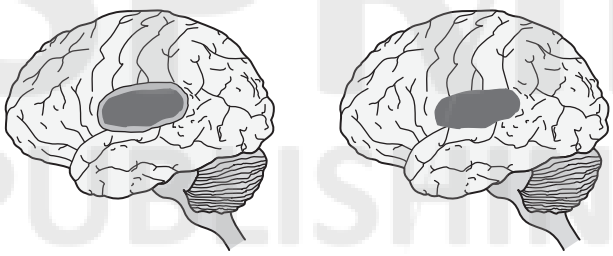

FIGURE 40.2 Reperfusion of ischemic penumbra.

Neuroplasticity, or cortical reorganization, is an important underlying rationale for poststroke rehabilitation, although the degree to which it accounts for functional recovery continues to be a source of debate.

IMPORTANCE OF PREDICTING STROKE RECOVERY

Accurate prediction of stroke recovery, or its potential, will greatly assist in the planning of rehabilitation interventions. Prediction and prognostication allow the setting of practical rehabilitation goals as well as appropriate discharge planning. Accurate prognostication will assist in providing accurate planning information to patients and caregivers, thus allowing realistic adjustments to recovery expectations. Accurate prognostication also leads to appropriate triaging, ensuring that suitable patients receive timely and appropriate rehabilitation. With accurate triaging, functional goals are more likely to be met, which in turn will improve the overall efficiency and effectiveness of the rehabilitation process. This is especially important given the increasing necessity to maximize limited health care resources.

Stroke recovery is influenced by a myriad of factors. Predictors reported in the literature include stroke

TABLE 40.1 Potential Predictors of Stroke Recovery

INTRINSIC FACTORS
Patient characteristics
• Age
• Gender
• Comorbidities
Stroke characteristics
• Lesion size and site
• Laterality
• First-ever versus recurrent stroke
• Type of stroke
Stroke severity
• Global stroke severity
• Impairment-specific severity
EXTRINSIC FACTORS
Service delivery
• Timing of rehabilitation
• Rehabilitation therapy: intensity, task-specificity
• Rehabilitation setting
• Social support

severity, age, gender, unilateral spatial neglect (USN), depression, cognitive impairment, dysphasia and bladder incontinence (13–15). It is worth noting that the initial severity of stroke and age of the stroke patient are the two most consistently reported and strongest predictive factors of stroke recovery (Table 40.1).

For the purpose of discussion, predictive factors for stroke recovery can be divided into intrinsic and extrinsic factors. Intrinsic factors are specific stroke survivors' attributes (age, gender, comorbidities) and the characteristics of the stroke (size, site, laterality, first-ever versus recurrent, stroke type, and associated impairment(s)). Extrinsic factors that help predict the course of stroke recovery largely revolve around the provision of rehabilitation services or social supports. This encompasses the concepts of time from stroke onset to the initiation of rehabilitation, therapy intensity, and task specificity as well as the setting of rehabilitation delivery (e.g., stroke units). In addition, the external social support that an individual receives (e.g., family support) may also influence recovery.

INTRINSIC PREDICTIVE FACTORS

Patient Characteristics

Age

Animal Studies. The impact of age on stroke and recovery in animals is not entirely clear. Shapira et al. (16) examined the effects of age on the development of ischemic injury in rats and discovered that young rats were affected more by the stroke than old rats, with more pronounced neurologic impairments and poorer performance in a water maze task. However, the duration of motor impairment after brain lesion appears to increase with age (16,17). The regenerative response of neurons and glial cells, although largely preserved with age, appears to be delayed or occurs at a diminished rate the older the animal (18,19). Reactive neuronal synaptogenesis declines, sprouting responses are less robust, and synaptic replacement rates diminish as age increases (19,20).

Clinical Studies. In humans, age has long been thought to limit poststroke neurologic recovery. Evidence suggests that, compared with older patients, younger patients recover at a faster rate and more completely (21,22). When compared with older stroke survivors, younger stroke survivors—defined as persons less than 65 years old—tend to have a better chance of regaining independence in activities of daily living (ADLs) and returning home at discharge (23). Herman et al. (24) reported that, when compared to those stroke survivors over 85 years of age, odds of successful discharge home, although dependent on many factors other than stroke recovery, were 18 times greater if the stroke survivor was under 65 (24). The effect of age on recovery was demonstrated even within a cohort of younger stroke survivors. Bogousslavsky and Pierre (25) reported that, following first-ever ischemic stroke, the prognosis of stroke survivors between the ages of 16 to 30 was better than that of stroke survivors aged 31 to 45 years. Nakayama et al. (26) reported that although older stroke survivors achieved the same degree of neurologic recovery as younger stroke survivors, the functional gains were lower. It was suggested that elderly stroke survivors had fewer compensatory abilities than younger stroke survivors with comparable neurologic impairments (26).

In a study on 43,163 subjects prospectively enrolled in the Austrian Stroke Unit Registry, Knoflach et al. (27) demonstrated that increasing age is a highly significant negative predictor of good functional outcome three months after ischemic stroke, independent of stroke severity, etiology, sex, risk factors, and stroke complications. The regression-adjusted probability of good outcome was highest in the age group 18 to 35 years and gradually declined by 3.1% to 4.2% per decade until age 75, with a steep drop thereafter (27).

Even though younger age has been associated with improved recovery, the results from several studies challenge the concept that age necessarily limits recovery. Kugler et al. (28) studied the effect of patient age on early stroke recovery and found that relative improvement decreased significantly with increasing age. Stroke survivors younger than 55 years of age achieved 67% of the maximum possible improvement, compared with only 50% for patients above 55 years (28). They also found that age had a significant, but relatively small, impact on the speed of recovery; younger stroke survivors demonstrated slightly faster functional recovery. Bagg et al. (29) found that even though age was a significant predictor of motor and total functional independence measure (FIM) scores at discharge, age alone accounted for only 3% of the variance in a multivariable model (30) and at most 1.3% of the variation in functional outcome after adjustments for other factors including admission FIM. The authors concluded that although age had a significant impact, it was a

poor predictor of individual functional recovery and could not be regarded as a limiting factor in the rehabilitation of stroke survivors (29).

Age appears to affect functional recovery more for severe strokes. Younger stroke survivors fare significantly better than older stroke survivors if they have low functional status upon admission, but not necessarily if both belong to a high-functioning group (31). Using the admission functional independence measure (AFIM) score as a proxy for stroke severity, Black-Schaffer and Winston (31) examined the relationship of advancing age to functional outcome, which included FIM gain, length of stay (LOS), LOS efficiency (defined as change in FIM/day of hospital stay), and the percentage discharged home. To control for the influence of AFIM score, the samples were divided into three groups: AFIM less than 40, AFIM 40–80, and AFIM greater than 80. Analysis was made based on 5 age groups: less than 55, 55–64, 65–74, 75–84, and more than 85 years old. Overall analysis showed that increasing age was related to decreasing total FIM change, LOS efficiency, and the likelihood of home discharge. When results were analyzed based on the AFIM groups, striking results were seen in the lowest functional group (AFIM <40). In this group, FIM gain, LOS efficiency, and rate of home discharge were significantly greatest in the youngest age group and declined as age increased. In those with AFIM less than 40, the oldest group, aged more than 85, improved at only half the rate (LOS efficiency = 0.44) of those aged less than 55 (LOS efficiency = 0.85). In the less functionally impaired group (AFIM >80), there was no relationship between increasing age and any outcome variables. Results were mixed in the moderately functional group (AFIM 40–80). The authors concluded that for subjects with severe strokes as measured by lower functional admission scores, younger stroke survivors generally do better than older stroke survivors. For patients at a high functional level, age does not affect the degree of improvement (31).

Gender

An earlier review by Jongbloed reported that gender was not a predictor of stroke recovery (13). However, in later studies, gender has been reported to have an impact on functional recovery after stroke. Compared to men, women stroke survivors have lower functional recovery at three months after discharge from rehabilitation (32,33) and at six months after stroke (34,35). Data from the Registry of the Canadian Stroke Network showed that at 6 months, when compared to men, women experienced a less favorable outcome as measured by the Stroke Impact Scale-16; they had longer lengths of stay and higher rates of institutional care (34). Data from China's National Stroke Registry also yielded similar findings, as researchers reporting that women demonstrated a significantly higher dependency rate at 12 months when compared to men (36).

A combined hospital-based registry from a number of centers in seven European countries also highlighted the role of gender in stroke recovery (32). After controlling for baseline and clinical factors, female sex proved to be a significant predictor of disability and handicap at three months after stroke (32). Similar findings were obtained from the Michigan state stroke registry, which reported that female stroke survivors had lower functional recovery and poorer quality of life three months after discharge; differences were not explained by the females' greater age of onset or other demographic and clinical characteristics (33).

Comorbidities

Greater medical complexity contributes to the severity of functional impairment following stroke and may impede recovery. Comorbidities may affect the outcome of stroke rehabilitation through a number of mechanisms, either by affecting response or participation in rehabilitation (36). In general, the presence of multiple comorbid diagnoses or increased comorbid burden is associated with decreased functional status, both at admission to and discharge from rehabilitation (37–39). Individuals with more than one comorbid diagnosis may experience less functional gain and more incomplete recovery than individuals with no comorbid burden. In a study of 1,020 adult rehabilitation patients, Stineman and colleagues (40) determined that the odds of full functional recovery decreased as the number of comorbid medical conditions increased (40). Similarly, within populations of individuals with stroke, increasing comorbid burden has been associated with reduced gain in functional ability over the course of rehabilitation as well as decreased rehabilitation efficiency (14,41). Furthermore, among community-dwelling stroke survivors, comorbid burden has been identified as a significant predictor of functional outcome (40) and has been associated with an increased risk of physical decline and new problems in ADLs (42).

Comorbidity indexes have been used in stroke outcome studies to adjust for patients' comorbid conditions. The Charlson Comorbidity Index, adjusted for ischemic stroke, has been validated for use in stroke outcome studies (43,44). Studies utilizing the Charlson Comorbidity Index have shown that higher comorbidities are associated with poorer stroke outcomes (43,45–47). Logistic regression adjusting for initial stroke severity showed that those patients with a high Charlson Comorbidity Index had a 36% increased chance of having a poor outcome at discharge, with every 1-point increase in the index resulting in a 15% increase in the odds of a poor outcome (43). Multivariate analyses have found that coronary heart disease and diabetes (45,46), as well as atrial fibrillation (46), were associated with poorer outcome as reflected by modified Rankin Score at three to four months after stroke. In a long-term population-based study, diabetes mellitus was also noted to be a significant negative predictor of functional outcome over a course of five years (48).

There is an association between age and comorbid burden such that elderly individuals tend to experience an increasing number of comorbidities (38,39). Hence, the presence of multiple comorbidities is not uncommon in the stroke population (42,49). Rigler et al. (42) reported that, in a sample of community-dwelling stroke survivors, only 6% were free from comorbid conditions, whereas more than 40% had three or more comorbid conditions (42). Even though comorbid burden may be an important modifier in the prediction

of future functional status, it appears not to be as important as either age or initial/baseline functional status (42,49).

Stroke Characteristics

Lesion Size and Site

The cerebral cortex undergoes functional and structural reorganization for weeks and months following injury, with compensatory changes extending up to six months in more severe strokes (8). Animals with induced small strokes experienced functional and structural recovery occurring spontaneously for weeks to months after stroke (50,51). Underlying neural changes appear to be related to surrounding intact brain regions taking over the lost function. Animals with larger lesions show much less return of function, and the function that returns may take weeks or months to stabilize (52,53). Compensatory movements may play an important role here, with activation and reorganization occurring in more distant cortical areas (53). Kolb suggested that the differences between recovery from small and larger strokes are related to the mechanisms of neural recovery (53). For smaller strokes, the mode of recovery is most likely related to changes in the remaining intact motor cortex, whereas for larger lesions, changes in related, but more distant, cortical regions facilitate compensatory behavior that improves with practice (53).

Lesion volume is believed to be an important parameter reflecting the extent of the pathological condition, and thus may serve as a predictor of the severity of neurological impairments such as paresis and functional outcomes such as ADL dependency after a stroke (55). Lesion volume, whether assessed during initial hours of symptom onset by diffusion-weighted imaging or assessed at a later time point by T2 or FLAIR, was noted to be an important predictor of outcome after ischemic stroke (56).

However, different stroke locations lead to different deficits and may confound the relationship between lesion volume and outcome (55–57). Even small lesions, particularly within the subcortical white matter and brainstem, may produce a disproportionate degree of impairment (56,57). Deep white-matter lesions involving major tracts can produce greater clinical deficits than superficial cortical lesions with a comparable volume. The site of stroke must be considered, as it will impact the outcome regardless of size (56,57).

Laterality of Lesion

Right-sided hemispheric strokes have been associated with a poorer functional outcome, as determined by the Barthel index (BI), when compared to a left-sided stroke (48). Lesion site has also been shown to influence FIM change: patients with bilateral and right-sided strokes do worse than patients with left-sided strokes (14). Right hemispheric stroke survivors also had lower FIM efficiency scores than left-sided stroke survivors (14). Right-sided lesions are associated with potentially more disabling cognitive disorders, such as USN and visuospatial perceptual disorders, which likely accounts for the difference (14).

Occurrence: First-Ever Stroke Versus Recurrent Stroke

A previous stroke has been identified as a significant adverse predictor of functional recovery in patients with stroke (13,58). Subjects with ischemic stroke enrolled in the Management of Atherothrombosis with Clopidogrel in High Risk Patients (MATCH) study underwent a long-term prospective assessment of modified Rankin Scale (mRS) score at baseline, 1, 3, 6, 12, and 18 months. The authors studied the evolution of the proportion of stroke survivors switching from functionally dependent (defined as mRS score 3–5) to functionally independent (defined as mRS score of 0–2). The rate of functional recovery was greatest within the first 6 months but continued in some patients for up to 18 months. At 18 months, stroke survivors who had a first-ever ischemic stroke demonstrated a greater rate of recovery compared to those with a previous history of ischemic stroke (58).

The Copenhagen Stroke Study on stroke recurrence showed that the mortality rate for subjects with recurrent stroke was almost double that compared to subjects with first-ever stroke (59). Upon completion of rehabilitation, the Scandinavian Stroke Scale (SSS) was administered to reflect neurologic recovery, whereas the BI was used to reflect functional recovery. Among the stroke survivors, both neurologic and functional outcomes and the speed of recovery were almost similar (59). When compared to stroke survivors with ipsilateral recurrence, stroke survivors with recurrence contralateral to their first stroke had significantly more severe functional disability after completion of rehabilitation despite having comparable neurologic recovery. The discrepancy in functional recovery implies that there is decreased ability to compensate using the contralateral hemisphere in stroke survivors with contralateral stroke recurrence (59).

Stroke Type

Approximately 10% to 15% of all strokes are the result of an intracerebral hemorrhage (ICH) (60,61). Paolucci et al. (60) matched hemorrhagic and ischemic stroke patients on the basis of initial stroke severity (same Canadian Neurological Scale [CNS]), baseline disability (same BI) score, age, sex, and time interval between stroke onset to rehabilitation admission. A trend toward better BI at discharge was observed in hemorrhagic compared with ischemic etiology. In addition, there was a bigger proportion of high responders of BI (defined as patients whose BI score was higher than the mean BI score) in the hemorrhagic compared to the ischemic group. The probability of achieving higher therapeutic response on the BI was 2.5 times more in the hemorrhagic compared to the ischemic group (60). The authors attributed these greater gains in hemorrhagic strokes to better neurological recovery associated with resolving brain compression (60).

Kelly et al. (61) demonstrated that stroke survivors with ICH made significant greater recovery than those with cerebral infarction. Upon admission to rehabilitation, total

admission FIM was, on average, lower in stroke survivors with ICH when compared to those with ischemic stroke. However, there was no significant difference in total discharge FIM score between the two groups (61). During rehabilitation stay, stroke survivors with ICH significantly gained more FIM points compared to those with ischemic stroke. When stratified by initial severity, stroke survivors with ICH who had the most severe strokes had greater functional improvement than those with cerebral infarction of similar severity (61). Katrak et al. (62) reported on a prospectively maintained database of all stroke survivors admitted to a rehabilitation unit during a 9.5-year period; 718 consecutive stroke admissions (589 ischemic, 129 hemorrhagic strokes) were included in the study. Outcome measures (FIM gain, FIM efficiency, Motor Assessment Scale change), gait velocity, and discharge destination were compared between the two groups. Stroke survivors with ICH were more severely disabled on admission but by discharge there was no difference in the mean FIM scores between groups. However, the ICH group made significantly greater gains on their FIM scores, leading to a higher FIM efficiency in hemorrhagic compared to ischemic strokes. After adjusting for admission FIM, LOS, age, and days from stroke onset to rehabilitation admission, it was found that stroke survivors with ICH obtained a better functional outcome than those with ischemic stroke (62).

Jørgensen et al. (63) found that stroke type (ischemic vs. hemorrhagic) did not influence mortality, the time course of neurologic recovery, neurologic outcome, or the time course of recovery from disability (63). Poorer outcome among stroke survivors with ICH was found to be a consequence of greater initial stroke severity (63).

Stroke Severity

The most important predictor of stroke recovery is initial stroke severity as determined by clinically based scales. As a general rule, the severity of the initial deficit following stroke is inversely proportional to the prognosis for recovery (2,3). Numerous scales have been used to denote the degree of stroke severity, both for global and for impairment-specific contexts. Examples of scales commonly used to reflect global severity are the SSS (2,3,50), National Institute of Health Stroke Scale (NIHSS) (48), CNS (33), and admission FIM (14). Examples of impairment-specific scales used are the Motricity Index and the Fugl-Meyer Assessment for sensorimotor impairment after stroke (64,65).

Global Stroke Severity

In the Copenhagen Stroke Study, stroke severity was reported using the Scandinavian Neurological Stroke Scale (SSS), which evaluates the degree of neurological impairment. The time to maximal neurological recovery was achieved sooner among those who had a milder severity stroke (66): 95% of stroke survivors with mild strokes reached their maximal neurologic recovery within 6 weeks. For stroke survivors with moderate, severe, and very severe strokes, 95% of the group had achieved their maximal recovery within 10, 13, and 15 weeks respectively (66). Maximal neurologic recovery occurred, on average, two weeks earlier than marginal functional recovery (2,3). Among surviving stroke survivors, the best neurologic recovery occurred within 4.5 weeks in 80% of the stroke survivors, whereas best ADL function was achieved by 6 weeks. For 95% of the patients, best neurologic recovery was reached by 11 weeks and best ADL function within 12.5 weeks (2,3). The specific timeline for neurologic and functional disability recovery is presented in Tables 40.2 and 40.3.

Subscales of global severity scores have also been reported to be strong outcome predictors. A systematic review by Veerbek et al. (67) found that the severity of neurological deficits based on upper-limb subscores of the NIHSS and CNS were found to be a strong predictor of better ADL outcome beyond three months after stroke (67). Based on the motor subscale of SSS, Jørgensen et al. (2) reported that the best walking function was reached within 4 weeks for stroke survivors with mild paresis of the affected lower extremity, 6 weeks for those with moderate paresis, and 11 weeks for those with severe paralysis (2).

Impairment-Specific Severity

Motor Impairment. Motor impairment has been identified as a predictor of discharge outcome including mobility and ADLs (41,68,69). Recovery of the upper limb is a major concern for many stroke survivors. A systematic review and

TABLE 40.2 Impairment and Neurologic Recovery of Stroke Patients in the Copenhagen Stroke Study

CATEGORY (SSS)	ADMISSION[a]	DISCHARGE[a]	SURVIVAL (%)	WEEKS TO 80% BEST RECOVERY[b]	WEEKS TO 95% BEST RECOVERY[b]
Very severe (0–14)	19%	4%	38	10	13 (11.6–14.4)
Severe (15–29)	14%	7%	67	9	15 (13–17)
Moderate (30–44)	26%	11%	89	5.5	10.5 (9.5–11.5)
Mild (45–58)	41%	78%	97	2.5	6.5 (5.4–7.6)

[a]Percentage patient distribution on admission, grouped by stroke severity subgroups, as measured by SSS (scores range from 0–58 points).
[b]Neurologic recovery as measured by Scandinavian Stroke Scale.

TABLE 40.3 Disability and Outcome of Stroke Patients in the Copenhagen Stroke Study

CATEGORY (BI)	DISCHARGE[a]	SURVIVAL (%)	WEEKS TO 80% BEST RECOVERY[b]	WEEKS TO 95% BEST RECOVERY[b]
Very severe (0–20)	14%	50	11	17 (15–19)
Severe (25–45)	6%	92	15	16 (13.5–18.5)
Moderate (50–70)	8%	97	6	9 (7.5–10.5)
Mild (75–95)	26%	98	2.5	5 (4–6)
No (100)	46%			

[a]Percentage patient distribution on discharge, grouped by stroke severity subgroups, as measured by BI.
[b]Functional recovery as measured by BI.

meta-analysis by Coupar et al. (70) demonstrated that the most important predictive factor of upper-limb recovery following stroke was the initial severity of upper-limb motor impairment and upper-limb function. In addition, motor- and somatosensory-evoked potentials (neurophysiologic measures of corticospinal and spinothalamic tracts) were also consistently identified as being strongly associated with upper-limb recovery following stroke (70). Muscle strength of the paretic upper limb, including shoulder abduction, elbow flexion, and finger extension as measured by the Motricity Index, as well as two-point discrimination, were noted to be the best predictors of dextrous hand function recovery at six months (71).

In a prospective study by Smania et al. (72), three outcome measures (Nine Hole Peg Test, Fugl-Meyer Arm subtest, Motricity Index) evaluating upper-limb function were assessed at 7, 14, 30, 90, and 180 days after stroke. Four potential predictors of recovery, which included active finger extension, shoulder abduction, shoulder shrug, and hand movement scale, were assessed. Active finger extension was found to be a strong predictor of short-, medium-, and long-term poststroke recovery (72). Houwink et al. (73) found that patients with minimal shoulder abduction and upper motor control of the paretic limb upon admission to rehabilitation had a reasonably good chance of regaining some hand capacity, whereas patients without proximal arm control had a poor prognosis for regaining hand capacity (73).

Recent studies have focused on determining if outcome after stroke can be accurately predicted in the early phase, while a patient is still in a hospital acute stroke unit, using clinical parameters (63,64). As part of the early prediction of outcome after stroke (EPOS) study, Nijland et al. (63) attempted to determine if upper limb function using the Arm Reach Action Test (ARAT) at 6 months after stroke can be predicted using clinical parameters within 72 hours after stroke onset. The results demonstrated that stroke survivors with some finger extension and shoulder abduction on day 2 after stroke onset had a 98% probability of achieving some degree of dexterity at 6 months, in contrast to only 25% of those who did not show similar voluntary motor control. In addition, 60% of stroke survivors with finger extension within 72 hours had regained full recovery of upper-limb function according to ARAT score at 6 months. This suggests that the functional recovery of the hemiplegic arm at 6 months can be predicted within 72 hours after stroke onset using 2 simple bedside examinations, namely active finger extension and shoulder abduction (63).

In the EPOS study, Verbeek et al. (64) attempted to predict the likelihood of regaining independent gait in nonambulant stroke survivors within 72 hours of stroke onset. They found that nonambulant patients who regained sitting balance and some voluntary movement of the hip, knee, and/or ankle within the first 72 hours after stroke had about a 98% chance of regaining independent gait within 6 months (64). In contrast, those who were unable to sit independently for 30 seconds and could not contract the paretic lower limb within the first 72 hours after stroke had a 27% probability of achieving independent gait (64).

Trunk balance and severity of motor impairment have also been identified as significant predictors of ambulatory outcome (74,75). Verheyden et al. (75) examined the predictive ability of the trunk impairment scale (TIS) and its static sitting balance, dynamic sitting balance, and coordination subscales to predict the Barthel Score at six months after stroke. Participants were first assessed upon admission to rehabilitation (median time since stroke onset of 20 days) and at 6 months. The best predictors of BI score at six months were the total TIS and static sitting balance subscale score on admission (75).

Mood Disorders. Poststroke depression (PSD) is a frequent consequence of stroke, with reported frequency ranging from 20% to 65%, depending on the selection of stroke survivors and time elapsed after stroke. In general, depression identified acutely or within the first three months following stroke has an adverse effect on both functional status and physical recovery in both the short (76–78) and long term (76,79,80). Pohjaasvaara et al. (76) evaluated the effect of depression at 3 months on functional outcome at 15 months following stroke. Results showed that stroke survivors with depression (Beck's Depression Inventory score ≥10) and major depression (*DSM-III-R* major depressive disorders, bipolar disorders with depressed episodes, organic depressive disorder and *DSM-IV* dementia with depressive mood) demonstrated

higher dependence on the BI score and poorer functional outcome (Rankin Scale > II) at 15 months after stroke when compared to nondepressed stroke survivors (76). In a logistic regression analysis, depression at 3 months correlated with poor functional outcome (Rankin Scale > II) at 15 months, with an odds ratio of 2.5 (76). In this study, depression was an independent and powerful predictor of poor long-term functional outcome after stroke (76).

However, the presence of depression does not preclude recovery, and over the course of rehabilitation, stroke survivors with depression may experience significant improvements, although functional ability may remain at a lower level despite rehabilitation interventions (81,82). Physical impairment and poststroke depression appear to interact with each other, and each influences the recovery of the other. Reports on the contribution of physical impairments to the development of poststroke depression vary from a low 5% to 15% (83) to a high of 48% (84). Van de Port et al. (85) published the results of a prospective cohort study, which demonstrated that mobility decline was experienced by 21% of participants between 1 and 3 years after stroke (85). Significant predictors of this decline in mobility status were level of activity, cognitive problems, fatigue, and depression. Given that the relationship between depression and physical impairment may be reciprocal, depression may contribute to deteriorations in mobility that may, in turn, contribute to increased feelings of depression. Because depression is a treatable condition that affects both function and functional recovery, it should be taken into account in the evaluation and treatment of all stroke survivors (77). Early recognition and treatment of depression may optimize rehabilitation potential and reduce significant human and financial costs associated with poststroke functional impairment (77).

Anxiety also can occur following a stroke. Follow-up findings of the Collaborative Evaluation of Rehabilitation in Stroke across Europe (CERISE) project showed that approximately 40% of the subjects initially classified as being anxious or depressed remained so at 6-month follow-up. The severity of anxiety and depression increased significantly between six months and five years (86). Hama et al. (87,88) highlighted that neuropsychiatric consequences after a stroke can also include apathy, defined as reduced motivation or lack of initiative. Depression and apathy often coexist. The apathetic state after a stroke may prevent stroke survivors from engaging in rehabilitation programs, resulting in delayed physical and social recovery (87,88). In a study designed to examine the effect of depression or apathy on functional recovery after stroke, Hama et al. (87) found that when compared to depression, apathy was more frequently associated with poorer functional abilities and more likely to interact with the recovery process (87).

Cognition. It has been suggested that higher-order cognitive abilities, such as abstract thinking, judgment, short-term verbal memory, comprehension, and orientation, are important predictors of the stroke survivor's functional status at discharge (89–91). Reduced cognition has been associated with a decreased ability to perform ADLs, with poorer physical functioning at discharge and a greater likelihood of mortality within one year of discharge (91–97). Zinn et al. (98) reported fewer discharges home among stroke patients with cognitive impairment than among cognitively intact patients (98).

Although the presence of cognitive impairment may be associated with decreased ADL function, it has been demonstrated that it is not a significant predictor of ADL function at six months after stroke (98). Instrumental ADL (IADL) function may be more severely impacted by the presence of cognitive impairment. At six months after stroke, the presence of cognitive impairment was associated with and predictive of decreased IADL function (98). Similarly, Mok et al. (99) determined that higher levels of cognitive impairment after stroke were associated with greater deficits in IADL function and greater levels of prestroke cognitive decline (99). Identified predictors of IADL performance were stroke severity, executive dysfunction, age, and prestroke cognitive decline (94).

Early poststroke cognition approximately 2 to 3 weeks after hospital admission was found to be a significant and independent predictor of functional outcome at 13 months as determined by the mRS (100). Within the domain of cognition, executive function appears to be the most robust cognitive predictor of poor functional recovery after stroke. Stroke survivors with executive dysfunction had a seven-fold greater likelihood of remaining functionally dependent at one year (101).

Aphasia has also been reported as a predictor of both functional and social outcomes after stroke (102). Compared to stroke survivors without aphasia, those with aphasia had lower motor FIM and cognitive FIM scores both upon admission to rehabilitation and at discharge. FIM effectiveness (defined as proportion of potential improvement achieved during rehabilitation) for both motor and cognitive scores was also poorer in patients with aphasia (102). Multivariate regression analysis demonstrated aphasia to be a predictor of the final score of the motor and cognitive FIM and discharge destination (102).

USN has been highlighted specifically as an important and independent predictor of poor functional recovery after stroke (103). The presence of USN has been shown to affect functional recovery and has been consistently associated with slower functional progress during rehabilitation, lower motor FIM efficiency scores, longer LOS, and reduced ADL and mobility performance (103–108). Monaco et al. (109) examined the relationship between the severity of USN and the functional recovery in ADLs after a right hemispheric stroke. USN severity was assessed at a median of 19 days after stroke using the Behavioral Inattention Test (BIT). Both sections of the BIT, the conventional section (BITC) and the unconventional/behavioral section (BITB), were administered and analyzed separately. BITC consists of six written subtests, and BITB consists of nine behavioral-task subtests. After adjusting for potential confounders, significant positive associations were noted between both sections of BIT scores

and FIM scores, FIM efficiency, and FIM effectiveness. Overall, the USN emerged as a factor that negatively impacted functional recovery and contributed to an unfavorable overall rehabilitation outcome (109).

EXTRINSIC PREDICTIVE FACTORS FOR STROKE RECOVERY

The manner in which rehabilitation is provided may also predict functional recovery after a stroke. The important components of rehabilitation are timing to rehabilitation, therapy intensity, task specificity, and the rehabilitation setting. In addition, level of social support may also affect the overall outcome.

Service Delivery

Timing to Rehabilitation

Previous evidence suggests that the brain is not only able to reorganize but is, in fact, primed to do so early on after a stroke (52,110,111). Animal studies have demonstrated that if therapy is delayed for several weeks after stroke, dendritic arborization is markedly reduced. The concept of a detrimental effect with rehabilitation delay was best shown through the animal work of Biernaskie et al. (112). After small strokes were induced in rats, they were subjected to 5 weeks of rehabilitation (consisting of exposure to an enriched environment) beginning at days 5, 14, and 30 after stroke. A group of control rats received no rehabilitation and were placed in social housing. Rats receiving early (day 5) rehabilitation showed marked improvement in neurologic recovery. Rats beginning rehabilitation at day 14 showed moderate improvement, whereas rats starting rehabilitation at day 30 showed no greater improvement than the control animals. In addition, enriched rehabilitation provided very early after stroke (at day 5) resulted in an increased number of dendritic branches and greater complexity of layer V neurons when compared to those rats receiving rehabilitation at day 30 and to those exposed to social housing only (112). The authors concluded that the poststroke brain was more responsive to rehabilitation early in the poststroke period and that responsiveness declined linearly with time, to the point of being not effective when delayed (beginning at day 30 in rats), The clinical implications of this finding are apparent; rehabilitation will have the greatest impact during that early time window when the brain is primed for behavior-dependent changes or cortical reorganization (112).

Several clinical studies have supported the association between early admission to rehabilitation and improved functional outcomes and/or decreased length of rehabilitation hospital stay (113–116). Paolucci et al. (115) suggested that early initiation of rehabilitation after stroke may be a relevant prognostic factor of functional outcome (115). This is supported by reports based on both American (117,118) and Canadian (113) data, which suggest that early admission to rehabilitation, regardless of initial severity of disability, is associated with greater functional gain and shorter lengths of stay.

Date on moderate or severe strokes from the Post-Stroke Rehabilitation Outcome Project (PSROP) database, showed that the time of onset of stroke symptoms to rehabilitation admission was a significant predictor of total and motor FIM at discharge (117). Earlier initiation of rehabilitation was associated with better functional outcome, as reflected in higher total, motor, mobility, and ADL discharge FIM scores after controlling for confounding variables (118). The severely impaired group demonstrated the strongest relationship between early rehabilitation and improved functional outcome (118). Earlier rehabilitation admission was also associated with shorter LOS (118).

The impact of timing to rehabilitation on overall functional outcome was not limited to patients transferred from acute care to rehabilitation. A positive impact was also observed on severe strokes in the stroke intensive care unit (ICU) setting. Hu et al. (119) examined the effect of timing of initiation of rehabilitation in a stroke ICU with a multidisciplinary stroke care team. The stroke ICU patients in general have more neurological deficits (NIHSS >10), stroke in evolution, or unstable medical conditions requiring intensive care. For acute patients admitted to the stroke ICU, early initiation of rehabilitation predicted better functional outcome. After adjusting for stroke severity and age, patients who started earlier rehabilitation had higher BI scores at discharge. Commencing rehabilitation 1 day earlier in the stroke ICU resulted in an increase of the BI score by 0.65 points (119).

In tandem with the importance of early initiation of rehabilitation, there has been increasing interest in very early mobilization (VEM) after a stroke (120–124). VEM has been defined as any intervention delivered with the aim of reducing the time from stroke onset to first mobilization (first out-of-bed episode) and increasing the amount of out-of-bed physical activity (120). The AVERT (A Very Early Rehabilitation Trial) is a large multicentered trial emphasizing on VEM in stroke rehabilitation (121). The trial consists of three phases: Phase I involves collection of baseline data on current practice, Phase II is a trial protocol regarding feasibility and safety of VEM, and Phase III focuses on efficacy and cost-effectiveness of VEM (121–124). In AVERT II, safety and outcome of commencing VEM were studied in comparison to standard care (SC) (122). In the VEM group, mobilization was initiated within 24 hours of stroke symptom onset and continued daily for the first 14 days after stroke or until discharge, whichever was sooner (122–124).

Results in AVERT II trial showed that there was no significant difference in the number of deaths between groups (122). After adjusting for age, baseline NIHSS score, and premorbid mRS score, the odds of experiencing a good outcome were significantly higher at 12 months for the VEM group (122). AVERT II trials also demonstrated that no significant differences in complications were encountered at 3 months for either the VEM or the control groups (123). In addition, patients in the very early and intensive mobilization group

returned to walking significantly earlier than those on standard stroke unit care controls, with a median of 3.5 days (VEM) versus 7.0 days in standard control (124). Multivariable regression demonstrated that exposure to very early and intensive mobilization was independently associated with good functional outcome on the BI at 3 months and on the Rivermead Motor Assessment at 3 and 12 months (124).

Therapy Intensity

Animal and clinical studies have demonstrated that training or inpatient rehabilitation increases cortical representation with subsequent functional recovery, whereas lack of rehabilitation or training decreases cortical representation and delays recovery. Animals exposed to enriched environments after stroke have improved functional outcomes when compared with animals exposed to nonenriched environments (125). Socialization alone can improve stroke recovery in animals, with the mediating factor appearing to be increased activity. In animal studies, the key factors promoting neurologic recovery include increased activity and a complex and stimulating environment. Therefore, it follows that, if training and stimulation lead to increased cortical reorganization, neurologic recovery, and functional improvements, then more intensive therapy is likely to result in a greater degree of recovery and improved functional outcomes (125).

The intensity of rehabilitation therapies is often cited as an important factor associated with both specialized stroke rehabilitation and improved functional outcome. Evidences suggest that increased intensity of therapy is beneficial (127,128). Langhorne et al. (126) examined the effects of differing intensities of physical therapy and showed significant improvements in ADL and function, and reduction of impairments was seen with higher intensities of treatment (126). Kwakkel et al. (127) evaluated the benefits of augmented physical therapy, which involved assessments on various interventions including occupational (upper extremity), physiotherapy (lower extremity), leisure therapy, home care, and sensorimotor training (127). Augmented therapy was associated with statistically significant treatment effects for the outcomes of ADL and walking speed, although not for upper-extremity therapy assessed using the ARAT (127). A 16-hour increase in therapy time during the first 6 months following stroke was associated with a favorable outcome (127). Veerbek et al. (128) studied outcomes specifically related to gait and gait-related activities, with results suggesting that augmented therapy produces small to moderate effects in walking ability, walking speed, and extended ADLs (128). Wang et al. demonstrated that stroke survivors who received a total therapy time less than three hours per day had significantly lower total functional gain than those who received more than three hours (129). The daily treatment time of physical therapy, occupational therapy, and speech and language therapy was also significantly associated with corresponding subscale functional gains.

The amount of exercise in the first week after a stroke has been reported to be able to predict walking speed and unassisted walking (130). In a prospective cohort study, Scrivener et al. (130) examined the predictor variables of walking speed and unassisted walking in 191 stroke survivors with an average modified Rankin Score of 4.29 (SD 0.8). During the first week of admission, the number of exercise repetitions achieved ranged from 0 to 5,522 (median = 703). Multivariate analysis showed that a higher dose of lower-limb exercise repetitions in the first week predicted a faster walking velocity (130). In addition, the completion of more repetitions was associated with a quicker recovery of unassisted walking. Participants who completed the median number of repetitions (703 or more) achieved unassisted walking after a median of 9 days of therapy as compared to 30 days for those who did not reach 703 repetitions (130).

The total amount of time that a stroke survivor spends engaged in rehabilitation activities can vary considerably between units, institutions, and countries (131,132). De Wit et al. (132) observed differences in the amount of time patients spent in rehabilitation activities among four centers in four European countries (Belgium, UK, Switzerland, and Germany) (132). Patients from Germany spent a larger percentage of the day in therapy time (23.4%), whereas those from the United Kingdom spent the least (10.1%). Therapy time ranged from one hour per day in the United Kingdom to about three hours per day in Switzerland (132). A subsequent follow-up analysis to determine degree of recovery noted that motor and functional recovery was better in the German and Swiss centers, compared to the UK center, suggesting that higher therapy intensity is beneficial for recovery (132).

Despite the positive effects, reviews have found that intensity of therapy is only weakly correlated with improved functional outcome (133–137). A review by Teasell et al. (134) found evidence that greater intensity of physiotherapy and occupational therapy resulted in improved functional outcomes, although the overall beneficial effect was modest and not maintained over time (134). Chen et al. (135) examined the relationship between intensity of therapy and functional gains and found that, even though admission function, LOS, and therapy intensity collectively contributed to greater functional gains, LOS and therapy intensity did not always predict those gains (135). The effect of intensity on functional outcome showed weak evidence of dose–response relationship (136) and limited support in favor of greater intensity therapy (137). Page (138) argues that intensity of therapy has been overemphasized and that less intense (30–45 min/day) task-specific training regimens with the more affected limb can produce cortical reorganization and correlative, meaningful functional improvements (138).

Task Specificity

Task-specific practice to relearn a motor skill is considered to be a critical variable enhancing plastic changes in neural circuits (139). Repeated, task-specific practice during motor skill acquisition has been shown to increase dendritic growth,

synaptic strength and number, and/or neuronal activity in brain or spinal circuits, creating long-lasting alterations in motor performance (125). Repetitive task training involves active motor sequences performed repetitively within a single training session, aimed towards a specific functional goal (141). Repetitive task training therefore combines the elements of intensity and task-specificity in a more functional relevance approach (141).

Intensive rehabilitation paradigms that focus on participation in specific tasks in the early poststroke period may improve locomotor recovery more than traditional techniques (139). Gait training over ground or on treadmill with or without body weight support (BWS) has been shown to elicit significant improvements in meaningful clinical outcome measures such as gait speed, timed distance, balance, gait efficiency, peak treadmill speed, and peak metabolic capacity in patients at least four months after stroke (139). However, data from the Locomotor Experience Applied Post Stroke (LEAPS) study indicates that treadmill training with BWS was not superior to home-based physical therapy in improving walking, although both groups improved (140). In a systematic review by Langhorne (141), repetitive task training seemed to be beneficial for mobility during rising to stand. Cochrane systematic review and meta-analysis on repetitive task training showed that repetitive task training resulted in modest improvements across a range of lower-limb outcome measures but not of upper-limb measures (142).

Rehabilitation Setting

Interdisciplinary specialized stroke rehabilitation units are associated with better outcomes when compared to conventional multidisciplinary care. The benefit has been attributed, in part, to the provision of higher intensities of stroke rehabilitation therapies delivered by individual clinicians specializing in stroke care and working more as a team. Even with baseline similarities between groups, Kalra et al. (143) demonstrated that subjects who received care on a stroke unit two weeks following an acute stroke had higher median BI discharge scores, which were achieved in a shorter length of time, compared with patients who were rehabilitated on a general ward (143). The rate of change of median Barthel scores was higher among stroke unit patients with a gain of 2.2 points/week compared with 0.9 points/week (143). The Stroke Unit Trialists' Collaboration showed that stroke patients who receive organized inpatient care in a stroke unit are more likely to be alive, independent, and living at home one year after the stroke (144). The benefits were most apparent on units based in dedicated wards. In addition, there was no indication that organized stroke unit care resulted in longer hospital stay (144). Chan et al. demonstrated that at six months after stroke, stroke survivors who were admitted to an inpatient rehabilitation facility (IRF) during their course of rehabilitation had functional scores on the activity measure for post-acute care (AM-PAC) that were at least eight points higher (twice the minimally detectable change) than those who went to a nursing facility skilled in all three domains and in two of three functional domains compared with those who received home health/outpatient care, after controlling for age, functional status at acute care discharge, and total hours of rehabilitation (145).

Social Support

Family function and support have an influence on stroke outcomes, in that high levels of social support have been associated with faster and more extensive recovery of functional status after stroke (146,147). Glass et al. (147) noted significant differences in functional status based on degree of social support. Stroke survivors receiving high levels of support recover more rapidly and to a greater extent, even when the initial severity is relatively high (147). These authors concluded that social support may be an important prognostic factor in recovery from stroke and predict a more functional favorable outcome (147).

Jørgensen et al. (15) also highlighted that in a cohort of subjects with the most severe strokes from the Copenhagen Stroke Study trial, the existence of a spouse at home increased the relative chance of a good outcome by threefold independent of age, sex, stroke severity, and other factors. This was thought to reflect the importance of a good social network on outcomes in general (15). Bhogal et al. (148) reported moderate evidence that improved social support as an intervention improved outcomes. This has been confirmed by multiple nonrandomized studies that have looked at the association between social support and improved outcomes. Despite a lack of randomized trials, the evidence as a whole linking social support to improved outcomes is quite impressive. Emotional support, in particular, is correlated with better functional outcomes, although the impact may not be noticeable in the acute phase of the stroke (148).

SUMMARY

A stroke can be a devastating event, leaving the stroke survivor with impairments and disabilities that threaten his or her independence. Stroke survivors recover to varying degrees, with the extent of recovery dependent upon various intrinsic and extrinsic factors. The two most important intrinsic factors affecting stroke recovery are stroke severity and the age of the stroke survivor. Lesion volume and site, stroke type, stroke recurrence, medical comorbidities, mood disorders, and cognitive deficits can also influence recovery and outcome. In addition, extrinsic factors comprising rehabilitation service delivery and social support may alter the recovery process. Our increasing understanding of factors that contribute to cortical reorganization, gleaned through the animal model, including complex stimulating environments and high activity levels, have corollaries in the clinical realm. These include early admission to rehabilitation, intensity of therapies, and task-specific therapies, all of which have been associated with better recovery and outcome. Clearly, focused and intensive rehabilitation is essential to ensure maximal stroke recovery.

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41

Stroke Services: A Global Perspective

Peter Langhorne and Anthony George Rudd

GLOBAL BURDEN OF STROKE

Stroke is recognized as being a global problem. In high-income countries, it is the third most common cause of death after coronary heart disease and cancer and one of the most important causes of severe disability (1,2). There is a common misconception that stroke is predominantly a disease of high-income countries. However, a broader estimate of the global burden of disease (3) suggests that the top three causes of death globally are ischemic heart disease (7.2 million deaths), stroke (5.5 million), and lower respiratory diseases (3.9 million), out of a total of 56 million deaths. On a worldwide basis, the leading causes of disability-adjusted life years (DALY) are those that affect predominantly younger patients, such as perinatal conditions (7.1% of global DALY), lower respiratory infections (6.7%), and diarrheal diseases (4.7%). Ischemic heart disease and stroke rank sixth and seventh, respectively, as causes of global disease burden (3).

Despite a prolonged investment in efforts to identify effective drug therapies, we still lack a medical therapy that significantly lessens the burden of stroke across an unselected population. Acute treatment with aspirin can reduce death and disability to a modest extent (approximately one extra independent survivor per 100 patients treated) (4). Thrombolysis with tissue plasminogen activator is more potent, but is applicable to only a minority of patients (5). Therefore, for the foreseeable future, the greatest hope for reducing the burden of stroke will depend upon prevention measures and effective systems for managing stroke patients from acute care through rehabilitation (5).

Governments, in particular those responsible for providing health care, are increasingly aware of the impact that stroke has on the health of the population and the cost to the community. Stroke patients account for about 5% of all Health Service costs in the United Kingdom (6). Studies from other countries (e.g., Sweden, the United States, Canada, the Netherlands, and Japan) suggest that the financial burden may be even greater than in the United Kingdom, possibly because of greater health service expenditure (7–14). Furthermore, demographic changes are likely to cause increasing mortality and morbidity, particularly in the developing world (15,16).

This chapter focuses on the organization of services for people who have had a stroke. We concentrate on care in the hospital, but we also mention the early postdischarge period. The discussion emphasizes models of care targeted at a broad range of stroke patients rather than at those with specific problems (e.g., aphasia). It largely reflects models of care in the United Kingdom and other European countries but also mentions other regions, particularly Australia and Canada.

FACTORS INFLUENCING STROKE SERVICES

The overall aim of stroke services should be to deliver the care required by stroke patients and their families in the most efficient, effective, equitable, timely, and humane manner possible. These services may not always be exclusively stroke-specific; parts may be embedded in general (internal) medicine, geriatric medicine, neurology, or rehabilitation medicine services.

In an ideal world, our decisions about the delivery of stroke services would always be informed by robust evidence from randomized trials, and priority would be given to those aspects of care that have been proven to be effective. However, we must recognize that carrying out randomized trials of complex interventions such as stroke services is challenging (17). At present, relatively few clinical trials are available, especially in rehabilitation and recovery, and these trials can be difficult to interpret and generalize.

Several factors other than evidence of effectiveness or cost-effectiveness may shape stroke-service delivery and constrain the options available to clinicians and service planners. These include the following:

1. Local health care culture and economy. The existing approach to providing health care, and the way it is funded or reimbursed, will influence the way services are delivered. Developing a stroke service in the United States or Germany presents different challenges from doing so in Scandinavia or the United Kingdom.
2. Needs of different patient groups. Stroke presents a complex challenge to service planners, in that most patients require a common basic service, although a smaller number (for instance, those eligible for hyperacute interventions) may require more specialized services.

TABLE 41.1 Objectives and Common Service Solutions for Managing Patients With Stroke

OBJECTIVES	PROPOSED SERVICE OPTIONS
Specific acute medical and surgical treatment	Acute or comprehensive stroke units; stroke centers
Identification and assessment of patient problems	Acute or comprehensive stroke units
Secondary prevention of further vascular events	Acute or comprehensive stroke units
General care, including interventions to resolve problems (includes many aspects of rehabilitation)	Comprehensive or rehabilitation stroke units
Terminal care for patients who are unlikely to survive	Stroke units
Hospital discharge and reintegration into the community	Early supported discharge services; discharge planning
Continuing or long-term care for severely disabled patients	Therapy-based rehabilitation services; stroke liaison worker services; day hospital services
Follow-up to detect and manage late-onset problems	Chronic disease management; outpatient clinics

See Table 41.4 for some definitions of terms.

3. Views of patients and families. One of the common complaints from patients and caregivers is the discontinuity of services they receive (18,19), resulting in fragmentation of care and dissatisfaction with services.
4. Resources available. It is relatively easier to organize or reorganize a stroke service if the basic levels of staffing and investigation services are already available. For this reason, much of our discussion will be relevant mainly to well-resourced services in high-income countries. However, we recognize that there is an urgent need to develop affordable health care solutions for low- and middle-income countries.

EVIDENCE BASE FOR STROKE SERVICES

Before outlining the pattern of stroke services in different regions, and the evidence base underpinning them, we should provide some service terms and descriptions.

Comprehensive Stroke Service

We have used the term *comprehensive stroke service* to mean a stroke service that covers most of the needs of patients with stroke and is integrated in a way that provides a continuous patient journey—a "seamless service" (Table 41.1).

Organized Inpatient (Stroke-Unit) Care

Throughout most European countries (and, indeed, further afield), there is now widespread acceptance that stroke services in hospitals should be organized within stroke units (20,21). Much of the evidence comes from a systematic review of clinical trials that compared the outcomes for stroke patients cared for in a specialist stroke unit with the outcomes of those cared for in general wards. Patients managed in stroke units are more likely to survive, return home, and regain independence (Table 41.2). The units included in the systematic review were run by geriatricians, neurologists,

TABLE 41.2 Summary of Patient Outcomes in the Stroke-Unit Trials

	STROKE UNIT	CONVENTIONAL CARE	APPROXIMATE NUMBER OF OUTCOMES PER 100 ADMITTED
Home (independent)	44%	38%	5 (1, 8)
Home (dependent)	16%	16%	0 (–2, 3)
Institutional care	18%	20%	–2 (–5, 0)
Dead	22%	26%	–3 (–6, –1)

This table shows the proportion (%) of patients with various outcomes at the end of scheduled follow-up (median one year) in the randomized trials of stroke-unit care versus conventional care.
The absolute risk difference is the proportion of outcomes achieved (+) or avoided (–) with stroke-unit care. The next column is the number of outcomes achieved (+) or avoided (–) for every 100 patients cared for in a stroke unit, assuming the absolute risk of an outcome in the population is similar to that in the trials. These figures are based on data from 31 trials (6,900 patients).

Source: From Ref. (21). Stroke Unit Trialists' Collaboration. Organised inpatient (stroke unit) care for stroke. *Cochrane Database Syst Rev.* 2007;(4):CD000197.

general (internal) physicians, and rehabilitationists. Patients with mild, moderate, and severe strokes and of all age groups appear likely to benefit from stroke-unit care (20,21).

Although comprehensive stroke-unit care is a complex and multifaceted intervention, the key components are reasonably well described (22) and include all of the following (Table 41.3):

- Ward base—effective stroke units have usually been based in a distinct ward with dedicated nursing staff.
- Specialist staffing—they have been staffed with medical, nursing, and therapy staff with a specialist interest and expertise in stroke and/or rehabilitation.
- Multidisciplinary teamwork—they have always included good multidisciplinary communication (defined as a formal meeting of all staff at least once per week to plan the management of individual patients).
- Education and training—they have included programs of education and training for staff and provision of information for patients and caregivers.

Several consistent features of the process of care in stroke units have also been described (20,22). These typically do not depend on high-technology facilities, but include a systematic approach to care (Table 41.3) that incorporates the following:

- Careful assessment and monitoring of medical, nursing, and therapy needs
- Early active management, incorporating management of food and fluids, control of pyrexia, hypoxia, hyperglycemia, early mobilization, careful positioning and handling, and avoidance of urinary catheterization
- Ongoing multidisciplinary rehabilitation, with early goal setting, early involvement of caregivers in rehabilitation, and provision of information to patients and caregivers. This also includes early planning of discharge needs.

Many of these processes of care will come as no surprise to those experienced in stroke care, but audit studies raise concerns that many are not routinely provided (23).

Beyond describing the basic components of stroke-unit care, it is difficult to determine whether the effectiveness of the stroke units is a result of the total package of care or of particular components. Although the basic principles of stroke-unit care are reasonably well described, they have been delivered in a variety of ways, and the term *stroke unit* means different things to different people. Thus, it is important to define our terms (see Table 41.4).

TABLE 41.3 Characteristics of Comprehensive Stroke-Unit Care

Structure
- Geographically discrete ward
- Multidisciplinary staffing (nursing, medical, physiotherapy, occupational therapy, speech therapy, social work)
- Medical staff with specialist interest in stroke and rehabilitation
- Nursing staff with specialist interest in stroke and rehabilitation

Coordination of care
- Regular multidisciplinary team meetings (formal meeting of all staff once weekly, informal meetings 2–3 times per week)
- Close linking of nursing and multidisciplinary team care
- Educational programs for staff

Assessment and monitoring
- Rapid admission to stroke unit
- Medical history and examination
- Standard routine investigations (biochemistry, hematology, ECG, CT scanning)
- Further selective investigations (carotid Doppler ultrasound, echocardiogram, MRI scanning)
- Nursing assessments (vital signs, general care needs, swallow test, fluid balance, pressure areas, neurologic monitoring)
- Therapy assessments of impairments and disability

Early management
- Careful management of fluids/food
- Pyrexia management, paracetamol for pyrexia, antibiotic for suspected infection
- Hypoxia management; oxygen if hypoxia, drowsiness, or cardiorespiratory disease
- Glycemic management, insulin for hyperglycemia
- Careful positioning and handling
- Pressure-area care
- Avoidance of urinary catheterization if possible
- Early mobilization: up to sit, stand, and walk as soon as possible

Ongoing multidisciplinary rehabilitation
- Early goal setting
- Early involvement of caregivers in rehabilitation
- Provision of information to patients and caregivers

Discharge planning
- Early assessment of discharge needs
- Discharge plan involving patients and caregivers

Acute Stroke Unit

Acute refers to the policy of rapid admission of the stroke patient to the stroke unit. In some regions such as North America and Germany (and increasingly in the United Kingdom), there has been a pattern of admitting stroke patients to ward areas with facilities for intensive monitoring of physiological functions (cardiac, respiratory, and neurologic). Interventions are introduced to correct these abnormalities (e.g., raised intracranial pressure, systemic hypertension). Broadly speaking, two approaches have been described:

- Intensive care units, which can offer all monitoring (including intracranial monitoring) and life-support options (e.g., respiratory support).
- "Semi-intensive" units are similar to coronary-care units, where monitoring and intervention focus on physiological variables but not life support. More recently, these have also been termed *hyperacute stroke units*.

There have been three small clinical trials of semi-intensive units that have reported rather inconclusive findings.

Comprehensive Stroke Units

Perhaps the most successfully implemented model has been the comprehensive stroke unit, which admits patients for acute care and then provides at least a few weeks of reha-

TABLE 41.4 Classification of Different Forms of Organized Inpatient (Stroke-Unit) Care

TYPE	PHILOSOPHY OF CARE	PATIENT GROUP	MDT BASE	TIMING OF ADMISSION	TIMING OF DISCHARGE	TYPE OF CARE
Acute (intensive) stroke unit	Acute	Stroke	Ward	Acute (hours)	Early (3–7 days)	Acute medical and nursing care (with high staffing levels)
Acute (semi-intensive) stroke unit	Acute	Stroke	Ward	Acute (hours)	Early (3–7 days)	Acute medical and nursing care. Monitoring and management of physiological variables
Comprehensive stroke unit	Acute care and multidisciplinary rehabilitation	Stroke	Ward	Acute (hours)	Later (days–weeks); some referral to specialist rehabilitation	Acute medical and nursing care. Nonintensive management of physiological variables. Early active multidisciplinary rehabilitation
Rehabilitation stroke unit	Multidisciplinary rehabilitation	Stroke	Ward	Delayed (days)	Later (weeks)	Multidisciplinary rehabilitation
Mixed rehabilitation unit	Multidisciplinary rehabilitation	Stroke and other disabling illness	Ward	Early (hours–days)	Later (weeks)	Multidisciplinary rehabilitation
Mobile stroke team	Acute care and/or multidisciplinary rehabilitation	Stroke	Mobile (no ward) base	Early (hours–days)	Later (weeks)	Acute medical care and/or multidisciplinary rehabilitation. No specialist nursing input

This table summarizes, in broad terms, the characteristics of different types of stroke unit.
Abbreviation: MDT, multidisciplinary team.

bilitation. This approach, which is widespread in Norway and Sweden, is supported by several clinical trials included in the systematic review and results from a national stroke register in Sweden (24). A major advantage of this approach is that rehabilitation can start on the day of the stroke. In practice, although these units provide good care to most patients, it is common to refer some patients with ongoing, complex rehabilitation needs to other rehabilitation services.

Rehabilitation Stroke Units

Several trials have indicated benefit from rehabilitation units that admit patients a few days after stroke onset and continue rehabilitation for several weeks. These trials have inevitably examined a more select patient group, with patients who are stable enough for that environment and have ongoing rehabilitation needs (21).

Some trials also explored the impact of organizing stroke care within generic rehabilitation services (e.g., geriatric medicine or neurologic rehabilitation services); patients achieve better outcomes in mixed rehabilitation units than in general wards (21). Comparisons with stroke-specific units indicate a trend toward better outcomes in stroke-specific units, but the data are limited.

Mobile Stroke Teams

Overall, the trials in the meta-analysis indicated that a stroke team working across several general wards may improve aspects of the processes of care (e.g., access to specialist assessments) but cannot achieve patient outcomes as good as those of a team based in a stroke unit (25,26).

Transfer From Hospital to Community

One of the main areas of concern to patients, and perhaps even more so to caregivers, is the organization (or rather the lack of organization) of hospital discharge (18,19). A number of approaches have been attempted to reduce the stress of the transition from hospital to home:

- Providing adequate information and training to the caregivers while the patient is in the hospital; for example, inviting the caregivers to therapy sessions and involving them in the patient's care on the unit. However, trials of information provision and patient education do not provide clear evidence to guide practice.
- Programs for training caregivers to manage their new role have been tested in one moderately large randomized trial (27). This involved stroke-unit staff training caregivers about stroke and in practical caring skills. This approach was initially reported effective but not confirmed in a larger cluster randomized trial (28). However, most clinical guideline groups still recommend providing information and training for carers.
- Predischarge home visits with the patient and one or more members of the team to ensure that the home environment is tailored to the patient's needs. Although this is a well-established procedure in many centers, we could not identify any published clinical trials of such policies.
- Predischarge case conferences to allow the patient and caregiver to meet with the hospital-based team and any professionals who are to be involved in their care in the community, including clear guidelines about who to contact in the event of problems. Once again, this is a well-established approach for which we could not identify any clinical trials.

Early Supported Discharge Services

Early supported discharge (ESD) services aim to accelerate discharge home from the hospital but provide more continuity of rehabilitation in the home setting. To date, 14 randomized trials have tested this approach to care in a variety of settings around the world (29,30). Most were centered around a small, multidisciplinary team of physiotherapy, occupational therapy, nursing, and assistant staff—with input from medical, speech and language therapy, and social work professionals. These teams were either hospital based (and went out to the patient's home) or community based (and came into the hospital to recruit patients). All incorporated regular multidisciplinary team meetings to plan patient care. A typical pathway of care (30) is shown in Table 41.5. Typically, these services can reduce hospital stay by about one week and provide input in the patient's home for up to three months, but this has been shorter with handover to other community services (30).

Even when compared with high-quality care in a hospital-based stroke unit, an ESD team could not only accelerate the discharge procedure (with an average reduction in length of stay of eight days), but also could result in the patient having a greater chance of remaining at home and regaining independence. Overall, for every 100 patients randomized to early supported discharge services, an extra four remained at home and/or were independent at

TABLE 41.5 Typical Care Pathway in an Early Supported Discharge Service

- Early identification of eligible patients in hospital
- Early assessment by a "key worker" from the ESD team (an individual who supervises the care of the patient)
- Assessment of home needs through a home visit (with or without the patient present)
- Identification of recovery goals with the patient and caregivers
- Discharge home with very early input (within 24 hours) by members of the ESD team
- Continuing rehabilitation in the home setting (up to five days per week if necessary)
- Negotiated withdrawal of the team as recovery goals are achieved
- Multidisciplinary review of the patient's progress
- Planned discharge from the service with later follow-up and review

6 to 12 months after the stroke. Good results were most likely with a well-resourced, coordinated multidisciplinary supported discharge team and with patients who had mild to moderate stroke severity (30). There is a suggestion that such services may not work as well in more dispersed rural populations (31), but this requires confirmation. Overall, ESD services may be relevant to about half the stroke patients admitted to hospitals (30).

Economic analyses (29) indicate that the additional costs of community rehabilitation are more than outweighed by the savings in hospital bed days. In addition to the "harder" outcomes mentioned earlier, it is also noteworthy that patients and caregivers allocated to ESD services were more likely to report satisfaction with their services. Early supported discharge services appear to be an important component of a truly comprehensive stroke service and should particularly target patients with mild to moderately severe strokes.

Continuing Rehabilitation and Reintegration Into Normal Life

Even when stroke patients have received good care in hospital and around the discharge period, they may still have difficulty maintaining independence and reintegrating into normal life. At this stage of the patient's journey, services are often quite variable and may be completely nonexistent (32). This probably reflects the diversity of approaches in different countries, but also limits the evidence base indicating that effective interventions can really improve recovery. In general, two broad approaches have been tested in clinical trials:

- Therapy-based rehabilitation services (provided by physiotherapy, occupational therapy, or multidisciplinary staff and primarily aiming to increase activities in daily living). In practice, this might include a range of task-related interventions aiming to improve mobility, activities of daily living (ADLs), or specific tasks such as dressing. In a systematic review (33) of therapy-based rehabilitation services, therapy-based rehabilitation (when compared with no routine intervention) helped prevent stroke patients from deteriorating in their ability to carry out ADLs, and improved ADL scores. Therefore, even relatively late (several months) after stroke onset, patients may gain from input from a therapist. Less clear is the absolute benefit likely to be achieved and the cost-effectiveness of these services.
- Stroke liaison-worker services provided by stroke nurses, family support workers, or specialist social workers primarily aim to improve participation in normal living and quality of life (34). In practice, these have included a mix of interventions, which could deliver a program of rehabilitation or respond to identified problems. These services often involve approaching patients and families during hospital admission, when staff can provide information and education about stroke. Assistance is also available for input after discharge, particularly to identify problems or unmet needs and to develop customized solutions. At least 15 randomized trials have tested this type of service in the United Kingdom, Australia, the United States, and the Netherlands. Their impact on patient outcomes is modest (34), but some aspects do appear to be valued by patients and caregivers.

STROKE SERVICES IN DIFFERENT REGIONS

Having outlined some general principles, background research, and different approaches to providing stroke care, we can discuss in more detail the delivery of stroke services in various parts of the world, particularly in Europe.

The subsequent discussion is, of course, very general, and there will inevitably be many local exceptions. However, we aim to indicate the different approaches that have been adopted in different parts of the world (Table 41.6). For each section, we try to briefly mention the local health care economy, those medical specialties largely providing stroke-unit care, the types of stroke-unit care and coverage available (including issues of equity of access), and access to other services. Finally, we try to mention evidence of successful implementation of service components.

Scandinavia (Norway, Sweden, Denmark, Finland)

The Scandinavian countries have mature social democratic economies with largely publicly funded health services (24,35). The main medical specialties managing stroke in Norway, Sweden, and Denmark tend to have been general (internal) medicine and geriatric medicine, although neurologists also play an important role, particularly in Finland. The most common stroke-unit model has been the comprehensive stroke unit, which was developed and pioneered in Norway and Sweden, although more acute systems of care have evolved, particularly in Finland (36).

Recent surveys suggest that most hospitals (more than 90%) have stroke units, and the majority of patients (70%–80%) obtain access to stroke units during their hospital stay.

Evidence of successful service implementation comes from studies of the Swedish (24) and Finnish (36) stroke registries, which aimed to register all admitted stroke patients and follow them up after discharge from hospital. These publications indicate that admission to a hospital with a stroke unit is an independent predictor of good outcome such that stroke-unit admission is associated with fewer deaths and more patients returning home.

Scandinavian countries have also pioneered the development and evaluation of early supported discharge services (29). Such services are becoming more widespread, but current figures are unclear.

United Kingdom (England, Scotland, Wales, Northern Ireland)

The United Kingdom also has a largely publicly funded health service (23,37–39). Traditionally, stroke care has been provided in departments of geriatric medicine and

TABLE 41.6 Summary of Predominant Service Patterns in Different Regions

	SCANDINAVIA	UNITED KINGDOM	CONTINENTAL EUROPE	MEDITERRANEAN	AUSTRALIA AND NEW ZEALAND	CANADA	DEVELOPING WORLD
Health care economy	Public health services	Public health services	Mixed health economies	Mixed health economies	Mixed	Mixed	Variety
Specialties providing stroke-unit care	General medicine, geriatric medicine, neurology	Geriatric medicine, general medicine	Neurology, rehabilitation medicine	Neurology, general (internal) medicine	Neurology, rehabilitation medicine	Neurology, rehabilitation medicine	Variety
Type of stroke-unit care and coverage	Comprehensive stroke-unit model	Rehabilitation (and comprehensive) units	Acute and rehabilitation units	Acute and rehabilitation units	Acute and rehabilitation units	Acute and rehabilitation units	Very limited access
Equity of access to stroke units	Most hospitals (> 90%) have stroke units, and most patients get access (70%–80%)	More than 90% of hospitals have stroke unit (80% of patients gain access)	Less than 50% access at last surveys	Variable access (10%–20%) in PROSIT register in Italy	Incomplete SU access Australia and New Zealand	Incomplete SU access	Very few stroke units established (usually in private hospitals)
Evidence of successful implementation of stroke units	Swedish RIKS—Stroke and Finnish register show effective implementation	National sentinel audit showed improved outcome with admission to stroke unit	Registries show some effective implementation (but also inequities of access)	PROSIT register (Italy) suggests that effective implementation is possible	Reports indicate improved outcomes with stroke-unit care	Register indicates improved outcome with SU care	Limited information available
Services after hospital discharge	Some early supported discharge services	Increasing community rehabilitation services	Variable	Limited	Variable	Variable	Very limited access

Abbreviation: SU, stroke unit.

general (internal) medicine (40), and stroke units have tended to evolve from rehabilitation services. Some specialist rehabilitation services (e.g., for younger adults) are provided by rehabilitation medicine physicians.

Relatively little attention was paid to stroke in the United Kingdom until the publication of the King's Fund Consensus Conference (1988). This highlighted the many deficiencies in the services provided for stroke patients (19). Since then, stroke has moved up in the political agenda. These changes have led to a substantial interest in stroke in general, and in stroke services in particular. Over the past few years, an increasing amount of research has been implemented to determine the best and most cost-effective ways of providing care for stroke patients.

In the most recent audits of services in England and Wales (38), 100% of hospitals reported having a stroke unit, and more than 80% of patients gained access to a unit during their admission. In earlier research with the National Sentinel Audit (23), admission to a stroke unit was an independent predictor of better survival, with an odds ratio of death of 0.75 among those admitted to a stroke unit. Recent data from Scotland show similar patterns (40,41).

Supported discharge services provided by community teams are becoming more widely available, with up to 66% of hospitals in the United Kingdom having access to early supported discharge in the latest national audit (38,40).

West Continental Europe (France, Germany, Austria, Switzerland, the Netherlands)

This group of countries tends to have mixed health care economies with a mixture of public funding and private insurance (42–45). Traditionally, the acute phase of stroke care tends to be provided in neurology services (and sometimes geriatric medicine services for older stroke patients), with rehabilitation medicine providing the main rehabilitation services. In neurology departments, acute units (intensive care or semi-intensive care units) appear to predominate. After the acute illness, rehabilitation services tend to be provided in rehabilitation stroke units. Some publications (46) have suggested incomplete access for stroke patients in Germany, but this appears to vary from region to region.

Studies of stroke-unit registries (45) suggest effective implementation but also some reduction in access for older patients.

Mediterranean Europe (Spain, Portugal, Italy, Greece)

This group of countries also has mixed health care economies, with a mixture of public funding and insurance (47,48). Once again, the acute management of stroke frequently occurs in departments of neurology and sometimes general (internal) medicine. In many neurology departments, acute semi-intensive units have been adopted, as well as rehabilitation services based in rehabilitation units. Studies from Italy (48) suggest variable access to stroke-unit care, but improved outcomes where implementation has taken place (49).

Eastern Europe (Poland, the Czech Republic, Hungary, Russia, Baltic States)

Many of these countries have undergone a rapid economic transition, with health services moving from a publicly funded model to a more mixed economy (50,51). Traditionally, stroke services have often been provided in departments of neurology. Organized (stroke-unit) care has been developed in Poland and Hungary (50,51) but appears less well established in other areas. Postdischarge services appear to be quite variable (52).

Australia and New Zealand

The structures of health care in Australia and New Zealand originally developed from a United Kingdom model of service. However, in recent years, both countries have developed a more mixed health care economy.

Much of acute stroke care in Australia is carried out in departments of neurology, with more of a mixed picture in New Zealand. Rehabilitation is frequently provided by rehabilitation medicine specialists or in departments of geriatric medicine. In Australia, there have been concerns about the limited provision of stroke-unit care, and several promising initiatives have been implemented in Australia to develop stroke units in both acute settings and rehabilitation units (53). A recent report from New Zealand (54) indicated limited access to stroke-unit care.

Canada

The Canadian health care economy is based on a national health insurance system. Traditional stroke care has been provided by a range of specialties, predominantly neurology, rehabilitation medicine, and general (internal) medicine. Stroke-unit care has been available in an increasing number of hospitals (55), and is linked to better outcomes. A variety of postdischarge services exist, which appear variable in nature.

Low- and Middle-Income Countries (Especially Africa, Asia, South America)

It is recognized that low- and middle-income countries have some of the highest stroke mortality rates, accounting for two-thirds of stroke deaths worldwide (3). There appears to be a lack of organized stroke-unit care and rehabilitation services in these nations (56), although there is some evidence that stroke units may be effective in these less well-resourced settings (57). Some excellent services do exist, but frequently with poor access for the majority of the population. The authors concluded that there is a need to develop basic organized stroke-unit care in low- and middle-income countries (57).

CONCLUSIONS AND CHALLENGES

The challenges facing high-income countries clearly differ from those of low- and middle-income regions. Scandinavian countries appear to be facing the challenge of maintaining established standards through clinical guidelines and national quality registries. In the United Kingdom, there has been strategic investment to improve acute services and a widening of access to services. In western continental Europe, issues have been raised around the cost and the equity of access to services, and we have seen an expansion of stroke-unit care and may see the adoption of a less-intensive model of acute stroke care. In the Mediterranean region, there has been underdevelopment of specialist stroke services, and it is expected that strategic investment may be required. In low- and middle-income countries, the major challenge is determining how to provide stroke services that are effective, affordable, tailored to local needs, and available to the majority of people who need such services.

Research Frontiers

The value of the stroke-unit model of care is clearly demonstrated. Future studies should explore the impact of different components of the stroke-unit "package" (e.g., early mobilization). In particular, we need to identify simple, widely applicable inventions that could be applied in low-resource settings in low- and middle-income countries. Effective ways of improving discharge procedures, reintegrating to normal life, and relieving caregiver burden also require identification.

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42

Postacute Rehabilitation Care and Patient Triage

Anne Deutsch and M. Elizabeth Sandel

Health care delivery in the United States involves a patchwork of private and public (government) insurance and financing with service delivery that is provided by a mix of for-profit, not-for-profit, and government-owned entities. Following the acute care hospital stay in the United States, patients with stroke may continue to receive rehabilitation services from one or more postacute care (PAC) providers, which includes inpatient rehabilitation facilities (IRFs), skilled nursing facilities (SNFs), home health agencies (HHAs), long-term care hospitals (LTCHs), and outpatient therapy providers. This chapter describes the structure and trends of PAC in the United States and includes an overview of each of these types of providers, including the provider definition and characteristics, the provider payment system, and, where available, patient characteristics and quality data. Clinical and nonclinical (e.g., insurance) factors associated with PAC utilization are described, and the chapter ends by discussing current issues facing PAC providers and efforts to reform the delivery of health care services in the United States.

PAC PROVIDERS

Following the implementation of the acute care prospective payment system (PPS) in 1983, acute care lengths of stays (LOS) decreased and PAC utilization increased (1,2). The number of PAC providers increased dramatically in response to shorter acute care stays. Between 1985 and 1996, the number of IRFs increased from 454 to 1031; the number of SNFs increased from 6725 to 14,548; the number of HHAs rose from 5983 to 9808; and the number of LTCHs increased from 86 to 183 (3,4). As shown in Figure 42.1, Medicare payments to these four types of PAC providers continue to grow and were estimated to be $63.5 billion in 2011 (4). Although each type of PAC provider generally offers a unique mix of services from physicians, nurses, therapists, and other clinicians, there is overlap of some or all services across IRFs, SNFs, HHAs, LTCHs, and outpatient therapy providers.

Inpatient Rehabilitation Facilities

IRFs, including both distinct-part units within acute care hospitals and freestanding rehabilitation hospitals, provide intensive (i.e., 3 hours of therapy at least 5 days a week or an average of at least 15 hours per week) interdisciplinary therapy services, including physical, occupational, and speech therapy, rehabilitation nursing, and close medical supervision to patients recovering from a major injury, illness, or surgery. Patients admitted to IRFs must be able to tolerate and benefit from three hours of therapy from physical therapy (PT), occupational therapy (OT), speech–language pathology (SLP) or prosthetics/orthotics services (5).

There were approximately 359,000 Medicare beneficiary IRF stays in 2010, and total Medicare payments that year were $6.32 billion (4). There are approximately 1,179 IRFs (2010), of which 80% are units and 20% are freestanding facilities. About one-quarter of IRFs are for-profit entities, whereas 62% are not-for-profit and 13% are government owned. Most (83%) IRFs are located in urban settings and 17% are in rural locations (4).

After the Medicare program determined that IRFs would not be included in the acute care diagnosis-related group payment system, a set of criteria was developed to define an IRF. One criterion that has been used by the Medicare program to define an IRF is the current "60% rule" (for many years this was the "75% rule"). The 60% rule requires that at least 60% of a facility's patients have one of thirteen specified medical conditions that typically require an intensive rehabilitation program (6). Stroke is listed as one of the thirteen conditions and is now the most common primary impairment condition for patients admitted to an IRF (4). Many patients with stroke who are admitted to IRFs are 65 years of age or older, and thus Medicare, the federal insurance program for the elderly and disabled, accounts for approximately 69% of payments for IRF care (7).

Since 2010, the Medicare program has required documentation in the medical record that the decision to admit the patient was reasonable and necessary (8). Documentation includes a preadmission screening, postadmission physician evaluation, individualized plan of care, physician orders, and the IRF patient assessment instrument (IRF-PAI). Medicare's criteria for an IRF admission to be considered reasonable and necessary are: multiple therapy disciplines, intensive level of rehabilitation services, the ability to participate in an intensive therapy program, physician supervision, and an interdisciplinary team approach to care. Measurable, practical

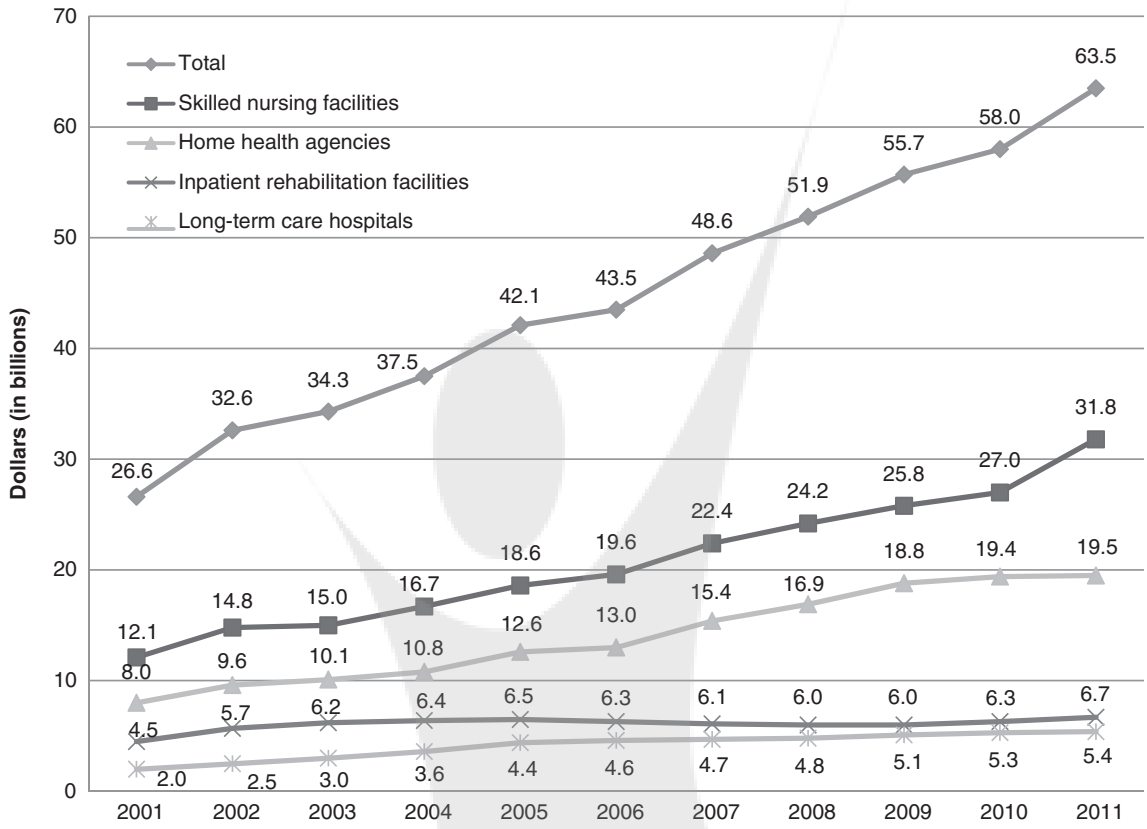

FIGURE 42.1 Medicare postacute care spending, 2001–2011.

Source: From Refs. (3,4).

improvement in the patient's functional status is expected within a predetermined and reasonable period of time, and for most patients, the goal of IRF care is the patient's safe return home or to a community-based setting (8).

Medicare has paid IRFs under a PPS since 2002 (9). The IRF PPS provides facilities with a predetermined per-discharge payment for each Medicare fee-for-service patient based on the patient's clinical condition, with adjustments for facility-specific factors. Under the IRF PPS, each patient is assigned into one of 92 case-mix groups (CMGs), of which 10 are for patients with stroke, based on data reported on the IRF-PAI. A patient's CMG assignment is based on the primary impairment, admission motor and cognitive functional status, and age. Additional adjustments are made based on the presence of certain comorbidities. Five of the CMGs are for patients with stays of three days or fewer (short-stay outliers) and patients who die. A transfer rule adjusts payments for patients who are transferred to another facility and have a length of stay that is less than the mean stay for patients with the same CMG/comorbidity tier group (10).

The Medicare payment is calculated based on the CMG/comorbidity group; each has a relative weight that reflects the average costliness of patients in that group relative to the average IRF Medicare patient. A base payment amount, which is updated each year, is multiplied by the CMG/comorbidity (case mix) relative weight and the labor portion (70% in 2012) is adjusted with the facility wage index. Additional adjustments are made for rural IRFs, the share of low-income patients, teaching status, and high-cost outliers (10).

Medicare began an IRF Quality Reporting Program in 2012, with two quality metrics: (a) National Health Safety Network (NHSN) Catheter Associated Urinary Tract Infection Outcome Measure, and (b) percentage of patients with new or worsened pressure ulcers (11). Failure to submit required quality data for these two quality metrics will result in a 2% point reduction to the annual increase factor for payments made for discharges occurring during the next federal fiscal year (fiscal year 2014 for October to December 2012 data) (8). The IRF Quality Reporting Program is expected to evolve in the future to include additional quality metrics and public reporting of quality metric data for each IRF.

Patient data from IRFs have been submitted to national databases, which provide national-level statistics on patient characteristics and IRF hospitalization stay information as well as patient outcomes. Over time, patients with stroke have been admitted to IRFs sooner after the stroke, the rehabilitation stays have been shorter, and a lower proportion

of patients were discharged home from the IRF (12,13). Between 1990 and 2008, the mean onset time decreased from 22.0 days to 10.6 days. Admission functional status, as measured by Total FIM® score (score range 18–126, with higher score indicating more independence), decreased from 62.1 in 1990 to 55.1 in 2008. In 1990, the average IRF LOS for patients with stroke was 32.0 days. By 2002, with the introduction of the IRF PPS, the average IRF LOS was 19.6, and in 2008, it was 16.5 days. Discharge functional status, as measured by Total FIM® score, decreased from 87.0 in 1990 to 79.8 in 2008. The percent of patients discharged to the community decreased from 76% in 1990 to 70% in 2008, as more patients are transferred back to acute care (10% in 2008) and to other PAC providers (7.5% in 2008) (12,13).

Skilled Nursing Facilities

SNFs, the most numerous of the PAC providers, are certified by the Centers for Medicare and Medicaid Services to provide skilled nursing and therapy services. SNFs provide varying levels of physical, occupational, and speech therapy services; sufficient staff to provide 24-hour nursing services; and a physician who supervises patient care and is available 24 hours a day on an emergency basis. The patient must be seen by a physician at least once every 30 days during the first 90 days after admission, and then at least once every 60 days thereafter. In addition, respiratory therapy, dietary, pharmaceutical, dental, and medical social services are available (5).

Following the implementation of acute care PPS in the 1980s, some SNFs began providing more therapy services and admitted patients with greater needs for therapy, nursing, physician, and other services, and some referred to their programs as "subacute rehabilitation" (14). *Subacute care* is not formally recognized by the CMS, and the term has been used to describe many different types of programs. One description of *subacute rehabilitation* is: "A level of rehabilitative care designed to meet the needs of patients who medically and physically are too frail to participate in the rigors of a conventional inpatient physical rehabilitation program (i.e., 3 hours or more of daily therapy). Subacute rehabilitation also may be appropriate for patients who do not require intense multiple therapies but may have medical comorbidities and complicating factors that require the medical supervision of a physiatrist, geriatrician, or internist. Physicians usually visit patients in subacute rehabilitation two or three times per week, based on medical necessity" (15, p. 60).

There are approximately 15,207 SNFs (2010 data), of which 94% are freestanding nursing homes and 6% are units colocated in acute care hospitals or rehabilitation hospitals. Freestanding nursing homes often provide SNF services and long-term care services. Most SNFs (70%) are for-profit entities, 25% are not-for-profit entities, and 5% are government owned; 30% are situated in a rural location. Medicare payments to SNFs in 2010 totaled $27 billion (4).

Medicare beneficiaries must have a hospital stay of 3 or more days in the 30 days prior to the SNF stay to be eligible for covered SNF services. The Medicare SNF benefit covers skilled nursing care, rehabilitation services, and other goods and services up to 100 days per episode of illness, if the patient meets established criteria (5,16).

Since 1998, Medicare has paid SNFs under a per diem PPS, which covers all operating and capital costs, with certain high-cost, low-probability ancillary services paid separately. PPS payments are determined based on a patient's clinical and utilization data with adjustments for facility-level factors (16). The patient classification system for reimbursement under the SNF-PPS is the resource utilization groups (RUGs IV), and clinical data are from the patient assessment instrument called the Minimum Data Set (MDS) 3.0. Patients are assigned into one of the sixty-six RUGs (i.e., payment groups) based on the number of minutes of therapy (physical, occupational, or speech) that the patient received or will receive, an activities of daily living index based on the patient's ability to perform four activities (eating, toileting, bed mobility, and transferring), the need for certain services (e.g., specialized feeding, respiratory therapy), and the presence of certain conditions (e.g., pneumonia, dehydration). Facility-level adjustments are made for rural locations and geographic differences in labor costs (16).

Although there is no required minimum amount of therapy for patients in SNFs, when patients receive more therapy, Medicare payments are higher under the SNF PPS. Therefore, several studies have examined the amount and intensity of therapy provided to SNF patients and whether a higher intensity of therapy is associated with better patient outcomes. For example, Wodchis et al. (17) found that the amount of rehabilitation therapy was associated with a higher likelihood of patients being discharged to the community, and the relation between "dose" and outcome was strongest for patients for whom discharge to the community was uncertain or not expected. Jette et al. (18) found that higher-intensity PT and OT was associated with greater odds of improving at least one stage of mobility and self-care function for patients with stroke. Higher OT intensity and higher SLP intensity were associated with greater odds of improving by at least one stage of social cognition function. Higher SLP intensity was associated with greater odds of improving by at least one stage of mobility function.

The Medicare program has been reporting quality metric data and other information about nursing homes, including short-stay residents, on its website (www.medicare.gov/NursingHomeCompare) for several years. The current set of quality metrics includes a mix of outcome measures and process measures: (a) the percentage of short-stay residents who self-report moderate to severe pain; (b) the percentage of short-stay residents with pressure ulcers that are new or worsened; (c) the percentage of short-stay residents assessed and given, appropriately, the seasonal influenza vaccine; (d) the percentage of short-stay residents assessed and given, when appropriate, the pneumococcal vaccine; and (e) the percentage of short-stay residents who are newly administered antipsychotic medications. Additional information about facilities provided on the site includes health

inspection results and complaints, nursing home staffing (number of registered nurses, licensed practical or vocational nurses, physical therapists, and nursing assistants), and penalties levied against the nursing home. Five-star quality ratings on the website provide a summary rating that considers health inspections, quality metrics, and hours of care provided per resident by staff performing nursing care tasks.

Home Health Agencies

HHAs provide therapy, skilled nursing services, and other services to patients in their homes. Medicare beneficiaries eligible for medical services at home are generally restricted to their home (i.e., homebound) and need skilled care, either nursing care or therapy, on a part-time or intermittent basis (5). In 2011, Medicare implemented a requirement for a face-to-face encounter prior to the certification of the patient's eligibility for Medicare home health care. The certifying physician, the physician in the acute or PAC provider, or a nonphysician practitioner must have a face-to-face encounter with the patient no more than 90 days prior to the start of care or within 30 days after the start of care (5).

There are 11,815 HHAs (2010), and the average number of home health visits per user was 36.2. Approximately 3.4 million Medicare beneficiaries used HHA services in 2010, and total Medicare payments that year were $19.6 billion (4).

The CMS has been paying HHAs under a PPS since 2000. The PPS predetermined payment rate for each 60-day HHA episode is determined based on the admission assessment and service use with adjustments for geographic wages based on the patient's location, high-cost outliers, and nonroutine medical supplies (e.g., wound care products) (19). If fewer than 5 visits occur during the 60-day episode (short-stay outlier), the payment is determined per visit and per visit type instead of by the episode payment method. Patients with 5 or more visits during an episode are assigned into one of 153 Home Health Resource Groups (HHRGs) based on clinical, functional status, and service utilization data reported on the patient assessment instrument called the Outcome and Assessment Instrument (OASIS) data set. The clinical data include the primary home care diagnosis, intravenous/infusion or parenteral/enteral therapy, vision limitation, wound or lesion, multiple pressure ulcers, most problematic pressure ulcer stage, stasis ulcer status, surgical wound status, shortness of breath, bowel incontinence, and injectable drug use; these data are used to assign a patient into a low, moderate, or high clinical score group. The functional status data include dressing, bathing, toileting, transferring, and locomotion and are grouped into low, moderate, and high functional groups. Service utilization data includes the number of therapy visits and the episode's timing in a sequence of episodes (19).

The Medicare payment is calculated based on the HHRG relative weight that reflects the average costliness of patients in that HHRG relative to the average home health Medicare patient. A base payment amount is adjusted for the HHRG group (case mix) and the labor portion (77% in 2012) is adjusted with the wage index. A 3% add-on payment is provided for providers in rural locations for services provided from April 2010 through 2015 (19).

HHAs have many quality metrics that are publicly reported on the Home Health Compare website (http://medicare.gov/homehealthcompare) including: (a) how often the home health team began patient care in a timely manner; (b) how often the home health team taught patients (or their family caregivers) about their drugs; (c) how often patients got better at taking their drugs correctly by mouth; (d) how often the home health team checked patients' risk of falling; (e) how often the home health team checked patients for depression; (f) how often the home health team checked patients for pain; (g) how often the home health team treated their patients' pain; (h) how often patients had less pain when moving around; (i) how often the home health team checked patients for the risk of developing pressure sores; (j) how often the home health team included treatments to prevent pressure sores in the plan of care; (k) how often the home health team took doctor-ordered action to prevent pressure sores; (l) how often patients got better at walking or moving around; (m) how often patients got better at getting in and out of bed; (n) how often patients got better at bathing; (o) how often patients receiving home health care needed any urgent, unplanned care in the hospital emergency room without being admitted to the hospital; and (p) how often home health patients had to be admitted to the hospital. Other quality metrics focus on assessing whether patients received an influenza vaccine and a pneumococcal vaccine, treatment of heart failure symptoms for patients with heart failure, improvement in breathing for patients with breathing problems, wound improvement or healing after an operation, and foot care for individuals with diabetes.

Long-Term Care Hospitals

LTCHs are certified as hospitals and provide medical, nursing, respiratory therapy, PT, OT, and SLP services to patients with clinically complex problems who need hospital-level care for an extended period of time. Many LTCH patients are considered critically ill; common medical issues include ventilator dependence and multiorgan failure (5). LTCHs have the highest average nurse staffing hours per patient day among PAC providers, often have respiratory therapy services 24 hours a day and 7 days a week, and physicians have daily contact with LTCH patients. Medicare defines LTCHs as hospitals that have an average LOS of 25 days or longer (5). Several proposals have been put forth to redefine LTCHs based on patients' clinical characteristics, but there has not been agreement on a definition.

Medicare is the payer for approximately two-thirds of LTCH care. The number of LTCHs has grown from 86 in 1985 (3) to 406 in 2007 (4), and this rapid growth of LTCHs led to a moratorium in 2007 that is due to expire in 2017. Many of the newer LTCHs are located within acute care hospitals, and are considered a "hospital within a hospital" with their own administration and medical, nursing, and therapy staff. More

than two-thirds (75.9%) of LTCHs are for-profit entities, 19.2% are not-for-profit entities, and 4.9% are government-owned. Most (61.7%) are freestanding hospitals and 93.4% are situated in an urban location. In 2010, approximately 118,300 Medicare beneficiaries had almost 134,700 LTCH stays costing Medicare $5.3 billion (5).

Medicare implemented a per-discharge LTCH PPS in 2002, which covers all operating and capital costs, with the exception of certain high-cost ancillary services, which are paid separately (20). The patient classification system for the LTCH PPS is the Medicare severity long-term care diagnosis related groups (MS-LTC-DRGs). Data from the hospital bill (e.g., diagnosis, procedures, patient characteristics) are used to assign each patient into one of the MS-LTC-DRGs (payment groups). The MS-LTC-DRGs are the same groupings used in the acute care inpatient PPS, but the LTCH relative weights for each group are different from the acute care weights. The relative weight assigned to each MS-LTC-DRG reflects the average costliness of patients in that group relative to the average LTCH Medicare patient. A base payment amount, which is updated each year, is multiplied by the MS-LTC-DRG (case mix) relative weight. Payments are adjusted for short-stay and high-cost outliers, indirect medical education, and geographic differences in labor costs. A transfer policy discourages transfers between an LTCH and a colocated acute care hospital and transfers to colocated SNFs, IRFs, and psychiatric facilities. A "25% rule" reduces payments for LTCHs that exceed the established percentage thresholds for patients admitted from certain referring hospitals during a cost-reporting period. Less strict thresholds are applied to LTCHs located within hospitals and satellites in rural areas or in urban areas where the facility is the only LTCH and there is a dominant acute care hospital (5,20).

Medicare began an LTCH Quality Reporting Program in 2012, with three quality metrics: (a) NHSN CAUTI Outcome Measure; (b) percent of patients with new or worsened pressure ulcers; and (c) NHSN Central Line-Associated Bloodstream Infection Outcome Measure. Failure to submit required quality data for these three quality metrics will result in a 2% point reduction to the annual increase factor for payments made for discharges occurring during the next federal fiscal year (fiscal year 2014 for 2012 data) (21). Beginning in 2014, data collection begins for two additional measures: (a) the percent of patients who were assessed and appropriately given the seasonal influenza vaccine and (b) influenza vaccination coverage among health care personnel (21). With the implementation of the LTCH Quality Reporting Program, LTCHs began collecting standardized clinical assessment data on a patient assessment instrument called the LTCH CARE data set. The LTCH Quality Reporting Program is expected to evolve to include additional quality metrics and public reporting of quality metric data for each LTCH.

Outpatient Therapy Services

Outpatient therapy services include PT, OT, and SLP services and are provided in a variety of settings: private practices, hospital outpatient departments, outpatient rehabilitation facilities, comprehensive outpatient rehabilitation facilities (CORFs), and, in some circumstances, at home. For Medicare fee-for-service beneficiaries, Part B of Medicare pays for outpatient services as well as therapy services for individuals who are nursing facility residents in nursing homes. Medicare covers outpatient therapy services if they are provided by a skilled professional, are appropriate and effective for the patient's condition, and are reasonable in terms of frequency and duration.

Medicare pays for outpatient therapy based on fees established in the physician fee schedule and services are classified and reported using the Healthcare Common Procedure Coding System. Payments are based on relative weights called *relative value units* (22). There are annual spending limits, referred to as *therapy caps*, on Medicare payments for outpatient therapy services. One spending limit applies to PT and SLP services and a separate limit applies to OT services. If additional services are considered reasonable and medically necessary, an exemption from the therapy caps may be requested. Research examining outpatient therapy alternatives is underway. Medicare spending on outpatient therapy services was approximately $5.7 billion in 2011, with almost three-quarters of therapy services attributed to PT (22).

UTILIZATION OF PAC SERVICES

Utilization of PAC services increased when acute care LOS decreased. The acute care LOS for patients with stroke decreased dramatically between 1989 and 1999, but not in the 10 years thereafter. The average length of stay was 10.2 days in 1989, 5.4 days in 1999, and 5.3 days in 2009 (23). Patients in the acute hospital with disabling strokes may be discharged to institutional settings or home, depending on a variety of factors such as severity of stroke; care needs (including need for continued hospitalization in a rehabilitation hospital setting); coexisting medical conditions; payment systems; availability of beds and caregivers; options within the geographic area; provider, patient, and family preferences; or cultural factors.

Population-based studies have documented significant differences in the percentages of patients who are discharged to each of the different types of PAC providers. An analysis of 2006 Medicare claims data showed that among patients who were assigned to the Medicare severity diagnosis related groups intracranial hemorrhage or cerebral infarction, with comorbidities or without complications in acute care, 75.0% used PAC services. Of these patients, 37.0 were discharged to an IRF, 36.8% were discharged to an SNF, 17.3% were discharged to home with HHA services, 7.7% used outpatient services, and 1.2% were discharged to an LTCH (24). Studies have shown significant geographic variation in PAC utilization, however. One study found that IRF, SNF, and HHA care among Medicare stroke patients varied from 82.1% in Washington state to 59.1% in Oklahoma (25). In a more recent Medicare study, IRF utilization ranged from a high of

57% in Massachusetts to a low of 34% in Alaska; as IRF and SNF utilization tend to vary proportionally, the ratio of IRF to all inpatient care received across states varied from 22% in Connecticut to 59% in Nevada (26).

Patient characteristics that may play a role in decisions about PAC care include age, severity of stroke, burden of care, comorbid conditions requiring physician decision making or nursing care, and cognitive and physical capacity to participate in a therapeutic program of activity and exercise. Many studies have found that older patients are more likely to go to an SNF than an IRF (25–31). In one study, stroke patients treated in IRFs were more functionally independent on admission, had better cognitive function, and were more likely to have caregivers (32); however, in a recent study in another health system, IRF patients were more functionally impaired than patients in other PAC groups (28). Not unexpectedly, studies have found that living alone or being unmarried, widowed, or divorced, or being a woman increased the likelihood of discharge to SNF rather than IRF (32,33). Patients being discharged to home after an acute care stay tend to have shorter stays in the acute hospital and be less impaired at the time of acute care discharge (32,34).

Race and ethnicity may be a determinant of discharge destination or care trajectories for stroke patients, likely because of cofactors such as stroke severity, socioeconomic status, or availability of caregivers. Black patients, and those with low incomes, experience more severe strokes and a worse "trajectory of functional recovery" in the first year after the stroke (35–37). A Medicare sample analysis from 297 hospitals in 5 states showed more black patients than white patients receiving PT and OT services, but black patients had more motor deficits (36). A Los Angeles study of community-dwelling patients with stroke and other diagnoses found that minority populations, patients with less education, and the oldest patients were significantly less likely to use PT and OT outpatient services (38). Results of both a Maryland study and a California study suggested that black patients experiencing a stroke were more likely than white patients to go to an IRF (39,40). In the same California study, Asian patients were more likely to go to IRF as well (33). Hispanics and Asian populations have a greater incidence of hemorrhagic stroke, and hemorrhagic strokes are associated with greater degrees of functional impairment than ischemic strokes (40), and thus patients with these conditions may be more likely to go to an IRF (33). A study of stroke patients in the Veterans Administration system, however, found no racial differences in IRF care (41). Patient characteristics may not explain all of this variance, and cultural factors such as the availability of caregivers are a possible unstudied cofactor (33,42).

Different health service markets are likely drivers of some of these variations (43,44). Distance to IRF or SNF facilities in a geographic area also influence utilization and create variation in care (33,42). As SNFs are represented in greater numbers than IRFs in most areas of the country, the likelihood of patients going to an SNF is proportionally greater when geographic factors influence decisions. Choice of provider may be influenced by both provider and patient/family choices owing to these factors. One study found that SNF utilization increased as SNF bed availability increased (27). In the same study, 50% of stroke patients received care in an acute hospital with an SNF distinct-part unit, and nearly 38% received care in one with an IRF distinct-part unit. Having either type of unit increased the likelihood of patients being treated in that unit.

Payment systems also influence discharge destinations following acute care. Payment systems for PAC have undergone dramatic changes over the past few decades. The change to PPSs for PAC providers has had a major impact on utilization (45,46). For example, after PPS implementation in SNFs and HHAs in 2001, there was a 46% decrease in HHA utilization (number of episodes), whereas SNF care episodes increased by 28%, and those involving LTCH, IRF, or psychiatric inpatient care increased by 33%; episodes of SNF care followed by HHA care decreased by 13%; and those involving other trajectories increased by 17% (47). Another study of patients with stroke and other diagnoses showed substantial increases in the use of IRFs when the SNF PPS was being instituted (48). Copayment systems, more prevalent over the last decade, have also influenced patient and provider choices. One study found that patients with a second source of health insurance in addition to Medicare were more likely to use SNFs than HHAs (49).

The specialty of the physician may influence decisions about PAC selection. One study found that neurologists were more likely to discharge patients to IRFs (21.9%) as compared to internists (16%) or family practice physicians (13%). Conversely, family practice physicians and internists were more likely to discharge patients to SNFs (39.6% and 33.1%), compared with neurologists (22.2%) (50).

Triage of stroke patients from the acute care hospital to a PAC provider usually occurs with input from clinicians, patients, and families. Beginning in the 1980s, stroke guidelines have been developed by organizations and health systems in the United States and abroad that include decision-making criteria and care delivery processes (51–53), including care transitions and interdisciplinary care (54). The Joint Commission certification process for stroke centers also includes a requirement for assessment for rehabilitation (55). CARF, formerly known as the Commission on Accreditation of Rehabilitation Facilities, developed stroke program accreditation standards that include information for decision making about rehabilitation following discharge from an IRF (56).

Variation in utilization of PAC services by stroke patients is still incompletely explained. One study found that half to two-thirds of practice variation in utilization of rehabilitation services could not be explained by differences in patient characteristics and market conditions (43). As further changes in health care delivery systems take place, undoubtedly more changes in PAC utilization will also occur. Reimbursement for episodes of care rather than reimbursement based on each care setting, for example, will further drive changes in how care is delivered over time for patients with

stroke (57). Both in the United States and abroad, stroke care is being organized across the care continuum (58).

TRACKING OUTCOMES ACROSS PROVIDERS OF CARE

A number of studies have tracked functional outcomes of patients with a history of stroke over many months and even years. In a Framingham study several decades ago, researchers found that "significant recovery" occurred primarily during the first three months, with marginal gains made after that time point. In a Danish study, patients were assessed at the end of the rehabilitation program and then at six months. The researchers concluded that a reliable prognosis is possible by 12 weeks of stroke onset. Best ADL function was reached, for example, within 8.5 weeks for mild strokes and within 20 weeks for patients with severe strokes. In an Italian study, postdischarge outpatient rehabilitation, performed on 46.5% of the sample, was significantly and positively associated with functional improvement and absence of functional worsening in the year following discharge from the rehabilitation hospital. Age greater than or equal to 65 years and hemi-neglect were predictors of functional worsening at follow-up. In an Australian study, two-thirds had good functional outcome, 22.5% had cognitive impairment indicative of dementia, 20% had had a recurrent stroke, 15% were institutionalized, and almost 30% had symptoms suggesting depression at 5 years after stroke.

Transfers from one PAC provider to another have increased with the implementation of the PAC PPSs and reduced length of PAC stays. Most patients with moderate to severe strokes are treated by multiple providers over the months following a stroke. An analysis of all Medicare patients (all diagnoses) showed that among patients who were discharged from an acute care hospital to an IRF, only 12.3% did not use additional PAC services in the episode. More than a quarter (27.3) completed the episode with HHA care, 16.9% went from acute care to an IRF to outpatient, and 0.2% used LTCH services after the acute and IRF stay (59). In a recent study of stroke patients in an integrated health system, patients were followed for six months from one provider to the next. The most common pathways for patients whose first PAC provider was an SNF or IRF also included HHA and outpatient services, and some patients had PAC in every type of provider (HHA, outpatient, IRF, and SNF) (28,34).

The increase in utilization of multiple PAC providers makes utilization and outcome research difficult. The PAC PPSs and the quality reporting programs have been largely developed for each type of provider. Each type of provider collects clinical data, and much of the data covers similar concepts, but data are collected using different assessment items. Therefore, functional status data from the different PAC providers cannot be compared directly. This provider-based framework does not encourage or incentivize collaboration or accountability among providers in care placement decisions or quality measurement. Furthermore, no single provider is accountable for patient outcomes at the end of the episode. Efforts are underway to develop and test a standardized set of clinical items, including functional assessment items, to assess and track patients across the care continuum (28,34,60).

Under the current fee-for-service program, Medicare pays the PPS payment amount for each provider separately, so transferring a patient from one PAC provider to another means each provider receives a payment from the Medicare program. This may encourage utilization of multiple PAC providers, and raises concerns about added costs owing to duplication of services, overuse of services that do not benefit the patient, and poor coordination of services across multiple transitions, including provider-to-provider transitions and provide-to-home transitions.

The Agency for Health Care Policy and Research (AHRQ) defines care transition interventions for stroke in a report that included a systematic review of the literature (61). Although there was limited evidence for a benefit of these interventions in stroke populations (only for early supported discharge), further research using standard definitions was recommended. The categories are outlined in Table 42.1.

As new models of health care delivery evolve with changing incentives and reimbursement models, there will likely be collection of common assessment items and quality metrics within health systems to track outcomes after stroke. The new models of care will require sophisticated and well-defined care transition interventions, and clear roles

TABLE 42.1 Care Transitions Interventions (AHRQ)

Type 1: Predetermined integrated-care pathways, early supported discharge, extended stroke unit services, and rehabilitation coordination with community services, referral for subsequent subspecialty care, and follow-up (if it was part of discharge planning), and education of the patient and family prior to discharge
Type 2: Direct teaching by subspecialty trained nurses
Type 3: Following hospital discharge, community-based support of the patient and family provided through advanced practice nurse care managers, primary and specialty care medical practitioners, and multidisciplinary care teams (including doctors; nurses; social workers; and physical, occupational, and speech therapists), provided in person at the patient's home, by telephone, or at a clinical practice setting and patient and family education at the community level
Type 4: Chronic disease management

and responsibilities for care providers and other administrative staff within these systems (34). Electronic health records (EHRs) present opportunities for decision support and for tracking and measuring outcomes, if they are appropriately designed and staff are trained to utilize them effectively. Three outcome measures that are important to measure within and across the various PAC providers are readmissions to the acute hospital, function, and mortality.

Stroke patients are at high risk for hospital readmissions, and risk-standardized models are required to compare rates across time or across providers of care (62). Acute care hospitals are financially penalized for high readmission rates for patients with selected diagnoses, and stroke is likely to be one of those conditions identified in the future, according to an AHRQ report on the process of transitioning the care of patients from the hospital to the community (61). In the future, the report states, "Better management of patients' care will require management across multiple providers and settings. It will soon be expected that acute-care settings accept the responsibility to manage care transitions and avoid rehospitalizations" (p. 2). The report goes on to state, "These policies will increase the incentives for acute-care hospitals to develop effective transition of care programs and support integrated care. It will be important for health systems to develop and implement sustainable transition of care models in collaboration with primary care, other postacute health care systems (e.g., home health, rehabilitation centers, SNFs), community-based services, and patients and their families" (p. 2). In addition to the acute care readmission efforts, IRFs, SNFs, HHAs, and LTCHs are also expected to have readmission data publically reported and may be financially penalized for higher than expected unplanned readmission rates.

Several studies have examined outcomes for patients with stroke treated in IRFs and SNFs and found that IRF patients tended to have better outcomes at PAC discharge (30,60) or after discharge (31,63). Most recently, in one large population study funded by CMS, IRF patients with nervous system disorders, including stroke, achieved 32% better functional improvement in self-care than SNF patients, whereas HHA and LTCH patients' outcomes were not statistically different from those of SNF patients after controlling for patient acuity. Provider setting was not a significant predictor of change in mobility from admission to discharge in this study (60).

Few studies have measured outcomes in stroke populations across multiple types of PAC providers. In a recent study of patients with stroke who were treated in one integrated health system and followed across care settings over a six-month period, care in an IRF following discharge from the acute hospital was associated with greater functional outcome at six months when compared to SNFs and HHA care after controlling for age, functional status at acute care discharge, and total hours of rehabilitation, even though patients had more severe strokes in the IRF group (28). Studies with larger numbers of subjects will further the work in studying both utilization and outcomes for patients with a history of stroke.

FUTURE DIRECTIONS

Patients with stroke may receive PAC services from an IRF, SNF, HHA, LTCH, or outpatient provider. Increasingly, patients are receiving care in multiple PAC settings. Efforts are underway to move away from the current provider-centric health care delivery system that rewards volume (i.e., PAC-to-PAC transfers) toward a patient-centered system with a value-based purchasing program that includes incentives for quality and safety—measured with both process metrics and outcome metrics. Although the quality initiatives for each type of provider have largely been developed separately, there are efforts to align and harmonize the assessment items and quality metrics across PAC providers. The CMS Innovation Center has several initiatives and demonstrations underway, including the Bundled Payments for Care Improvement efforts and the Accountable Care Organizations initiatives (http://www.innovations.cms.gov/initiatives/index.html). It is not clear which models of care might be implemented beyond initial testing or how these models might evolve over time. It is challenging to identify delivery system reform that aligns incentives for all key stakeholders, including patients, providers, payers, and policy makers. However, there are opportunities to improve care management for patients discharged from acute care hospitals. There is a need for clinical integration between acute and PAC providers and between PAC providers. Key drivers of cross-provider clinical integration should include physicians participating in decision making and overseeing care across multiple services settings, availability of electronic health records and information technology for decision support, and transmission of information (i.e., interoperability) across sites of care (64).

The conclusions of a recent Institute of Medicine (IOM) Report suggest that there will be a much greater focus on PAC given the findings that if there were no variation in PAC spending, variation in Medicare costs would fall by 73% (65).

CONCLUSION

Major changes in PAC have taken place over the past several decades. Changes in the delivery of care and payment systems are occurring rapidly and will likely drive more integration of PAC and possibly result in less variation in care. Common systems of data collection and measurement of patient characteristics, structure, and processes of care, including staffing models, therapeutic interventions, and process and outcome measures, will provide the foundation for comparative effectiveness research in PAC.

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43

Rehabilitation of Children After Stroke

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Over the past two decades, there has been growing recognition of the incidence, severity, functional ramifications, and therefore, rehabilitation needs of pediatric stroke survivors. Although mortality related to stroke in the pediatric population appears to have lessened over the past 20 years (1), cerebrovascular disease remains one of the top 10 causes of death in children (2). Five to ten percent of all pediatric patients who suffer a stroke will expire (3,4), with the highest death rates encountered during the first year of life (2).

Stroke is now a well-recognized cause of chronic morbidity in children that interferes with the normal development of cognitive, gross and fine motor, communication, and psychosocial skills. Disability caused by pediatric stroke and its impact on a child's quality of life endures over a lifetime, typically lasting decades. The economic costs to society of childhood stroke in the acute phase and over the subsequent 5 to 10 years are substantial (5–7). Lifelong economic burden attributable to pediatric stroke on an individual basis is likely equivalent to that of stroke in an adult (6).

As a result, services must be provided over an extended period of time to address the deficits caused by stroke in this young population. Stroke recovery and rehabilitation in the perinatal/childhood population differ significantly from that in the adult population. In children, the profound disruption created by a stroke is often exacerbated secondary to impairment of development, psychological maturation, and, in some instances, physical growth. Although brain injury from a stroke is not progressive, the resultant deficits in neurological function almost always evolve over time commensurate with ongoing maturation of the central nervous system (CNS). Residual neurologic dysfunction is seen in the majority of pediatric stroke survivors. This chapter reviews epidemiology, clinical manifestations and diagnosis, outcomes, and acute management for all classifications of stroke in children, although the primary focus is on the subacute rehabilitation program, neurobiological mechanisms of stroke recovery, and novel therapeutic options to enhance stroke recovery.

Our common goal of improving rehabilitative therapies for young and old stroke patients will be greatly aided by a more profound understanding of the basic mechanisms of stroke recovery (8). Brain reorganization strategies following adult stroke are an important focus of research (9,10) and increasingly are being incorporated into new rehabilitative approaches. For pediatric stroke, a greater understanding of brain recovery should also translate into more meaningful and effective treatments that promote the best possible functional outcomes (11).

CATEGORIES AND EPIDEMIOLOGY OF PEDIATRIC STROKE

Types of Pediatric Stroke

In pediatrics, classification of stroke begins with determining when the event occurs. *Perinatal stroke* is defined as a cerebrovascular event that transpires between 28 weeks of gestation and 28 days of postnatal age. A subtype of perinatal stroke, labeled *presumed perinatal arterial ischemic stroke*, has also been described (12). This refers to infants who appear to be neurologically normal at birth and up through the first few months of life before developing signs of hemiparesis, most commonly in the form of an early hand preference (13); brain imaging studies on these infants demonstrate a prior lesion consistent with a perinatal, typically ischemic, stroke. *Childhood stroke* is defined as a cerebrovascular event that occurs between 29 days and 18 years of age. In addition to age at onset, stroke in the pediatric population can further be subdivided by the type of vascular involvement (arterial and/or sinovenous), the presence (thrombotic) or absence of a clot, and the predominant mechanism of injury (ischemic and/or hemorrhagic), although overlap is considerable. Ischemic stroke is either arterial (AIS) in origin or secondary to cerebral sinovenous thrombosis (CSVT). In AIS, occlusion may be associated with an arteriopathy or thromboembolism; the resultant focal infarction is localized to the vascular distribution of the artery. In contrast, CSVT is defined by thrombosis of the cerebral veins and/or dural venous sinuses. The thrombosis usually produces symptoms but may not result in parenchymal venous infarction; when present, the infarct may be ischemic or hemorrhagic. Over the past 30 to 40 years, the incidence of all forms of pediatric stroke appears to be increasing (14,15).

Pediatric Stroke Epidemiology

Historically, the incidence of all stroke subtypes in the pediatric population was thought to be 2 to 3 per 100,000 children (16,17). Although these findings are consistent with some recent studies (1,18), other data on pediatric stroke suggest a near-doubling from 2.8 to 5.4 per 100,000 in the years 1989–1999 (19). Higher incidence levels have also been reported in a population-based study from Europe (13 per 100,000) (20) and by Lynch (10.7 per 100,000) utilizing a National Hospital Discharge Survey (14). Even taking a conservative approach to the incidence of pediatric stroke (roughly 5–8/100,000 children/year), this figure makes stroke in older infants and children more common than pediatric brain malignancies (14). Despite the relatively large number of publications assessing the incidence rate of pediatric stroke, there remains confusion regarding the relative contributions of ischemic and hemorrhagic stroke to the total number. In some studies, ischemic injury predominates; in others, hemorrhagic stroke is more common; and in a third set, the rates are seemingly equivalent (1,14,16,17,20,21).

The increased frequency with which childhood strokes are being recognized relates predominantly to the development and greater availability of noninvasive and sensitive imaging techniques, most importantly magnetic resonance imaging (MRI). Diagnoses are being made earlier (22–26) and often under circumstances in which stroke previously might not have been a strong diagnostic consideration. Two notable examples are so-called silent cerebral infarcts (SCI) in patients with sickle cell disease (SCD) and perinatal stroke (presumed and overt). Ischemic stroke carries the highest risk in the neonatal period, where an incidence of 1:2500–4000 live births makes it a common cause of brain injury and resultant cerebral palsy. Another important factor contributing to the rise in pediatric stroke recognition is the lowering in mortality that has occurred in a wide spectrum of childhood diseases predisposing to stroke, such as pediatric cancers and congenital heart disease.

PEDIATRIC STROKE PATHOPHYSIOLOGY AND RISK FACTORS

Childhood AIS

It is incumbent upon clinicians to ascertain any and all causes of ischemic brain injury in a timely fashion, so as to inform potentially appropriate interventions (27–29) and predict the risk of stroke recurrence. Important information regarding risk factors for childhood stroke can be found in population-based studies and through large databases, most notably the International Pediatric Stroke Study (IPSS) group (29,30). However, potential etiologies for childhood AIS are numerous and there are frequently multiple risk factors in a single child. Despite thorough investigation, up to one-third of the cases of children with AIS are classified as idiopathic, that is, no cause can be uncovered. Although chronic diseases predispose to childhood AIS, nearly 50% of the cases occur in a previously healthy child (31). However, more than half of the pediatric patients will have two or more risk factors identified if properly evaluated, thus again emphasizing the need for thorough and overlapping assessments (29). The conditions that lead to stroke in adults, such as diabetes, high blood pressure, or atherosclerosis, are uncommon in children (32,33). For the pediatric patient, the variety of risk factors is expansive (34). There are, however, four major categories of risk factors: arteriopathy, SCD and other hematologic disorders, cardiac disease, and prothrombotic disorders (Table 43.1).

TABLE 43.1 Risk Factors for Pediatric Stroke

Childhood Arterial Ischemic Stroke
Arteriopathies—including "transient cerebral arteriopathy," craniocervical dissection, and moyamoya syndrome
Hematological—especially sickle cell disease
Cardiac—including congenital heart disorders (especially those with complex cyanotic anatomy) and catheterization procedures and bypass surgery
Prothrombotic—Factor V Leiden mutations, protein C deficiency, increased lipoprotein(a) levels, prothrombin G20210A mutations, lupus anticoagulant, and antiphospholipid antibodies
Hemorrhagic Stroke
Structural cerebrovascular anomalies—including AVM, vein of Galen malformation, congenital aneurysm, and cavernoma
Sickle cell disease
Tumor
Trauma
Childhood Cerebral Sinovenous Thrombosis (CSVT)
Head and neck infections—especially otitis media, mastoiditis, and sinusitis
Dehydration
Trauma
Prothrombotic—see above
Perinatal Stroke and CSVT
Cardiac disease
Acute systemic illness
Maternal prothrombotic and autoimmune disorders
Neonatal infections
Complications of labor and delivery
Pregnancy as a naturally occurring prothrombotic state

Arteriopathies

Cerebral arteriopathies have emerged as a leading cause of childhood AIS, being present in up to 50% of cases (27,28,30,31,35,36). In addition, these disorders typically result in a worse outcome and have an increased risk of stroke recurrence (22,28,37). Thus, detailed vascular imaging has become an increasingly important tool in the diagnosis of pediatric stroke (28,36,38,39). There are three most commonly identified forms of cerebral arteriopathies in childhood (40). The first is a relative common arteriopathy that occurs in otherwise healthy school-age children. Vascular studies typically

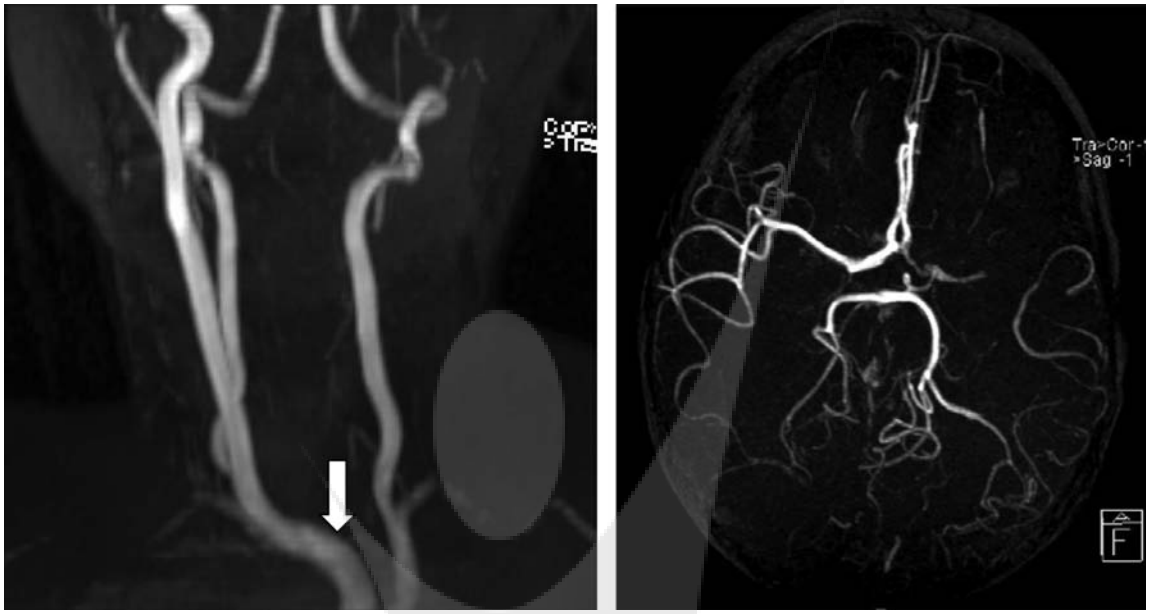

FIGURE 43.1 Occlusion of the left common carotid artery, just after the takeoff from the aortic arch (arrow) caused by a dissection, as seen on conventional angiogram on right and MRA on left.

reveal irregular narrowing or stenosis of an affected vessel wall within the distal internal carotid, proximal middle or anterior cerebral arteries, or some combination thereof. The resultant infarctions are within the lenticulostriate territory, producing unilateral basal ganglia injury. Initial descriptions were classified as "transient cerebral arteriopathy" (TCA) (35,41). It is now recognized that the vast majority are nonprogressive, although early follow-up with serial imaging may reveal increasing vessel narrowing followed by stabilization or lessening of stenosis after two to eight months. The specific etiology of TCA remains uncertain but includes infectious and inflammatory processes. Post- and parainfectious mechanisms have also been evoked in view of the similarity of TCA to postvaricella angiopathy. Indeed, data documenting the role of infection/inflammation in most forms of childhood stroke are accumulating rapidly (42).

The second type of pediatric arteriopathy is craniocervical dissection in either the carotid or posterior vertebrobasilar circulation (Figure 43.1). This dissection causes formation of a subintimal hematoma and represents up to 20% of childhood AIS, most commonly via a mechanism of artery-to-artery thromboembolism (43–45). In the pediatric population, extracranial dissection is three times more frequent than intracranial dissection (45). Dissection often is the result of mechanical distortion of the arterial wall, such as from trauma to the neck, spine, or retropharyngeal area or less overt insults, including exercise, contact sports, and the type of "minor trauma" that occurs on a daily basis in active children (44,45). As symptoms may not be expressed for up to 7 to 10 days following the precipitating event, determining an exact etiology often is a challenge. Finally, some preliminary studies have suggested that inherent differences in connective tissue structure, detectable on skin biopsy (but not physical examination) may predispose to arterial dissection (46,47). Regardless of the cause, a diagnosis of dissection is important, as the risk of recurrent stroke may be 20% or higher (43–45).

Moyamoya syndrome, the final common type of pediatric arteriopathy, is characterized by progressive occlusion typically of the distal internal carotid arteries bilaterally at the circle of Willis, resulting in the evolution of small collateral vessels; the syndrome produces the angiographic picture of a "puff of smoke" (48,49). In the United States, moyamoya as a syndrome is seen more commonly in SCD, trisomy 21, neurofibromatosis type 1, and postradiation vasculopathy, among others (49,50). Genetic causes of moyamoya have also been described, which may explain the prevalence of the idiopathic form in the Asian population (51).

Sickle Cell Disease

SCD is the most common hematological etiology of pediatric stroke. It has been estimated that children with SCD are 200 times more likely to experience an AIS compared to other children without sickle cell. About 12% of the pediatric SCD population will experience a clinically recognized cerebrovascular event, with an average age of onset being 7 to 8 years (52–54). In addition, roughly 25% of children with SCD, but without a history of an overt stroke, will have SCI detected on surveillance MRIs before 6 years of life (55) and up to 37% by age 14 (56). Risk factors for SCI include relatively high systolic blood pressure, low baseline hemoglobin, and male gender (57). Accumulatively, by age 14, almost 50% of SCD children will develop cerebrovascular complications, including vasculopathy/moyamoya, overt strokes, SCIs, or abnormal transcranial Doppler values (56).

Overt strokes are ischemic in roughly 75% and hemorrhagic in 25%, with the latter increasing above age 20 (58). Stroke is responsible for 10% of pediatric deaths in SCD (59).

AIS in SCD is secondary to two major pathophysiologic mechanisms. First, sickling in the small cerebral arteries distally causes thrombosis and occlusion, with resultant multifocal small infarcts typically within the deep white matter (60). In contrast, larger infarcts predominate in cortical areas within a defined vascular distribution or in watershed areas. These strokes often are related to progressive internal carotid vasculopathy consistent with moyamoya. The vasculopathy is hypothesized to be the result of chronic effects of increased carotid blood flow damaging endovascular surfaces, although proinflammatory genetic polymorphisms also may be operant in the evolution of vascular disease (58,61).

Over the last two decades, transcranial Doppler studies have noninvasively detected SCD patients with elevated flow rates (above 200 cm/s) who are therefore at high risk for stroke (62). It is now well accepted that in children with elevated TCD, regular transfusion therapy to lower hemoglobin S by 20% to 30% can significantly reduce (90% reduction) both the initial and recurrent stroke rates (56,62). Unfortunately, the risk of stroke returns following discontinuation of transfusions (63). A similar trial looking at children with SCI in the context of normal TCD values is nearing completion (64).

Cardiac Risk Factors

Abnormalities in cardiac structure and rhythm, ventricular and valvular function, and other factors common to cardiac disease such as altered blood viscosity and flow can generate both extra and intracardiac thrombi that may embolize to the cerebral circulation. Thus, heart disease is another major risk factor for pediatric AIS, present in up to 25% of stroke cases in infancy and childhood (27,31,65). In cases of congenital heart disease, typically the condition will have been recognized well before the stroke occurs. A distribution of ischemic lesions in multiple distinct vascular territories mandates a comprehensive cardiac evaluation, even in cases where another putative risk factor has been identified.

Congenital heart disease, most notably with complex cyanotic anatomy, imposes the greatest risk of stroke, partly because of the necessity for catheterization procedures and surgery with bypass. For example, approximately one child out of every 650 children evaluated with a cardiac catheterization will sustain a stroke (66). In pediatric patients undergoing cardiac surgery, the risk for AIS is 5 to 6 per 1000 (67,68). Surgical interventions, especially the Fontan procedure, significantly elevate the risk of stroke, with estimates for an acute or delayed stroke as high as 20% (69,70). Not all ischemic lesions in children with congenital heart disease cause clinically overt stroke symptoms; in fact, silent infarctions have been identified even in the absence of surgery (71).

Prothrombotic Disorders

Inherited and acquired defects in coagulation, fibrinolysis, and platelet adhesion are the final common risk factors for pediatric AIS, all through the pathological formation of thrombi. The exact role and frequency of thrombophilia in childhood stroke are less clear, because of the large number of disorders potentially involved; the inconsistent laboratory methods utilized; timing of the tests performed; and, most significantly, the sparsity of case-controlled studies available. In addition, many patients with prothrombotic disorders have additional risk factors for stroke (39,72). Nonetheless, coagulation disorders have been documented in 25% to 50% of children with AIS (73–76), with Factor V Leiden mutations causing resistance to factor degradation appearing as one of the stronger associations (39). Based on case-control studies, protein C deficiency, increased lipoprotein(a) levels, prothrombin G20210A mutations, lupus anticoagulant, and antiphospholipid antibodies are each found more commonly in children with AIS (31,75,77,78). Also, stroke has been reported in the context of acquired deficiencies of both protein S and C resulting from antibodies presumably secondary to viral infections such as varicella and bacterial sepsis (74,75,79). The role that platelet abnormalities may play in childhood AIS, though likely important, has not been examined in a critical fashion; more detailed reviews are available (75,76,80).

Pediatric Hemorrhagic Stroke

Initial figures suggest that roughly one-third of pediatric strokes are hemorrhagic when the perinatal population is included (1). In more recent studies, the incidence rates of the two appear comparable, estimated at 1–5/100,000 children/year (15). Risk factor(s) for hemorrhagic stroke can be identified in up to 80% to 90% of the cases. Structural anomalies of the cerebral vasculature, including arteriovenous malformation (AVM), congenital aneurysm, and vein of Galen malformation, collectively account for about 50% of all hemorrhagic strokes in the pediatric population (81–83). Other "ischemic stroke" conditions such as SCD and postinfectious vasculopathies can result in primary hemorrhage. In addition, significant hemorrhagic transformation occurs in more than 50% of CSVT ischemic stroke (84) (Figure 43.2). Intracranial tumors have been documented as the source of brain hemorrhage in roughly 2% to 10% of cases (81–83). Finally, trauma is a frequently observed cause of intracranial and intraparenchymal hemorrhage, whereas hematologic disturbances other than SCD must be considered in any child with intracranial bleeding in the absence of an anatomic disturbance (83).

Most hemorrhagic strokes are supratentorial, with approximately equal involvement of the hemispheres (81,82). Neurological deficits noted at presentation typically reflect impaired function as a result of direct neuronal injury or secondary impairment in cerebral perfusion and alteration in local metabolism. In pediatric survivors of hemorrhagic stroke, outcome generally is better compared to AIS patients, a finding often attributed to the phenomenon of a blood clot displacing neuronal tissue rather than destroying it.

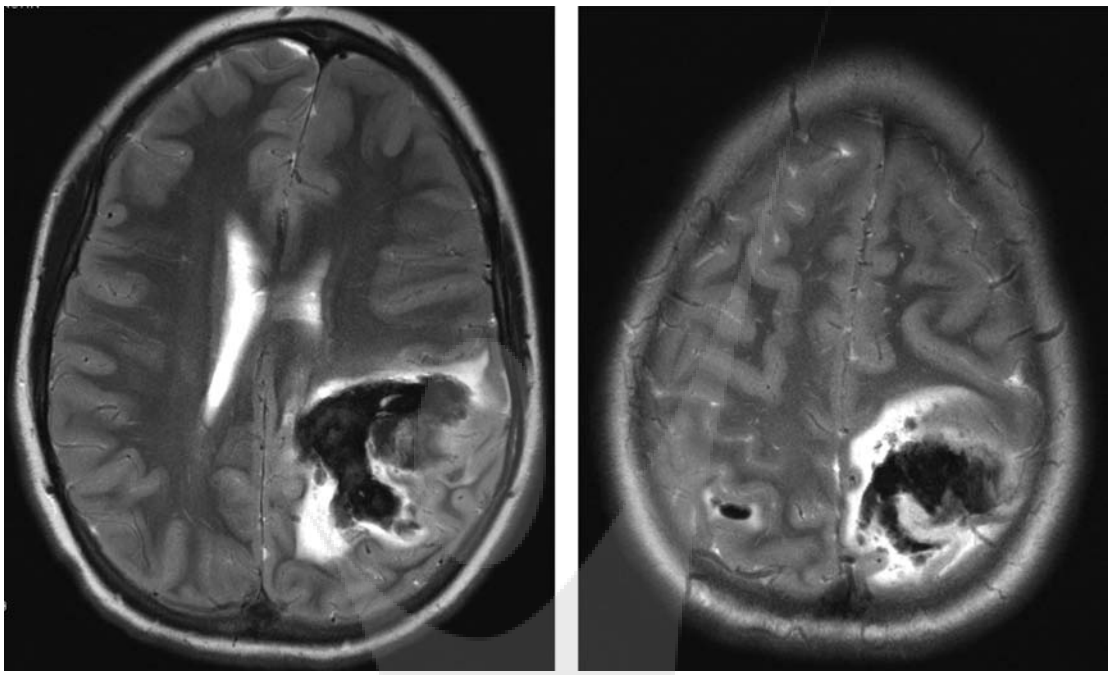

FIGURE 43.2 Noncontrast MRI demonstrating bilateral parietal hemorrhages (left much greater than right) with blood products undergoing evolution. These hemorrhagic strokes occurred in a patient with an acute systemic illness and the cerebral sinovenous thrombosis seen in Figure 43.3.

This same phenomenon also dictates that in contrast to ischemic stroke, treatment of hemorrhage often necessitates neurosurgical intervention caused by the evolution of cerebral edema and risk of herniation.

Cerebral Sinovenous Thrombosis

A recent analysis indicates that CSVT represents about 25% of childhood AIS. An incidence of one in 100,000 pediatric patients per year has been established, with the greatest risk in the neonatal period (85). CSVT includes thrombosis within the cerebral venous system (Figure 43.3), whether symptomatic or not. In contrast to AIS, half of patients will have a thrombus within the cerebral venous system but no visible parenchymal lesions at presentation, and some of these patients will be asymptomatic. In the remaining children, a venous infarction, often hemorrhagic, is observed (85,86) (Figure 43.2).

Risk factors for CSVT typically are multiple and related to age of onset. In the neonatal period (see below), acute systemic events and cardiac disease predominate, whereas in young children dehydration, head and neck infections, and other factors are more common. The latter includes trauma and systemic illness, especially in the older age groups. Otitis media, mastoiditis, sinusitis, and meningitis, which may be present in almost a third of preschool children, should

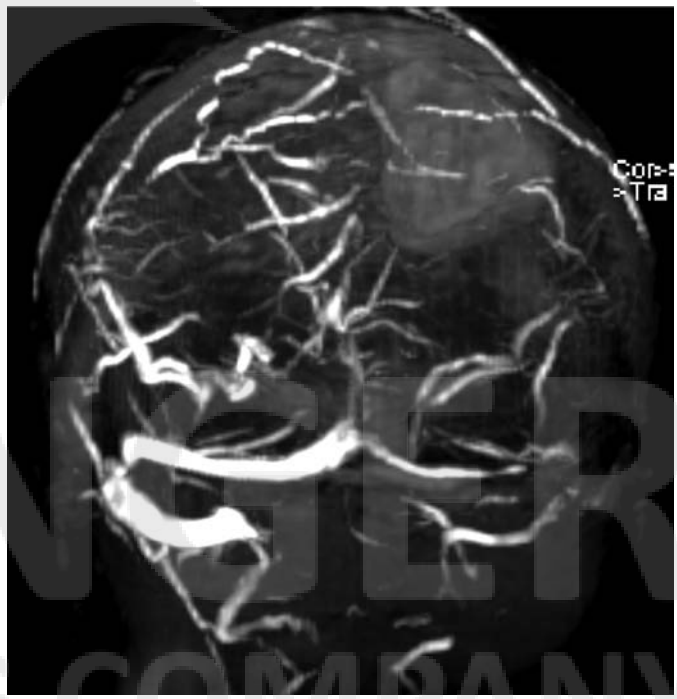

FIGURE 43.3 Magnetic resonance venogram (MRV) showing venous sinus thrombosis involving almost all of the superior sagittal sinus. The small size of the left transverse and sigmoid sinuses probably is a normal congenital variant.

TABLE 43.2 Differential Diagnosis of Acute Stroke-Like Symptoms

CATEGORY	FEATURES DISTINGUISHING FROM STROKE
Migraine	Complete resolution and shorter duration of symptoms, presence of headache
Seizures	Presence of tonic/clonic or other uncontrolled movements always precedes weakness (in cases of Todd's paralysis)
Cerebellitis	Predominant finding of ataxia in legs and trunk
Syncope	Awareness at onset of impending faint, absence of persistent neurological deficits
Meningitis	Fever, encephalopathy, meningeal signs
ADEM	Encephalopathy, multifocal symptoms and distribution of lesions in brain imaging
Psychogenic	Inconsistent or nonphysiologic findings on exam
Toxin ingestion	Encephalopathy, restricted age (typically between 1–3 years)

always be a consideration in CSVT (84,85,87). Prothrombotic disorders are fairly evenly distributed over the pediatric age range. The frequency with which they are documented is exceedingly variable, ranging from 20% to 80% (84,88,89), but these estimates clearly are in excess of those typically quoted for adult patients. Prothrombotic disorders implicated in childhood CSVT include anticardiolipin antibodies, increased lipoprotein(a) levels, Factor V Leiden mutations, deficiencies of proteins C and S, and antithrombin (84,89,90). Heterozygosity for the factor II G20210A mutation is a recognized risk factor for recurrent CSVT (91).

Perinatal Stroke and CSVT

Newborn strokes occur in 1 out of 4,000 births (14), that is, a stroke rate similar to that of individuals 75 years of age and older. For CSVT in neonates, the incidence is roughly 2 to 3 per 100,000 (90), with both term and premature infants affected. In more than 50% of the neonates, venous infarctions, which are often hemorrhagic, occur and intraventricular hemorrhage is a common feature. Risk factors have been reviewed in the previous three sections but also include maternal prothrombotic and autoimmune disorders, neonatal infections, and complications of labor and delivery (92,93). In particular, some studies have suggested that transplacentally delivered maternal anticardiolipin antibodies and lupus anticoagulant are important risk factors (94). In addition, pregnancy is a naturally occurring prothrombotic state caused by various hemostatic factors. Finally, in the fetus, thrombus development on the fetal side of the placenta can lead to emboli, which gain entrance to the cerebral vasculature via the patent foramen ovale.

CLINICAL MANIFESTATIONS AND DIAGNOSIS OF PEDIATRIC STROKE

In the absence of a known predisposing factor, such as congenital heart disease, SCD, or protein deficiencies in the blood, an initial diagnosis of stroke based on presenting symptoms may be missed or delayed, often beyond 24 hours (23,95–97). Delayed diagnosis typically reflects decreased awareness by the primary care providers and an exceedingly complex and expansive differential diagnosis. The frequency with which seizures occur at the onset of stroke in children may also cloud diagnostic judgment (98). Compared to adults with stroke, pediatric patients have a higher incidence of nonlocalizable symptoms, such as behavioral disturbances and headache, whereas even focal deficits may be hard to elicit in infants or children with premorbid developmental disability. Even recognizing the challenges, in many instances, the acute onset of neurological impairment in a child should be considered a stroke until proven otherwise. Thus, prompt utilization of imaging technology, especially MRI, is often necessary to distinguish stroke from the lengthy list of mimicking conditions (99), the most problematic of which are highlighted in Table 43.2.

DIAGNOSTIC IMAGING

MRI has greatly advanced the diagnosis and management of cerebrovascular disorders in pediatric patients, especially in the early detection of cerebral ischemia through the use of diffusion-weighted images (DWIs) (25,100,101) (Figure 43.4). The radiologic hallmark of acute AIS is restricted diffusion, as evidenced by DWI hyperintensity in combination with overlapping hypointensity on the apparent diffusion coefficient (ADC) map (101). In addition, more advanced MR modalities such as gradient ECHO and susceptibility-weighted studies can demonstrate even minute amounts of blood and thus assist in diagnosing hemorrhagic transformation (102). Most authors recommend that MR angiography (MRA) of intracranial and neck vessels be performed as part of the initial MRI study in children for whom acute AIS is a prominent diagnostic consideration. However, for specific arteriopathies or in cases concerning dissection, conventional angiography (CA) is often indicated (103,104). At the conclusion of the imaging workup, in addition to confirming that an acute vascular event has occurred, the radiological data should

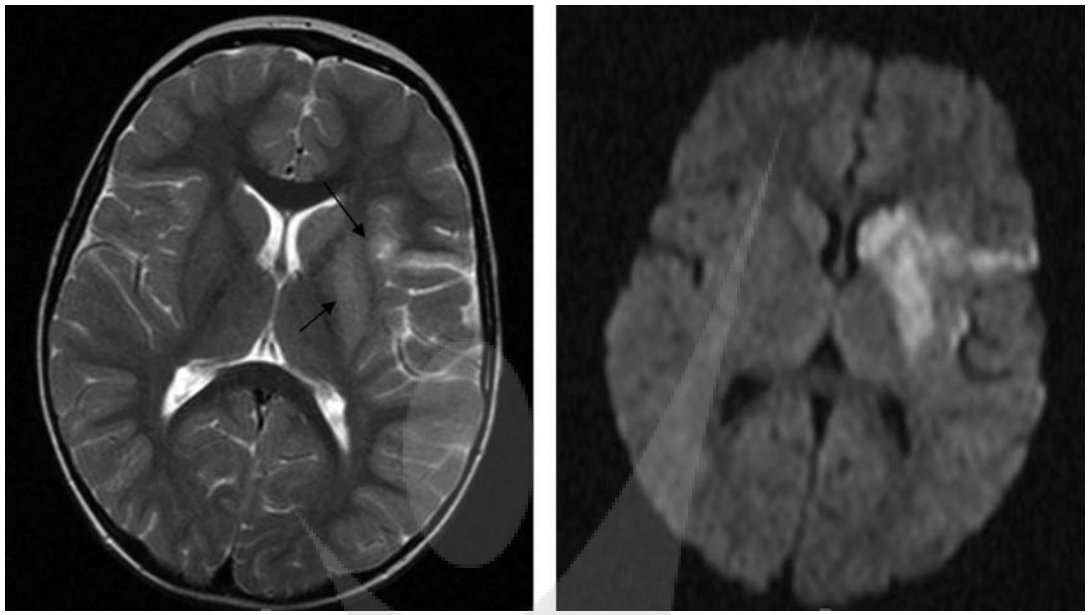

FIGURE 43.4 Left MCA arterial ischemic stroke. Left image demonstrates increased T2 signal in the left basal ganglia, left parietal lobe, and perisylvian region (arrows). These areas demonstrate restricted diffusion consistent with acute infarct, seen on DWI (right).

provide information regarding the extent and location of acute cerebral injury, the patency of major neck and intracranial arteries, and the degree of relative cerebral perfusion.

TREATMENT AND MANAGEMENT

Clinical management of pediatric stroke has evolved significantly over the past 20 years (105,106). Currently, the approach varies depending on the category of stroke and age of the child, but the immediate goal remains the prevention of secondary neuronal injury. Medical stabilization begins with adequate oxygenation, rehydration, seizure control, and management of infection. Treatment modalities can be reviewed based on specific forms of stroke and also the time frame in which intervention is necessary. For example, in cases of SCD, prompt red cell pheresis is indicated. In addition, current treatment of pediatric stroke is informed by three sets of consensus-based guidelines (105,107,108). Generated by expert panels of child neurologists, thrombosis experts, and others experienced in pediatric stroke, these publications attempt to integrate best available evidence with experience to provide practical guidance. These guidelines are predominantly concordant for major treatment recommendations, though they differ in certain areas (109).

Emergent Care

Neuroprotection—All Stroke Subtypes

Neuroprotective strategies have produced disappointing results in adult stroke trials (110). Nonetheless, the underlying basis of neuroprotection is to deliver an appropriate supply of both oxygen and metabolic substrate to ischemic tissues in the penumbra and simultaneously lower cellular metabolic demand. The former can be accomplished by optimizing delivery of oxygen and glucose, managing blood pressure, and maintaining cerebral perfusion. The latter can be assisted by controlling fever, managing infections, and minimizing seizures. This approach can and should be undertaken in all pediatric stroke patients, regardless of age and etiology of stroke (111). Treatment of intracranial hypertension often is essential to ensure adequate cerebral perfusion pressure, especially in cases of CSVT and hemorrhagic stroke. Given these considerations, initial management in an intensive care unit setting often is warranted (112).

Thrombolysis—AIS and CSVT

In cases of an evolving or rapidly progressing AIS, thrombolytic therapy may be a consideration, given that this treatment, typically in the form of tPA, has improved outcomes in adult stroke, with an approximately 15% risk reduction in poor outcome (113). The safety and efficacy of thrombolysis in the pediatric population, however, remain unproven. Studies of its use in children are limited mainly to database compilations (5) and isolated case reports (114,115). The IPSS reported that in 15 children with AIS (out of 680—2%) who were treated with tPA, the outcome was less than encouraging (116). Twelve were left with residual neurological deficits, two died, and only one recovered to normal. In addition, 4 (out of 14) sustained posttPA hemorrhage. The challenges confronting the use of tPA in childhood AIS patients are significant (116). Not surprisingly, the two most commonly quoted consensus-based treatment guidelines have

similar recommendations suggesting that thrombolytics (or mechanical-clot-retrieval therapies) should be carried out only within research protocols designed to address safety issues (13,108). One guideline does not entirely exclude consideration of tPA use in older adolescents with AIS, who otherwise meet standard adult tPA eligibility criteria (13).

Similar concerns regarding safety and efficacy exist for emergent recanalization strategies in childhood-onset CSVT. Endovascular thrombolysis, thrombectomy, or surgical decannulation are suggested only for selected patients with severe CSVT in whom there is no improvement or progressive deterioration, despite an adequate trial of anticoagulation. Thrombolytic agents are not recommended in neonates with either AIS or CSVT (107,108).

Hemorrhagic Stroke

Acute medical management of HS in the pediatric population requires the same "neuroprotective" measures discussed previously. In addition, the potential role of neurosurgical intervention should not be underestimated. In more than half of the reported cases of HS, emergent neurosurgical procedures such as hematoma evacuation and placement of intracranial pressure-monitoring devices have been documented (81–83). Despite this, there are only generic recommendations for treatment of HS delineated in the three pediatric stroke consensus guidelines, such as risk factor evaluation and identification and correction of congenital vascular anomalies. In part, this reflects the need to individualize treatment based on specific patient circumstances. Equally important, however, is the lack of randomized clinical trials on either medical or surgical interventions.

Urgent Care

Antithrombotic Treatment. Management of most pediatric patients with either AIS or CSVT (including neonates) centers on utilization of antithrombic agents, with the targeted site of impact being an intravascular thrombus. The goals of treatment are to prevent early propagation of the initial thrombus, minimize the possibility of re-embolization, inhibit new thrombi from developing, and stimulate prompt recanalization (34). Obviously, these potential benefits have to be weighed against the risk of hemorrhage. Fortunately, the risk of hemorrhagic transformation in childhood AIS does not appear to be appreciably increased by use of anticoagulation (117) and rarely produces additional neurological symptoms. Furthermore, it is clear that in the absence of antithrombotic therapy, the risk of early stroke recurrence is heightened (118). However, there is less compelling evidence regarding choice among the antiplatelet and anticoagulant medications available, given the lack of randomized controlled clinical trials. Based on the three most commonly referenced consensus-based guidelines, a rational approach to treatment of pediatric stroke can be presented (105,107,108). Dosing guidelines for all the agents utilized in the pediatric population and discussed in this chapter are also available (107,108).

Childhood AIS. In the setting of acute childhood AIS (with or without thrombophilia), initial therapy of either unfractionated heparin (UFH) or low-molecular-weight heparin (LMWH) is recommended when embolic etiologies and/or arterial dissection are being excluded. Once this occurs, daily aspirin prophylaxis should be initiated and maintained for at least one to two years. Recurrence of stroke or the onset of transient ischemic attacks (TIAs) would prompt a switch to clopidogrel or anticoagulant therapy with LMWH versus warfarin or another vitamin K antagonist (VKA); the latter two may also be preferable for long-term anticoagulation in selected hypercoagulable states. In contrast, if the AIS results from either a cardioembolic cause or extracranial dissection, then anticoagulant treatment with either LMWH or a VKA is indicated. Recommended duration of treatment varies considerably between six weeks to six months for dissection, depending on radiologic assessment of degree/extent of stenosis and evidence of recurrent ischemic events. For cardiogenic embolism, treatment is suggested for three months up to one year or until the lesion responsible for the risk has been corrected. In addition, one guideline indicates that in children with extracranial dissection, at some point an antiplatelet agent such as aspirin may be substituted (107). Stroke secondary to vasculopathies other than moyamoya also must be treated differently given the high risk of recurrence. Thus, initial treatment includes UFH or LMWH or aspirin for at least three months. Duration of antithrombotic treatment should be guided by the results of follow-up cerebrovascular imaging. Anticoagulation is not recommended for children with AIS secondary to dissection of an intracranial vessel or in those with subarachnoid hemorrhage from any type of dissection or vasculopathy.

Neonatal AIS. In neonates with AIS and a documented cardioembolic source or severe thrombophilic disorders, anticoagulation should be started with either UFH or LMWH. In the absence of a source, the guidelines recommend only supportive care, although recurrent AIS would prompt either use of an anticoagulant or aspirin therapy (107,108). No recommendations are listed for the duration of therapy.

Childhood CSVT. In patients with CSVT without significant intracranial hemorrhage, initial use of either UFH or LMWH is reasonable followed by at least three to six months of LMWH or a VKA. Continued treatment for an additional three months will be informed either by ongoing symptoms or continued occlusion of the thrombosed vessel. In CSVT with "significant hemorrhage" (not otherwise defined), the Chest guidelines suggest either anticoagulation as described earlier or supportive care and reimaging of the thrombus at five to seven days. Anticoagulation with either UFH or LMWH would then be initiated if thrombus extension is noted, if new-onset symptoms occur, or presumably once the hemorrhage is felt to be stable. Duration of treatment would be for a minimum of three months, with cessation of treatment dictated by the absence of symptoms and recanalization of the thrombosed vessel.

Neonatal CSVT. For CSVT in neonates, the guidelines are more divergent. One suggests that anticoagulation with either LMWH or UFH should be considered only in infants with clinical or radiological evidence of propagating CVST despite supportive therapy (107). The other recommends that for newborns without significant intracranial hemorrhage, initial use of either UFH or LMWH is indicated. If UFH is chosen, at some point LMWH is substituted, with a total therapy duration of between six weeks and three months (108). In newborns with CSVT and "significant hemorrhage" (again not otherwise defined), the Chest guidelines are identical to those described earlier for childhood CSVT, recognizing that duration of treatment may be shorter, as neonates recanalize faster than older children (108).

Moyamoya. Because of the exceedingly high risk of recurrent infarcts in moyamoya (as much as 66%), antiplatelet therapy with aspirin is recommended (107,108). In addition, surgical revascularization should be considered and the patient referred to an appropriate pediatric center (105,107,108). These procedures have been demonstrated to produce improved cerebral perfusion in children with moyamoya with a relatively high degree of success (49). In older children, extracranial blood vessels, such as the superficial temporal artery, can be connected to distal segments of the MCA or other intracranial vessels. For most pediatric patients, indirect procedures such as encephalodural synangiosis (EDAS) and encephalodural myosynangiosis (EDMS) are utilized in which extracranial arteries are approximated to the pial surface. Over the subsequent weeks to months, neovascularization of the previously underperfused cortex transpires (107,119).

Sickle Cell Disease. In children with SCD and acute stroke, prompt red cell pheresis is indicated (105,107,108), regardless of the patient's prior transfusion history. Studies have demonstrated that children who are treated with an exchange transfusion at the time of their first stroke have decreased risk for subsequent strokes compared to children who are treated with either a simple transfusion or no transfusion (120). Automated exchange transfusion (erythrocytapheresis) is preferred; simple transfusion or partial exchange transfusion is acceptable (64). Neuroimaging (MRI) should be obtained as soon as possible, as diagnoses such as central venous thrombosis, reversible posterior leukoencephalopathy (RPLE), and other cerebrovascular abnormalities (such as moyamoya and dissection) can significantly influence management in the acute and subacute phase of care (121). Ideally, utilization of routine TCD studies will minimize the prevalence with which new-onset strokes occur in this population (56). At present the role of hydroxyurea in stroke prevention remains uncertain (122,123), but it should be considered in patients who cannot continue on long-term transfusion (107). Aspirin is a consideration in cases of large vessel vasculopathy, although such an approach has not been studied in a systematic fashion (124). Alternatively, in moyamoya associated with SCD, there is some evidence that revascularization surgery can be of benefit (125). Finally, bone marrow transplantation may be an additional option, even in the absence of randomized controlled trial data (105,107,108).

PEDIATRIC STROKE RECURRENCE RISK AND OUTCOMES

As previously noted, cerebrovascular disease remains one of the major causes of death in the pediatric population, with the highest rates within the first year of life (2). However, advances in medical and surgical care have resulted in a substantial reduction in mortality in all major subtypes of stroke (3). With increasing survival, however, there is a heightened awareness of the substantial neurological morbidity in survivors of neonatal and childhood stroke.

AIS in Childhood

Death occurs in an estimated 3% to 13% of patients with AIS (13,37). Permanent and often moderate to severe neurological disability has been noted in survivors (13,37,126), including motor and cognitive deficits. Epilepsy is a long-term complication observed in 15% to 20% of childhood AIS patients. Infarct location (especially bilateral involvement) and size appear to be major factors in predicting a less favorable outcome. Younger age (most predominantly less than 12 months of age) and the presence of altered consciousness and seizures at onset also have been implicated in more adverse neurological morbidity (37,98,127,128). With respect to epilepsy onset, large cortical infarcts seem to impose the highest risk (129).

The risk of stroke recurrence varies considerably depending on age of patient, cause of stroke, and preventative measures undertaken following the stroke. Recurrence rates have been reported in selected series to range between 10% to 35% (27,65) but may be as high as 50% in the absence of antithrombotic therapy (22). With respect to etiology, arteriopathy (including moyamoya) seems to be the most important predictor of recurrence, perhaps accounting for nearly two-thirds of subsequent strokes (28). Other patients with certain cardiac and prothrombotic disorders also appear to be at a higher risk. For children with arterial dissection, a recurrence rate of 20% or higher has been noted (28,43–45).

AIS in Neonates

Similar challenging neurological outcomes have been documented in perinatal strokes, with motor and cognitive deficits and epilepsy observed in 50% to 75% (14,65,130). Involvement of the basal ganglia and/or internal capsule on imaging studies and certain other vascular classifications strongly predict motor disability and especially severe hemiparesis (12,131,132). Of note, long-term feeding and other sensory motor deficits seem to predominate and outcomes appear worse in preterm neonates (133). Fortunately, mortality in neonatal AIS is low, roughly 3% to 5% (134). Recurrence of stroke is even less common after neonatal AIS

(typically quoted as 2% to 3%) (92,135); when it does occur, prothrombotic risk factors are typically involved, often within a setting of other well-recognized risk factors such as infection, dehydration, and congenital heart disease (135). In addition, recurrent strokes after the age of 1 year are almost never seen.

CSVT in Childhood

Mortality rates in childhood CSVT of 9% to 29% are considerably higher than the rates documented in adult patients, likely a reflection of the severity of underlying or associated disorders such as malignancy and head and neck infection (84,85). Coma at the time of presentation strongly correlates with death. Neurological disability and seizure disorders occur in about one-half of the survivors. Compared with AIS, children with CSVT are more likely to demonstrate cognitive impairment and behavioral disturbances as opposed to motor deficits. In addition, cortical visual impairment and communicating hydrocephalus may occur in up to 30% of children with CSVT (15,87). Predictors for neurological sequelae include seizures or venous infarction at presentation, whereas worsening outcome correlates with deep vessel CSVT and bilateral infarction, often of central gray-matter structures (84,85). Finally, the risk of recurrent cerebral or systemic thrombosis appears comparable to that observed in adults, with a figure of 13% documented in one particularly well-studied population (84).

Hemorrhagic Stroke

Compared with childhood AIS, hemorrhagic stroke has an increased mortality, ranging from 6% to 54%. Mortality appears increased in posterior fossa hemorrhage, consistent with the potential life-threatening consequences of brainstem compression. In contrast, survivors typically demonstrate fewer and less severe disabilities, with roughly 50% to 75% having a good to normal outcome (81). Hemiparesis is seen in about one-third of survivors and epilepsy in 15% to 20%. The most commonly reported neurological disability, however, is cognitive impairment, although this may reflect the greater intensity with which these types of sequelae have been investigated compared to AIS (81). Like mortality, morbidity in hemorrhagic stroke correlates with posterior fossa location, but delay in initiation of intervention and coma at presentation are also predictors of a worse outcome (83,136).

Risk of recurrence in childhood hemorrhagic stroke is roughly equivalent to that noted for AIS in similar-aged pediatric populations, ranging from 10% to 20% depending on the length of follow-up (81,137,138). Although most recurrences transpire within the first six months following initial diagnosis, the incidence of additional hemorrhage continues to rise over time. This is especially true in cases of abnormal vascular development such as AVMs, in which a 2% per year rebleed rate has been documented (137).

ASSESSMENT OF STROKE OUTCOMES IN CHILDREN

In studies of pediatric stroke, the estimates of patients with permanent neurological deficits have ranged from 50% to 90% (98,126,129,139,140). This wide range in deficit estimates demonstrates how difficult it is to assess stroke outcomes in children. As adult stroke assessment scales cannot be transferred to pediatric patients, novel measures of stroke severity (141,142) and outcomes (139,140) specific to children had to be developed. These metrics face the difficult task of evaluating disabilities in a population whose abilities change nonlinearly with age.

Many pediatric neurorehabilitation programs utilize either the Wee-Functional Independence Measure (Wee-FIM) (143) or the Pediatric Evaluation of Disability Inventory (PEDI) (144) to ascertain functional abilities in the domains of mobility, self-care, and cognition/social function (Table 43.3). To a greater or lesser degree, each scale measures impact of stroke via a determination of the burden of care or need for caregiver assistance that must be assumed by a parent or family member following the injury. A more recently developed and validated scale is the Pediatric Stroke Outcome Measure (PSOM), which measures neurological deficit and function across five domains: right and left sensorimotor, language production and comprehension, and cognition/behavior (7,139). Although the PSOM subscale scores demonstrate strong agreement for domain-matched neuropsychology

TABLE 43.3 Comparison of Outcome Measures

OUTCOME MEASURE	AGE RANGE	DESCRIPTION
Wee-Functional Independence Measure (Wee-FIM)	6 months–7 years	Administered by observation or structured questions. Item clusters include self-care, sphincter control, mobility, locomotion, communication, social, and cognition. Ratings of child on a seven-point scale of burden of care.
Pediatric Evaluation of Disability Inventory	6 months–7 years	Rated by informant or by interview. Includes three major content domains: self-care, mobility, social function. Assesses separate measurement dimensions of functional skills, caregiver assistance, and modifications.

test scores, the authors acknowledge that the PSOM likely is biased toward sensory and motor impairments as opposed to cognitive and behavioral deficits (139). Use of these tools enables a program to compare recovery with the national average for pediatric stroke, although improvement within stroke subtypes is harder to ascertain. In addition, the WeeFIM allows one to compute length of stay and expenditure of rehabilitation effort (units of physical therapy, for example) with functional gains. Neurological outcome using the PSOM also has been utilized to correlate cost of stroke care with disability. Not surprisingly, cost during the first year of recovery correlated positively with neurological impairment (7,144). A much more valuable use of these functional outcome measures will be in prospective clinical trials in pediatric stroke, especially those comparing potential benefits of therapeutic interventions.

Many abilities have not yet developed in children at the time of their stroke. Therefore, the full extent of the deficits caused by stroke can remain hidden for years (145,146). For example, the effects of stroke on reading ability can only be assessed once patients have reached the age at which children typically learn to read. More subtle cognitive and behavioral effects of stroke, such as attention deficits or mood disorders, may not be recognized until children are school age or even older. One can think of this as children with strokes "growing into their deficits" (11). Detailed neuropsychological testing in children with strokes suggests that almost all children who suffered strokes show neuropsychological abnormalities at follow-up neuropsychological testing (144,146–148). Because ongoing development can potentially mask deficits for many years in pediatric stroke patients, children who suffered a stroke should ideally be closely followed until adulthood, both for research studies and in routine clinical care.

Studies assessing quality of life in pediatric stroke survivors suggest that cognitive deficits lead to poorer socialization and lower quality of life (149,150). Thus, there have been increasing efforts to utilize standardized assessment tools designed to measure health-related quality of life (HR-QoL) in children and adolescent survivors of stroke. Such measures document more fully how a neurological deficit affects a pediatric patient's ability to live and function within the home, school, and community environments (150). When utilized in conjunction with an impairment measure such as the PSOM, most studies have demonstrated that increasing degrees of neurological deficit strongly predicted diminished well-being and, in older patients, impaired peer-related well-being. In the future, these types of HR-QoL assessments should be incorporated into any study assessing the efficacy and benefit of treatment or rehabilitation strategies in children with stroke. Despite the frequency and severity with which neurological disability occurs in survivors of pediatric stroke, as a general rule the long-term outlook is fairly good. For example, one study documented that children and adolescents with a history of stroke demonstrated fairly good outcomes in terms of transition to adulthood, including high rates of high school graduation and higher education. Thirty-two patients were followed over the course of about 10 years. Study results found that in early adulthood, most individuals were employed (90%) and could drive (76%). As far as general functional status was concerned, mobility outcomes were excellent, although assistive devices and orthotic use were common. Daily living skills, communication, and socialization fell in the moderately low range and were influenced by medical status (151).

MECHANISMS OF STROKE RECOVERY

The common goal of improving rehabilitative therapies for young and old stroke patients will be greatly aided by a better understanding of the basic mechanisms of stroke recovery. As many more adults suffer strokes than children, the vast majority of studies on stroke recovery mechanisms have been performed in adults and equivalent animal models. These studies have elucidated important mechanisms of stroke recovery at all representational levels of the CNS, from molecules to hemispheres. A common finding across this wide range of research approaches has been that stroke recovery mechanisms seem to follow a specific timeline (Figure 43.5).

Immediate Poststroke Period (Less Than Five Days)

Stroke induces acute changes in global brain metabolism and blood flow, as well as causing local inflammation and edema (152). The earliest functional gains in stroke recovery, within the first three to five days after stroke, are at least in part caused by normalization of these transient alterations (153).

Neuroimaging of patients with motor deficits, within the first 72 hours after stroke, showed diminished coupling between primary motor cortex, supplementary motor area, and premotor cortex, when compared to the recovered state (154). Animal studies have shown that surviving neurons in the perilesional zone undergo significant dendrite loss in the first few days after stroke (155). Spontaneous neural activity in the perilesional zone consists mainly of polymorphic delta rhythms for the first 24 hours after stroke (156).

In rodents, initiation of activity programs immediately following stroke increases lesion size (157–160). Increased neural excitability during this immediate poststroke period can be harmful. For example, treatment with $GABA_A$ agonists, which promote tonic GABAergic inhibition, immediately following stroke decreases stroke size (159,161); in contrast, immediate treatment with $GABA_A$ antagonists, which decrease tonic inhibition, increases stroke size (159). Stimulating glutamatergic AMPA receptors, which is important for learning-induced neuroplasticity, immediately after stroke also increases stroke size (160). Based on these types of studies, carried out in rodents, it seems that by five days after stroke, the penumbra adjacent to the infarcted brain tissue is no longer vulnerable to neural overexcitation (159,160,162,163).

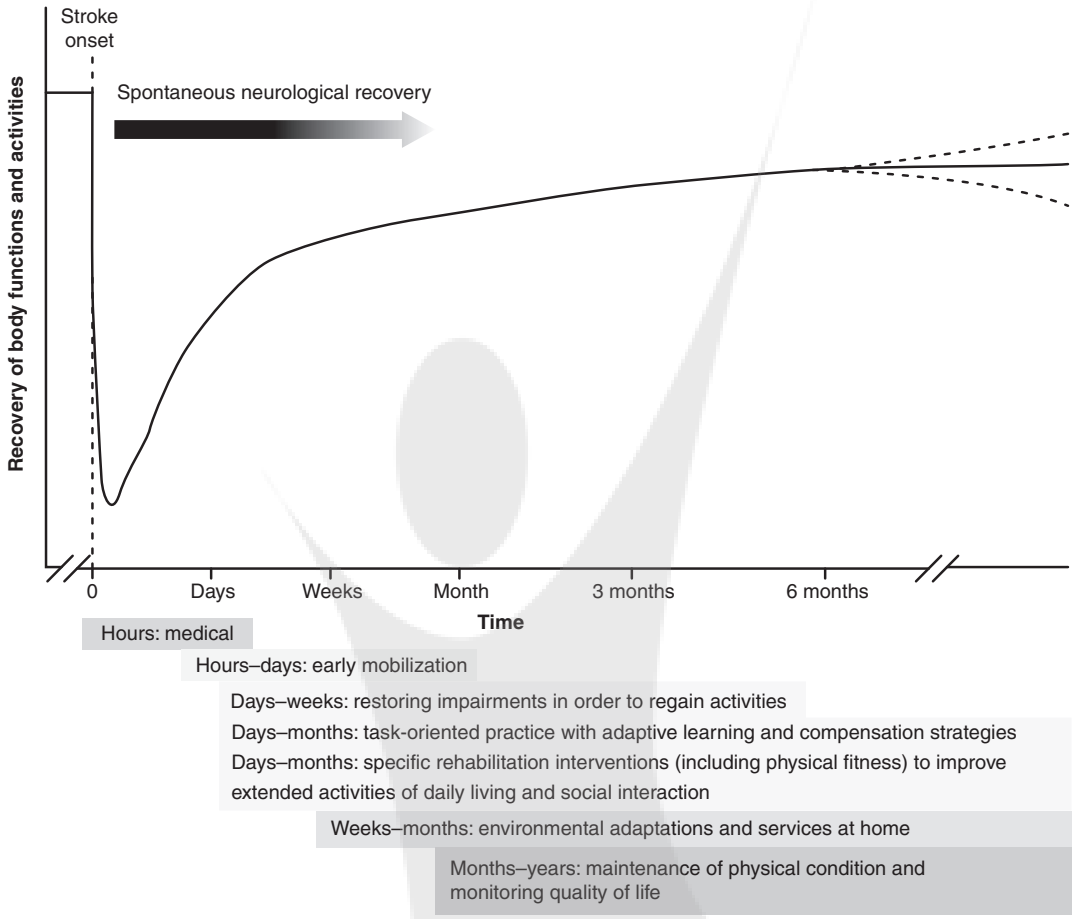

FIGURE 43.5 Proposed pattern of recovery after stroke with timing of recovery

Source: Adapted from Ref. (172). Langhorne P, Bernhardt J, Kwakkel G. Stroke rehabilitation. *Lancet*. 2011;377(9778):1695. Copyright 2011, Elsevier. Adapted with permission.

As soon as these acute disturbances subside, the brain initiates complex programs to recover functions previously supported by the now infarcted tissue. Within one to five days following stroke, systems-level, cellular, and molecular mechanisms are initiated that help mediate stroke recovery (156,159,164–171).

Subacute Stroke Recovery (Five Days to Three Months)

In rodent models of stroke, the critical phase for recovery lasts from five days after stroke until about one month (163,165). In adult humans, 95% of the poststroke motor recovery occurs within 3 months, whereas cognitive deficits can recover over a longer period (172). Not surprisingly, the initial severity of the deficits is a fairly good predictor of the eventual outcome (173). The timecourse of recovery in children is similar to that in adults, but on an average, children will show greater overall recovery from stroke deficits than adults (174).

Stroke Recovery at the Systems Level

The human brain is the most complex and computationally powerful system known. It has been shown to contain about 86 billion neurons (175), connected by an estimated 100 trillion synapses (176). Systems neuroscience has subdivided the brain into distinct functional areas based on differences in their cytoarchitectonics, topography, connectivity, and function (177,178). These functional areas are organized into widely distributed networks by massively parallel connections (177). Even though individual brain areas contribute specialized computations, all human behaviors are the emergent property of these distributed networks that include distant parts of cerebral cortex, subcortical structures, and the cerebellum. Abilities such as attention, movement, or executive control are not localized to individual parts of the brain, but rather are supported by widespread networks (179–183).

Functional neuroimaging techniques such as positron emission tomography (PET), functional MRI (fMRI), and functional connectivity MRI (fcMRI), as well as reversible, noninvasive neural stimulation and inactivation methods like transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS) have enabled researchers to study the functional neuroanatomy of stroke recovery at the level of functional systems and distributed brain networks.

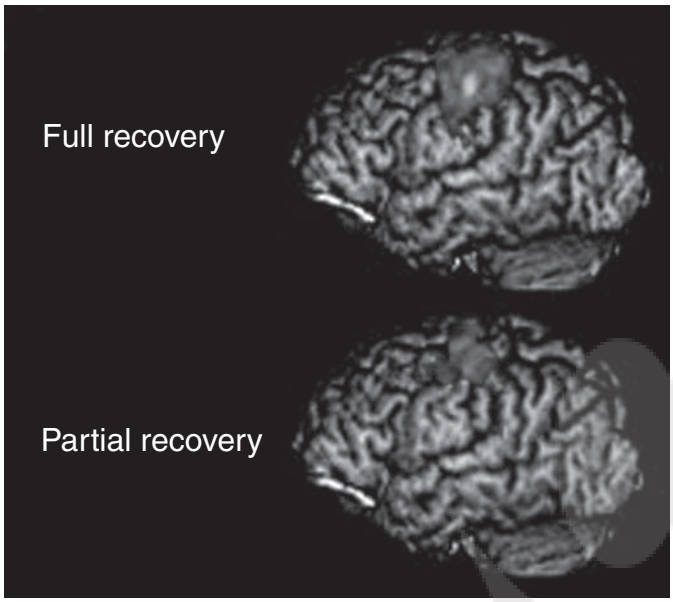

FIGURE 43.6 Greater ipsilesional fMRI activation has been associated with better motor performance following stroke.

Source: Adapted from Ref. (212). Cramer SC. Repairing the human brain after stroke: I. Mechanisms of spontaneous recovery. *Ann Neurol*. 2008;63(3):276. Copyright 2008, John Wiley and Sons. Adapted with permission.

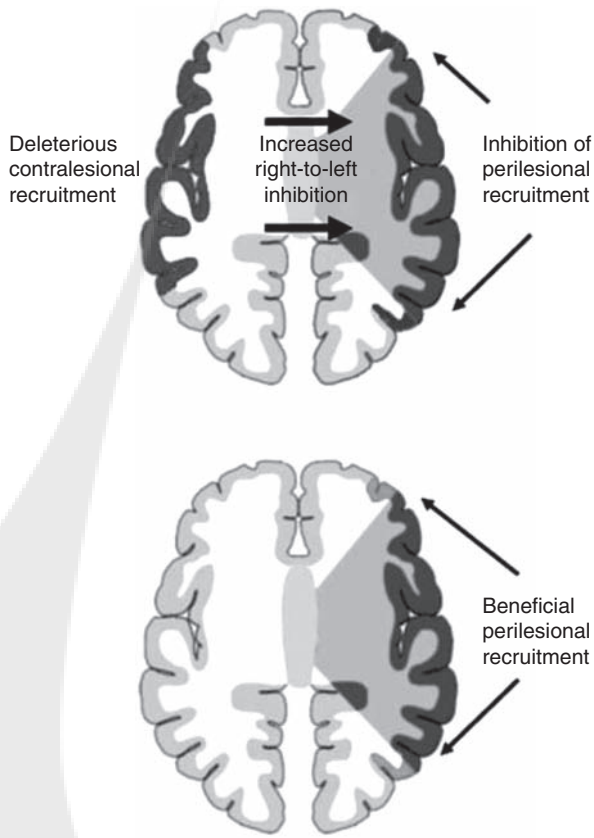

FIGURE 43.7 Interhemispheric inhibition (IHI) is thought to be deleterious because it prevents recruitment of perilesional areas and restoration of more natural brain activation patterns after stroke.

Source: Adapted from Hamilton RH, Chrysikou EG, Coslett B. Mechanisms of aphasia recovery after stroke and the role of noninvasive brain stimulation. *Brain Lang*. 2011;118:43. Copyright 2011, Elsevier. Adapted with permission.

Human Studies. Human neuroimaging studies of strokes that damage parts of the attentional and somatomotor networks have shown that they affect entire functional networks (179,184,185). Stroke alters local activity in distant, but functionally related, brain regions (184) and it changes the functional relationships between brain areas throughout a damaged network (185), including the opposite hemisphere (179). Fortunately, these organizational principles of the brain also point toward clear opportunities for stroke recovery. Redundancies in computational specialization and connectivity enable functional networks to reorganize in search of a new network state that allows the best possible performance given its new resource limitations (181,182).

Functional neuroimaging studies of humans recovering from strokes involving the primary motor cortex have shown more widespread activations throughout the motor system during the initial subacute recovery phase (186). Compared to unaffected controls, recovering stroke patients using the paretic upper extremity initially had greater activations in the contralesional primary motor and premotor cortex, midline supplementary motor areas, and perilesional primary and premotor cortex (187). Over time, the activation patterns of patients who made good functional recoveries became more similar to typical activation patterns, with greater lateralization and activations focused in perilesional areas (188,189) (Figure 43.6). Consistent with these imaging findings, timed inhibition of ipsilesional premotor cortex with TMS degraded motor performance in paretic patients, but not controls (190,191). This finding showed that recovered stroke patients relied on a different functional neuroanatomy to perform the same task.

Across studies, chronic persistence of increased activation in contralesional motor regions has been associated with poorer outcomes (188,192–194). Studies of patients with left neglect following stroke showed similar activation imbalances between the hemispheres that normalized with functional recovery (181,184). Functional neuroimaging and stimulation studies in humans suggest that the negative effects of contralesional activity could be caused by interhemispheric inhibition (IHI), exerted by the contralesional hemisphere onto the lesioned hemisphere, via transcallosal projections (195) (Figure 43.7).

Animal Studies. Studies of sensorimotor stroke in rats using fMRI and optical imaging are congruent with human studies, including correlation with functional recovery, thus lending credibility to rodent models of stroke (168). In addition, more fine-grained intracortical studies have shown that maps representing specific body parts in primary motor and somatosensory cortex in rodents and monkeys can reorganize after limb loss or disuse, as well as stroke (196–200). As predicted, the changes in these cortical maps

were use-dependent (196,197). Although rodent and even monkey brains lack the complexity of the human brain, animal models of stroke recovery have allowed researchers to detail the cellular processes thought to underpin the network-level changes described earlier.

Stroke Recovery at the Neuronal Level

Axonal Sprouting and Dendrite Morphogenesis. An important mechanism by which brains are thought to reorganize functional networks and maps is axonal sprouting (199–201). Rodent and primate stroke recovery models have all documented axonal sprouting correlated with functional recovery (202). In squirrel monkeys, stroke in the hand representation of primary motor cortex induced perilesional axonal remodeling and sprouting of novel axonal connections toward the distant ipsilesional premotor cortex (201). These findings provide a potential cellular mechanism for the increased activation of ipsilesional premotor cortex in humans with strokes affecting primary motor cortex (190,191). Multiple other studies in rodents have documented perilesional axonal sprouting and innervation of novel motor and sensory targets (155,165,170,200). These findings are congruent with the human studies, which have shown that persistent reliance on contralesional regions is a marker of more severe stroke (181,186).

Concurrent with the sprouting of new axons, dendritic spine turnover and synaptogenesis also increase in perilesional cortex (155,203). Moreover, the location of these cellular changes corresponds to areas of somatosensory cortex in which functional maps reorganize following stroke (155,165,203). Synaptogenesis and dendrite reshaping are maximal within a few millimeters of the infarcted region and mainly occur within the first two weeks following stroke (168).

Neuronal Activity Changes. The changes in axonal and dendritic structure during stroke recovery coincide with changes in neuronal activity thought to play an important role in activity-dependent recovery. In rats, one day after stroke, polymorphic delta rhythms (0.2–2.2 Hz) in perilesional cortex, thought to reflect injury, are overtaken by widespread, synchronized, spontaneous, lower-frequency (0.1–0.4 Hz) neural activity (156). These slow rhythms were maximal three days after stroke in perilesional cortex and they were also measured in the contralesional hemisphere. Pharmacological blockade of this slow synchronized neural activity blocked axonal sprouting.

Consistent with human imaging studies and horizontal perilesional axonal sprouting, in vivo imaging experiments in mice have shown that poststroke activations spread more widely into adjacent brain regions, and that these responses lasted three to four times longer than normal responses (155).

Neurogenesis. During stroke recovery, the activity, connectivity, and structure of neurons change in ways that are thought to support functional recovery of stroke deficits. Besides reorganizing the networks of existing neurons, another logical mechanism for stroke recovery at the neuronal level would be neurogenesis, or the generation of new neurons from neural stem cells. In adult brains, neurogenesis has been reported in the hippocampus, the olfactory bulb, and the subventricular zone of the lateral ventricle (170,204). Several studies have suggested that stroke triggers proliferation of neural stem cells and their migration toward the site of the lesion (166,205,206). However, out of these neuronal precursors only a small fraction survives to differentiate into neurons (207). Furthermore, it remains unclear how much neurogenesis contributes toward functional recovery after stroke. It has been proposed that some of the reported correlations between neural stem cell proliferation and improved outcomes may have been mediated by enhanced neural plasticity (170) or enhanced angiogenesis (208). There is currently no clear evidence that newborn neurons can take over the function of infarcted ones to a significant degree.

Stroke Recovery at the Molecular Level

Studies of stroke recovery have started to investigate some of the molecular machinery and signaling cascades that enable recovery at the neuronal and systems level. This research suggests that stroke triggers transcriptional programs that recapture a state of heightened neuroplasticity similar to earlier developmental stages (165). In the periinfarct zone, immediately beyond the glial scar, these transcriptional programs lower levels of growth-inhibitory factors and boost levels of growth-inducing factors (167,209). Many of the molecules differentially modulated during stroke recovery have also been found to be important for learning and memory, suggesting that molecules that enhance learning may also promote stroke recovery (160). For example, brain-derived neurotrophic factor (BDNF) and glutamatergic AMPA receptor signaling, known to be important for the reorganization of cortical maps and spine morphogenesis, are also important for learning-induced plasticity (160,210,211).

Chronic Stroke Phase (Greater Than Three Months)

Most functional recovery from stroke occurs within the first month, but improvements can continue for up to three months, especially in more severely affected patients (212). Among paretic stroke patients, 80% reached their new maximal arm function within 3 weeks, and 95% reached it within 9 weeks (213). In the same study, it was found that 95% of patients with mild aphasia return to their new baseline language ability within 2 weeks, whereas 95% of patients with severe aphasia do so within 12 weeks (214). It has been estimated that as many as 30% of patients with strokes causing cognitive deficits continued to improve beyond 3 months after stroke (215).

Animal studies also suggest a critical period for stroke recovery. Rats made the best functional recovery from a large stroke when they were placed within an enriched rehabilitative environment at five days after stroke (163). When placement within an enriched environment was delayed until 14 days after stroke, benefits were diminished. Waiting until 30 days after stroke abolished the benefits of an enriched environment completely, and there was no difference from

typically housed animals with stroke. Improved functional outcomes in those animals placed in an enriched environment five days after stroke correlated with greater dendritic arborization in perilesional cortex.

PEDIATRIC NEUROREHABILITATION FOR STROKE

The majority of pediatric stroke survivors will demonstrate some degree of neurological impairment. The long-term impact of childhood stroke often is substantial, with residual neurological disability typically including spastic weakness, as well as movement disorders, seizures, speech and language delay, visual impairments, orthopedic deficits, and cognitive and behavioral difficulties. Rehabilitation management of stroke in the pediatric population has been aided by recently developed guidelines emphasizing a multimodal and family-centered approach (105,216). Recent evidence-based practice guidelines for adult stroke rehabilitation are helpful (217). It must be acknowledged, however, that though the benefits of earlier and more intense rehabilitation clearly are documented in adults and buttressed by animal research (10), compelling evidence in childhood stroke is less available.

Principles of Pediatric Rehabilitation

Childhood stroke rehabilitation has several guiding principles based upon the age and developmental level of the patients requiring treatment, as well as the nature of stroke recovery and reorganization mechanisms (Table 43.4) (212,216). The distinguishing principle of pediatric stroke rehabilitation is that assessments of cognitive, motor, and psychosocial deficits and the corresponding therapies must be guided by an understanding of normative development (218). Detailed understanding of the patterns of cognitive development during maturation is especially important in the rehabilitation of infants and children, as these developmental milestones can be incorporated as sequential goals within an individual's therapy program (105). In addition, the manner in which rehabilitation can be provided to a child or adolescent and the patient's ability to engage in therapy may be restricted. This is especially true early in the recovery process of patients who lack the developmental skills necessary to learn complex strategies upon which functional substitution is predicated (216). An understanding of cognitive development allows more accurate prediction of which patients will lack the ability to understand and participate in a meaningful way in their therapy program. A developmental framework also informs the potential long-term effects of cerebral injury in young children. This is most pertinent for areas of the brain subserving functions that normally mature later in childhood and in cases of neonatal and presumed perinatal stroke.

Another principle of pediatric stroke rehabilitation is that the process mandates a coordinated multidisciplinary team working together to develop therapeutic interventions based upon integrated assessments (105). Important considerations of home and school accessibility, psychosocial adaptation to disability, and school reintegration mandate that the team include individuals to address these issues. The rehabilitation process must provide strategies designed to improve functional capabilities as opposed to enacting treatments that merely decrease symptoms.

To accomplish this goal, the team must have a clear understanding of the physical, emotional, cognitive, and social consequences of the child's stroke. The degree, extent, and rate of recovery, which vary considerably among children, are also influenced in a significant manner by the size and location of the infarct and the presence of associated medical conditions (10). In addition, the immature brain's response to stroke is both varied and dynamic (212). Thus, the evolving biological recovery in combination with substitute/alternative cognitive processes and movement patterns necessitates an ongoing program of assessment and reassessment (218). It is anticipated that progress from the baseline condition will be observed as a direct response to the therapeutic interventions. In pediatric stroke, rehabilitation often becomes a spiral management process in which, following an initial evaluation, a treatment program is initiated, which in turn is constantly revised and updated based on successive reassessments.

Finally, and perhaps most importantly, the core principle of family-centered care is recognizing that the child's family is a constant presence in the rehabilitation process, available to provide comfort and reassurance during times of stress (11,105). Practical management decisions must be endorsed by the family and not just by the patient (218). Family members need to be involved in the process of their child's recovery and should be expected to participate in the therapy programs.

TABLE 43.4 Principles of Pediatric Stroke Rehabilitation

1. Coordinated transdisciplinary team working in unison
2. Treatment strategies initiated as soon as possible following stabilization
3. Therapeutic interventions directed at producing functional improvement
4. Practical management decisions endorsed by patient and family
5. Continual reassessment of child and updating of therapy program
6. Reassessments guided by an understanding of normative developmental maturation

Pediatric Rehabilitation Settings

Rehabilitative therapy can and should be initiated even while the child is still in the intensive care unit or on the inpatient neurology service. This early phase of intervention is designed to limit maladaptive behavioral habits and movement patterns and to prevent or at least minimize complications that can take months to resolve if not properly and promptly addressed, especially prevention of physical

TABLE 43.5 Admission Criteria for a Comprehensive Pediatric Stroke Rehabilitation Program

1. Deficits from stroke require intensive and multidisciplinary rehabilitation care
2. Medically stable
3. Responsive to verbal or visual stimuli, and sufficiently alert to participate in therapy
4. Prestroke physical and cognitive levels indicate potential for recovery of function
5. Stroke condition allows a reasonable expectation for improvement and the potential to achieve clearly identifiable treatment goals within an appropriate time period

deformities such as contractures owing to spasticity and prolonged immobilization (216).

After all medical and surgical issues have been stabilized, a decision has to be rendered regarding how the stroke rehabilitation process should move forward. In some children with stroke, improvements are rapid enough that they can be discharged home from the acute care setting and institution of outpatient therapy or a day treatment program is appropriate. In rare cases, typically involving bilateral hemisphere strokes or brainstem hemorrhage, recovery has been and likely will continue to be very slow. In these cases, a subacute nursing facility with less intense therapy may be a more reasonable option.

However, for the vast majority of children and adolescents with moderate to severe brain injury secondary to stroke, a dedicated neurorehabilitation program is indicated. Eligibility criteria for admission to comprehensive neurorehabilitation services have been developed and refined over the past decade (Table 43.5). Many childhood stroke patients meet these criteria, which include: a medically stable stroke condition that mandates intensive and multidisciplinary rehabilitation care; a premorbid physical and cognitive level that allows for meaningful recovery; a patient who has sufficient alertness to participate in the rehabilitation process; and finally, a stroke for which there is a reasonable expectation for improvement and the potential to achieve clearly identifiable goals over a reasonable time frame.

Current Neurorehabilitative Care for Children With Stroke

A comprehensive pediatric stroke program should provide a very highly intensive service through a multidisciplinary coordinated team approach, with an initial minimum of three hours of therapy each day. As recovery proceeds and endurance improves, the duration and scope of treatment are expanded to a full day of activity. Although therapeutic interventions carried out by physical and occupational therapists and speech–language pathologists are the mainstay of any treatment program, most rehabilitation teams also include psychologists, social workers, child-life specialists, music therapists, chaplains, orthotists, and dieticians. Psychologists and neuropsychologists are essential members of the team, both in the acute setting and over the life of the patient, as psychological and social support and intervention likely will be required at frequent intervals. Written team evaluations typically are mandatory and often guided by the child's case manager. These evaluations measure progress; determine impediments to recovery and potential solutions to the impediments; reassess and adjust established goals; and develop and implement discharge plans (218). Although an inpatient setting provides support as the family learns to cope with the child's injury, the team must concentrate on a process that also facilitates transition into the community.

Rehabilitative Treatment of Motor Impairments

Perinatal stroke is the most common cause of congenital hemiplegic cerebral palsy. In addition, motor impairments after stroke in childhood and adolescence are frequent and often the most common source of functionally adverse outcomes, occurring in 40% to 50% of patients (22,126). Motor rehabilitation in the adult stroke population is predicated on long-standing therapies within the fields of physical and occupational therapy designed to improve motor performance (10). Similar strategies are endorsed in pediatric stroke patients (105), despite lack of strong empirical evidence to substantiate or quantify the actual benefit. The early phase of treatment in most pediatric stroke rehabilitation programs is similar to successful interventions employed in adults and includes physical, occupational, and speech therapy (219,220), along with utilization of assistive devices and/or medications to facilitate postural alignment and minimize abnormal tone. As recovery proceeds, aerobic conditioning, muscle strengthening, and task-specific training assume greater importance. In addition, newer techniques for improving motor function, such as constraint-induced movement therapy (CIMT) and both central and peripheral stimulation, have recently been implemented with varying benefit.

Treatment of Spasticity

Almost every single child requiring acute neurorehabilitation services following stroke will manifest alterations in tone (219,221). In addition, spastic weakness is a characteristic feature observed in infants, children, and adolescents with hemiplegic cerebral palsy secondary to perinatal stroke. Spasticity is characterized by excessive and inappropriately timed activation of skeletal muscles, which typically impedes a child's ability to move in a normal fashion. Clinical manifestations of spasticity will vary depending upon the extent of damage and the sites of injury within the brain; intrinsic characteristics of recovery also influence the presentation of spasticity. In many pediatric stroke patients, spasticity will impair static postural alignment and limit passive movement (216). In addition, impaired activation of volitional movement resulting in weakness and clumsiness is often associated with spasticity (222). The main focus of tone management in the earliest stages of pediatric stroke rehabilitation is to minimize the complication of joint and

TABLE 43.6 Management of Spasticity

REHABILITATIVE MEASURES	PHARMACOLOGIC AGENTS
Muscle stretching	Central-acting antispasticity medications
ROM exercises	Baclofen (oral and intrathecal)
Postural/positioning techniques	Tizanidine
Adjunct interventions	Diazepam/benzodiazepines
Splinting/casting	Gabapentin, modafinil, and pregabalin
Orthotics	Peripheral-acting muscle relaxants
Physical agents	Dantrolene
Heat, cold, sound	Botulinum toxins
Muscle strength training	

muscle contractures, with a secondary goal of eliminating painful spasms (218). Motor rehabilitation should be directed toward outcomes that improve a child's functional capabilities (222), such as increased upper-extremity utilization to achieve greater independence in activities of daily living or greater coordinated leg and trunk movement resulting in improved ambulation.

Role of Therapies. Proper positioning, range-of-motion (ROM) exercises, and often splinting (216), are mainstays in the treatment of spasticity in obtunded stroke patients (Table 43.6). It is essential that ROM be carried out daily to all joints regardless of alteration of tone; later, as recovery ensues, the ROM exercises can be combined with adjunctive physical agents such as heat, cold, water, and electrical stimulation and specific affected muscles targeted (223). These physical agents are thought to reduce spasticity through inhibition and fatigue that directly relax a spastic muscle; however, facilitation of the antagonists of a spastic muscle, thereby creating relaxation by reciprocal inhibition, has been suggested as an alternative mode of action. Positioning can facilitate appropriate proper postural alignment and correct weight-bearing distribution throughout the body. Using gravity to stretch spastic muscles and promote relaxation is also a function of postural techniques (224). In the latter stages of recovery, proper position can facilitate active contraction of functionally weak muscle groups, especially in the distal lower extremities. Other mainstays in the treatment of motor disability following stroke are casting and splinting, which are designed to prevent formation and worsening of contractures in a spastic extremity (225). Inhibitive casting may also result in a lowering of tone via multiple mechanisms. Splints or orthotics may be utilized in children who have progressed further in their recovery to produce functional benefit without necessarily altering spasticity (Figure 43.8). For example, an appropriately designed wrist and finger extension splint may improve functional hand activities such as keyboarding without altering the underlying tone (225). In the latter stages of recovery, or in patients with chronic motor deficits such as hemiplegic cerebral palsy, equipment typically is a very important adjuvant to the rehabilitation process. Standing frames allow a child with reduced weight-bearing ability to be placed in an appropriate position to minimize the development of contractures. Other benefits to partial weight bearing include improved bone maturation and better pulmonary function.

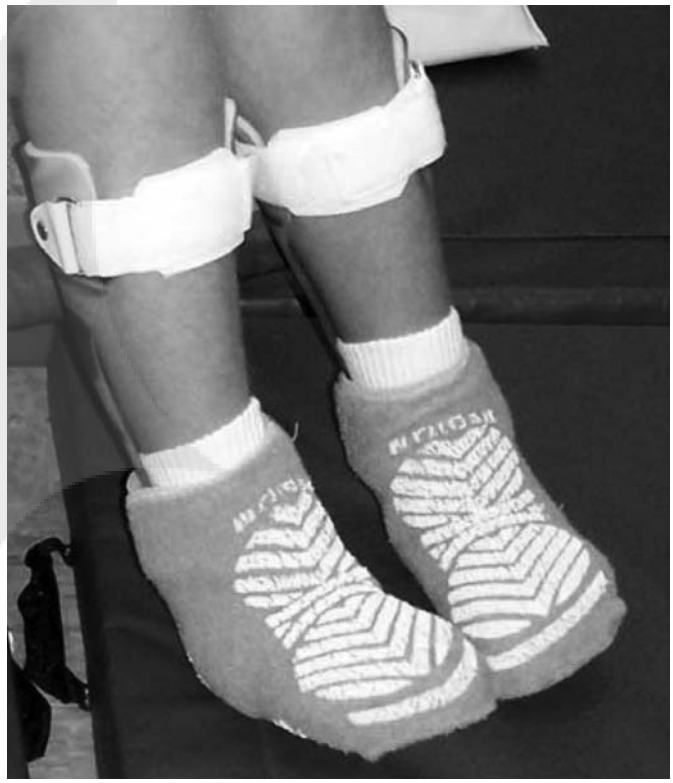

FIGURE 43.8 Ankle–foot orthotics often are a beneficial adjunct to promote greater independence in ambulation.

Oral Medications. Pharmacologic agents are a potential treatment modality for the management of spasticity in the acute pediatric stroke patient and in a child with chronic motor disability resulting from stroke. Despite the fact that a large

number of antispasticity medications have been available for many years, there are limited data available to conclude that any of these agents is truly effective in reducing spasticity in pediatric stroke patients (224,226,227). In children with hemiplegic cerebral palsy, efficacy data with regard to tone reduction exist, but there are no well-designed studies that have evaluated the impact of these agents on improving functional capabilities. In addition, studies have rarely analyzed outcome data as a function of stroke etiology. Thus, in view of the systemic and nervous system adverse side effects produced by antispasticity medication in the pediatric population, pharmacologic agents should be utilized only when severe spasticity cannot be adequately managed by other therapeutic modalities. In addition, continued use must be justified by ongoing demonstrable benefit to the child. Finally, antispasticity medication should be prescribed only for pediatric stroke patients who can achieve meaningful functional goals, as opposed to mere clinical ones (224). A notable exception to this recommendation is the institution of an oral medication to facilitate hygiene, improve appropriate positioning, reduce the requirements of caregiving, and ease rehabilitation procedures such as proper fitting of orthotics.

Commonly employed medications treating spasticity in the general pediatric population include diazepam (and other benzodiazepines), baclofen, tizanidine, and dantrolene (Table 43.6) (222,224,226–228). Based on adult studies, one could postulate that the efficacy of tizanidine and baclofen are comparable, with global tolerability data favoring tizanidine (224,228). Use of either medication may be limited owing to sedative side effects, often producing impaired arousal and attention even at relatively low doses. Dantrolene sodium is the least sedating of the antispasticity medications. Yet, as its site of action is within the muscle, it must be carefully titrated to minimize the potential for severe generalized weakness, even in unaffected muscles. Thus, dantrolene's usefulness in hemiplegic motor disability secondary to stroke is limited.

Concerns regarding efficacy and adverse side effects from the more standard antispasticity medications have prompted investigation of newer agents, such as gabapentin, modafinil, and pregabalin (224,229,230). However, presently there are no published reports on any of these medications in children with stroke. For further details regarding pharmacologic management of spasticity in childhood, an evidence-based practice parameter has recently been published (231).

Neuromuscular Blockade: Botulinum Toxin Injections. Botulinum toxin is increasingly being used to manage severe spasticity that involves only a few muscles or muscle groups (224,232). Reduction in spasticity and modest functional improvement in injected muscle groups both in the arms and legs have been documented in many studies, mainly in children with cerebral palsy (233–235). Unfortunately, it is not possible to separate out those patients whose chronic motor disability was the result of a stroke. On the adult stroke side, there is stronger evidence for a reduction in focal spasticity and increased gait velocity following botulinum toxin injection into the lower extremities. Evidence for improved function and quality of life is not as compelling (224,236). The effects of botulinum injections are local, dose dependent, and temporary. Thus, this form of therapy is best suited for those children with a limited number of "problem muscles" that interfere with major functional abilities such as ambulation or upper-extremity movement. A clinically apparent reduction in tone typically is most notable two to four weeks after injection, and ongoing benefit may persist for three to four months or longer depending on severity and the particular muscles involved. There are, however, significant limitations to the use of botulinum toxin, including: (a) maximum dose that can be administered at a single time; (b) appropriate spacing between injections (even to different muscles) to minimize the development of antibodies to the toxin; (c) cost; and (d) tolerability in pediatric patients (237,238). Judicious use of this agent in patients intolerant of splinting or with severe postural deformities can be a beneficial adjunct to maintain ROM. In children who demonstrate significant motor recovery and lessening of spasticity over time (221), the temporary neuromuscular junction denervation created by botulinum toxin is a favorable trait. In children with chronic motor disorders such as spastic hemiplegia, serial injections are typically coupled with an intensification of therapy and/or serial casting to secure maximum benefit (239). However, there have been reports of systemic side effects, including botulism, resulting in deterioration in respiratory and oral-motor function (240,241).

Intrathecal Baclofen Therapy. In patients with more severe or extensive spasticity, typically from brainstem hemorrhage or bilateral hemispheric infarction, intrathecal baclofen (ITB) therapy can be considered (218,224). The components of an ITB system include: a pump implanted under the skin on the abdomen that infuses the drug at a predetermined rate; a catheter that delivers the drug to the intrathecal space of the spinal cord; and a programmer that allows for adjustable and precise dosing (242). ITB therapy should be considered only in those pediatric stroke patients whose severe spasticity interferes with function or care. This population typically has chronic motor disability with either quadriplegia or a mixed pattern of both spasticity and dystonia. Timing of pump placement has not been adequately addressed in pediatric stroke patients, but a minimum of three to six months from stroke onset seems reasonable, given the typical rate of recovery witnessed in most children and adolescents.

Limitations in ITB therapy include: refilling the pump reservoir percutaneously every two to six months (depending on the daily dose) and replacement of the entire pump every five to seven years owing to limited battery life. Of greater concern are potential complications emerging from surgical implantation and refilling procedure, such as CNS infection and peritonitis. Complications from components of the device are also encountered, as are side effects such as somnolence, dizziness, headache, and hypotonia. Withdrawal from the medication is a medical emergency, presenting as somnolence, exaggerated rebound spasticity, muscle rigidity, and most notably fever and pruritus; this condition may advance to rhabdomyolysis and organ failure causing death (243).

Orthopedic Interventions. In stroke-related chronic motor disability, spasticity may progress and cause contractures and bony deformities despite optimal treatment. In such cases, orthopedic surgical intervention may be considered. The most common orthopedic procedures in this group of patients are tendon releases for fixed contractures at the ankle, surgery to correct hip subluxation or dislocation, and spinal instrumentation for scoliosis (105). The benefit of orthopedic surgery is most pronounced in patients who have achieved some degree of skeletal maturation (typically between ages 6 and 12 years), but evidence of efficacy specifically in the pediatric stroke population is limited. Many of these operations require intensification of a physical therapy program to strengthen muscles and improve the ROM in the involved extremity.

Selective Dorsal Rhizotomy. Selective dorsal rhizotomy (SDR) is thought to minimize aberrant muscle spindle input believed to trigger muscle overactivity and thus reduce spasticity in the legs. The operation is performed on the first two lumbar segments (244). Clinical investigation has demonstrated that the combination of SDR and physical therapy is beneficial in reducing spasticity in children with spastic diplegic cerebral palsy (245). Randomized studies indicate that SDR produces gains in strength, gait speed, and overall gross motor function (246,247) and that the degree of functional improvement relates directly to the percentage of dorsal nerve roots transected (248). Patients with spastic diplegia or mild quadriplegia who have good strength and trunk control (249) or those with a history of prematurity appear to be the most suitable candidates for SDR. Recently, however, favorable results have been reported for SDR in children with spastic hemiplegia, some of whom had a stroke as the cause of their motor disability (250).

Treatment of Dystonia and Other Hyperkinetic Movement Disorders

Dystonia following pediatric stroke, especially with basal ganglia involvement, has been reported with a frequency of roughly 1% to 3% (251) (Figure 43.9). Diagnosis may be a challenge given the often overlapping presence of spasticity and the typically delayed presentation, often measured in weeks to months (252,253). Treatment should be individualized based upon the type of movement disorder, recognizing that dystonia is observed most commonly. Though there are little data regarding the efficacy of pharmacologic agents in poststroke, acquired dystonia, trihexyphenidyl (anticholinergic), tetrabenazine (dopamine depleting), and botulinum toxin injections are often utilized (254).

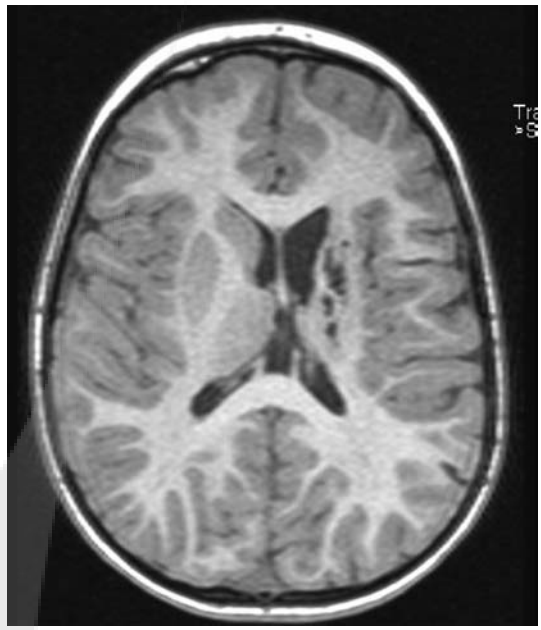

FIGURE 43.9 MRI demonstrating cystic encephalomalacia of the left basal ganglia in a 5-year-old with right arm and leg dystonia. He sustained an acute left MCA stroke 2 years previously, as seen in Figure 43.4.

Rehabilitative Treatment of Cognitive Impairments

Permanent cognitive impairments frequently are observed in survivors of pediatric stroke, impeding performance in academics and success in activities and even limiting independence in ADL skills (255,256). Childhood and neonatal stroke typically produces a moderate degree of global intellectual disability (147,257), with size and location of injury and age at stroke onset the strongest predictors of cognitive outcome (127,258,259). With dominant (usually left) hemisphere strokes, aphasia or other forms of language impairment are seen (256,260) and permanent deficits in complex language function often follow (261,262), as can memory and learning impairments (127,263). Academic skill impairments are more likely to be observed in children with stroke than in their adult counterparts. This finding is consistent with studies demonstrating that lesions acquired in childhood before literacy acquisition detrimentally affect the development of reading skills. This is true both in children who suffer general declines in verbal processing and in those who merely show a deficit in basic phonics skills without poor verbal IQ (264). Studies assessing language function following neonatal onset stroke have suggested that expression and comprehension skills are age appropriate at entrance to school (265,266), but subsequent development of more complex language-based abilities is impaired (267,268).

Age-appropriate neurocognitive evaluations are necessary in all at-risk stroke patients to ascertain educational and psychosocial support needs. Timing of initial assessment will be predicated on rate of recovery, age of patient, and intensity of educational demand (i.e., return to school). Subsequent evaluations typically are necessary, as deficits in higher cognitive abilities, such as executive functioning and specific language skills, may not become evident until years after the stroke when the skills fail to emerge at the expected developmental age (145,146,269).

Role of Therapies. There are several fundamental principles that should guide therapeutic interventions for communication and cognitive impairment in stroke rehabilitation, some of which have applicability to the pediatric population (270). First, therapy should be initiated in the acute care setting where the main focus is on providing appropriate sensory modulation. Cognitive retraining should pervade all aspects of the rehabilitation process; informal memory training should be attempted in every therapy or medical activity, including time spent with nursing, music therapists, and child life specialists. Interventions should be predicated on location of stroke, such as training of visuospatial skills following nondominant hemisphere stroke or cognitive interventions for specific language impairments, including reading comprehension in dominant hemisphere injury (270). Finally, rehabilitation should enhance preserved function as well as remediate residual deficits (218). Continual reassessment of cognitive and linguistic capabilities is essential to structure an appropriate program of therapeutic interventions. Sensory deficits, especially visual, should be ascertained, as they will impair the response to therapy as well as affecting the neurological assessment.

Oral Medications. In the early stage of childhood stroke rehabilitation, establishing an appropriate level of arousal and sustained attention is essential in furthering recovery. Agents that act upon the cholinergic, adrenergic, dopaminergic, and serotonergic neurotransmitter systems commonly are employed in the pharmacologic management of underarousal and/or reduced attention in pediatric patients with traumatic brain injury, but data on childhood stroke are scarce. Stimulants may have a role in children with poor arousal, inattention, and slow cognitive processing, which can be seen in younger stroke patients (263). Tricyclic antidepressants and dopaminergic agents, commonly amantadine, also have been utilized (271). Although not overwhelming, the results do demonstrate a likely overall beneficial impact on arousal/attention. Unfortunately, there are no credible published reports regarding the efficacy of pharmacologic intervention in children or adolescents with respect to memory and learning of new information (272,273).

Rehabilitative Treatment of Behavioral Impairments

Behavioral aberrations can be observed during recovery from pediatric stroke (256). Emotional regression and impaired information processing typically are seen in the initial phase of recovery. For most pediatric stroke patients, in contrast to other forms of acquired brain injury in childhood, their resolution typically occurs over the course of days to weeks. In stroke patients with more severe brain injury whose behavioral symptoms persist, sedative medications still should be avoided, as they often only aggravate the situation by further clouding the sensorium. Therapists and family members should strive to prevent these behavioral disturbances from evolving into learned patterns that can impair recovery and reduce the response to treatment. Unfortunately, there are rare children with stroke-acquired brain injury in whom aberrant and uncontrolled behavior persists. Though medication may be deemed necessary in such cases, use of pharmacologic agents to manage behavior in this clinical setting has not been investigated in children in a scientifically rigorous manner (274). The proposed benefits of most medications are derived from a limited number of studies typically involving only adult stroke patients carried out in a nonblinded fashion and without appropriate controls (275). The most pressing behavioral issues in the pediatric stroke population usually are aggression and severe agitation. Reasonable medications to try in these situations include beta-blockers, carbamazepine, valproate, and tricyclic antidepressants; others would advocate for clonidine, amantadine, and buspirone (276).

Permanent behavioral disorders in pediatric stroke patients can significantly impair social function (277), although the manifestations may not become apparent until midchildhood when the stressors of school are encountered (274). Lesions involving the putamen seem to predict attention deficit hyperactivity disorder (278), whereas bilateral hemispheric strokes raise the risk of emotional disturbances (256).

Psychosocial Family Support

Psychosocial family support must also be considered. Complete care of children with stroke includes their families. Complex psychosocial challenges are likely common and underestimated. Though psychosocial care resources are slowly improving, there is an ongoing need for the development of educational and emotional support to improve pediatric stroke care (105). Adverse effects of stroke on quality of life are measurable in most childhood stroke survivors and their families (279) and relate to both neurological deficits and psychosocial factors (255). Social factors and environment have been shown to affect adult stroke recovery and may be even more important in children (10). Therefore, it is important to introduce families to local and national pediatric stroke advocacy and support groups.

Family support also includes assistance in making informed decisions regarding the increasing number of controversial therapies and alternative medicines directed toward survivors of pediatric stroke. These interventions, such as hyperbaric oxygen and the Adeli suit, typically are quite costly and are marketed despite little to no evidence of efficacy and often well-recognized adverse effects (280–283). In addition, the time and effort wasted on these pseudotherapies both detracts from and often interferes with rational rehabilitation therapies (284). Stem-cell therapies are another controversial and increasingly sought-after intervention for childhood stroke and other forms of pediatric neurological disability (285). Despite their attractive promise, utilization of stem-cell treatments in either the acute or chronic management of childhood stroke is unlikely in the foreseeable future (286,287). A more appropriate focus for families of pediatric stroke survivors and their physicians is to ensure availability of rational therapies for all children with disabilities.

CURRENT RESEARCH ON ENHANCING STROKE RECOVERY

Fueled by the growing understanding of stroke recovery mechanisms at the systems, neuronal, and molecular levels, various novel rehabilitation treatments are currently in different stages of development and efficacy testing, mostly in adults (170,202). These novel treatments all build on some of the basic mechanisms thought to be important for stroke recovery. Many interventions known to improve learning are also being applied to stroke patients, because stroke recovery utilizes some of the same systems-level, neuronal, and molecular mechanisms as learning. Systems-level therapies are specifically aimed at enhancing activity in perilesional cortex and diminishing maladaptive interference from the contralesional hemisphere.

Currently, proposed stroke rehabilitation treatments fall into three basic categories. A large number of the proposed treatments consist of therapeutic training programs that build on existing physical, occupational, and speech therapy paradigms. Compared to more standard therapies, these treatments may incorporate novel technologies, or they may vary some of the specifics of training. A second group of novel treatments electrically stimulates the nervous system both centrally and peripherally. Finally, several medications are being tested in the hope that they might boost recovery from stroke. Not surprisingly, different combinations of novel treatments are also under investigation.

As with research on the basic mechanisms of stroke recovery, rehabilitation treatments have mainly been focused on improving motor deficits. However, efforts are under way to extend some of the more successful motor recovery therapies toward other domains, such as the restoration of sensory, language, attentional, and executive deficits (288,289). Treatments for children recovering from stroke have all been extrapolated from adult interventions.

Taken together, studies on the mechanisms of stroke recovery suggest that a critical period for stroke recovery spans from 5 to about 30 days after stroke. It is considered standard of care for stroke patients with significant deficits to receive multidisciplinary neurorehabilitation consisting of physical, occupational, and speech therapy during this period. However, for practical reasons, such as ease of recruitment, many clinical studies of novel neurorehabilitative interventions have been carried out in chronic stroke patients at a time when further functional improvements are much less likely.

Training-Based Therapies to Improve Stroke Recovery

Constraint-Induced Movement Therapy

Learned Nonuse. Edward Taub proposed that a process he termed "learned nonuse" might contribute to poor upper-extremity function after motor stroke, based on studies with macaque monkeys who stopped using a limb after it had been deafferented, even though they had full strength in the limb (290). He hypothesized that the additional effort and frustration of using a limb that could not provide sensory feedback drove the animals to rely on the unaffected limb. However, when these macaques had their healthy limb restrained, they regained use of the deafferented arm with the help of operant conditioning and behavioral shaping paradigms (291).

CIMT in Adult Stroke Rehabilitation. Taub's hypothesis led to the development of constraint-induced movement therapy (CIMT) as a treatment. Patients treated with CIMT have their unaffected arm restrained with a sling, cast, or mitt for the great majority of their waking hours. At the same time, as patients improve, they practice motor skills that advance in difficulty for about two hours a day. This intensive program is typically carried out for two weeks.

The largest published trial of CIMT to date (EXCITE) randomized 222 adults with hemiparesis at 3 to 9 months after stroke to either 2 weeks of CIMT or customary care (292). This trial showed clear motor benefits of CIMT over customary care at both 12 months (292) and 24 months follow-up (293). A crucial aspect of this study was that customary care meant very little or no rehabilitation therapy for many of the control patients. Thus, it was unclear if the benefits of CIMT were due to the upper-extremity restraint, the intensive motor skill practice, or the combination of both.

The follow-up VECTORS trial investigated CIMT within the first 4 weeks (mean 10 days) after stroke (294). This study randomized 52 patients to receive either intensive inpatient therapy, standard CIMT (2 hours practice, 6 hours restraint per day), or high-dose CIMT (3 hours practice, 90% waking hours restraint) for 2 weeks. No difference in outcome was noted between standard CIMT and dose-matched intensive inpatient therapy at two-week and three-month follow-up.

A meta-analysis that included the EXCITE and VECTORS trials and 16 additional CIMT studies found no significant effect of CIMT on disability and only a moderate benefit for arm function (295). Studies directly comparing CIMT to dose-matched intensive bilateral arm training paradigms showed both of them to be superior to lower-intensity approaches (296,297). Additional trials are needed to establish the parameters within which CIMT is most likely to be beneficial, as it still must be considered a promising treatment (172). Animal studies of CIMT have not provided a more detailed mechanistic explanation of how CIMT could augment stroke recovery in humans (298). A reasonable hypothesis is that in humans decreased activation of the contralesional hemisphere could lower harmful IHI and force systems-level reorganization toward the ipsilesional hemisphere.

CIMT in Children. Studies of CIMT in pediatric patients have focused almost exclusively on children with congenital hemiparesis, many of whom likely had a perinatal stroke. Standard pediatric CIMT used either a cast or a bivalved cast to restrain the more functional arm (Figure 43.10A). Just as in studies of adult stroke, CIMT caused lasting improvements in motor function when compared to standard treatment (Figure 43.10B), which was not dose-matched and therefore significantly less intense (299–301). A more recent study randomized 63 children with congenital hemiparesis to

A B

FIGURE 43.10 Constraint-induced movement therapy typically has two major components: constraint of the more functional arm via a cast (A); and a behavioral program that repetitively encourages graded unilateral movements of the more impaired arm and hand. Play activities, such as crawling over a ball pit, can be utilized to achieve therapy goals, such as finger and wrist extension on the less functional side (B).

dose-matched CIMT or a bimanual intensive therapy (BIT) regimen and found slighter better outcomes for CIMT immediately following the treatment period, but these differences were not sustained at 12-month follow-up (302–305). Given how important intensive practice seems to be for the efficacy of CIMT, a recent study in children with cerebral palsy noted no difference in the benefit of three hours per day of CIMT compared to six hours per day (306,307).

Robot-Assisted Therapy

With advances in robot technology, it has become a possibility that standard therapies could eventually be augmented by robot-assisted therapy. The largest trial randomized 127 patients with chronic (greater than 6 months) upper-extremity hemiparesis from stroke to either receive 36 hours of robot-assisted therapy, dose-matched intensive therapy, or significantly less intensive standard care (308). Patients were followed for 36 weeks. Overall, robot-assisted and dose-matched intensive therapy were equivalent, and both were more efficacious than standard care. Both robot-assisted and dose-matched therapy delivered about 1000 targeted movements per session, whereas standard therapy included about 45 movements per session. A cost analysis revealed that robot-assisted therapy was about $2,000 cheaper than dose-matched intensive therapy.

Robot-assisted therapy may eventually make it easier to deliver the high volume of repetitions needed to affect use-dependent neural plasticity even in the chronic stroke phase (309). A follow-up trial is currently comparing the efficacy of robot-assisted therapy at different doses, given the seeming importance of high numbers of repetitions (180). Besides fine-tuning the optimal dosing and timing of robot-assisted therapy, further technological advances are improving the sophistication of the movements that such robots can perform (310). Use of robot-assisted therapy in children with cerebral palsy and stroke (Figure 43.11) is now also under investigation (311).

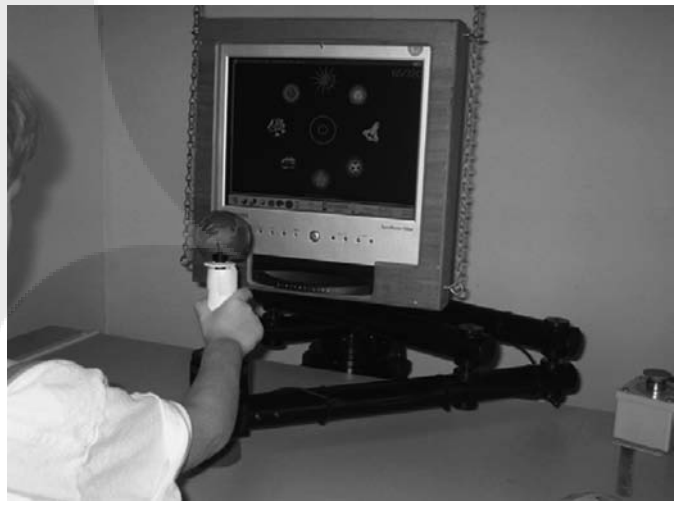

FIGURE 43.11 A child with right hemiplegia works to improve shoulder and elbow movement using the maze pattern on the robot.

Source: Adapted from Ref. (311). Fasoli SE, Ladenheim B, Mast J, Krebs HI. New horizons for robot-assisted therapy in pediatrics. *Am J Phys Med Rehabil*. 2012;91(11)(suppl 3):S281. Copyright 2012, Wolters Kluwer. Adapted with permission.

Dosing and Timing of Movement Training

One common denominator between CIMT and robot-assisted therapy is the high intensity of therapy. When matched for

dose, neither CIMT nor robot-assisted therapy is clearly superior to standard therapy or bilateral therapy. Thus, the main benefit of CIMT and robot-assisted therapy may be that they provide convenient approaches for the delivery of very intense therapy. Animal studies have only shown use-dependent neural plasticity after training programs that were many times more intensive than current standard stroke rehabilitation therapies (196,197,312). A better understanding of the dose-response curves for movement practice is critically important for the delivery of optimal stroke neurorehabilitation. Fortunately, such efforts are currently underway.

Effect of Feedback on Training-Based Therapies

Besides researching the impact of different dosing and timing regimens for task-specific practice regimens, much effort has been devoted to finding ways to further enhance the effectiveness of practice-based therapies. In healthy subjects, motor learning is improved by both implicit and explicit feedback (313). Moreover, it has been suggested that feedback discourages compensatory movements in favor of restoring typical movement patterns. Hence, a wide variety of different mechanisms for delivering feedback to stroke patients have been investigated. Meta-analyses of stroke rehabilitation interventions that provided feedback via different sensory modalities have concluded that feedback about the success and performance of movements seems to be generally beneficial (314). The divergences in methodologies and the small number of patients have precluded the identification of any significant differences between feedback methodologies.

Mirror Visual and Other Sensory Feedback. Mirror visual feedback (MVF) therapy initially was developed as a treatment for phantom pain (315). MVF is based on the hypothesis that the mismatch between motor commands sent to an amputated limb and the corresponding visual feedback contribute to phantom pain. Ramachandran and colleagues asked amputees to perform bimanual tasks while seated in front of a mirror that was placed perpendicular to the patient's chest (315,316). Mirroring the movements of the healthy arm created the visual illusion that patients were controlling two healthy arms and the mismatch between motor commands and visual feedback was alleviated. Mirror therapy has been applied to stroke patients, with the paretic extremity hidden from view by a cover or barrier, as it was thought that mismatched motor outputs and visual feedback might also contribute to learned nonuse of a limb.

A recent meta-analysis of 14 studies that together had enrolled more than 500 patients concluded that mirror therapy seems to improve arm function, but that, similar to the CIMT literature, many of these studies lacked appropriate control conditions (317). It has been proposed that mirror therapy works by activating the contralesional hemisphere, which has been correlated with greater stroke severity. Thus, mirror therapy may be most appropriate for severely paretic patients with the greatest mismatch between motor output and visual feedback and the greatest reliance on contralesional hemisphere involvement.

Other forms of visual feedback, as well as auditory and somatosensory feedback, have all been explored as adjuncts to standard stroke therapies, either alone or in different combinations (314). Overall, enhancing visual feedback seemed beneficial, but none of the relevant studies could demonstrate a clear additive effect of providing feedback in multiple sensory domains simultaneously.

Virtual Reality. Therapies using virtual reality technology have generated much excitement, because they can provide simultaneous feedback via several sensory streams. Virtual reality paradigms also have the potential for high numbers of repetitions, and they can provide motivating environments. The technical sophistication of virtual reality therapies can range from the use of a commercially available gaming console to the use of motion capture technique and concave head-mounted video displays.

So far, only several small-scale studies have evaluated the utility of virtual reality-based therapies (318–321). Most of these studies showed greater improvements for the intervention than the control groups, yet the control interventions were often inadequate, such as passively viewing someone else receive rehabilitation.

Effect of Imagery on Training-Based Therapies

Human neuroimaging experiments have clearly demonstrated that both observing and imagining movements reliably activate the brain's motor systems (322–324). Furthermore, several studies had documented instances of improved motor learning with motor imagery in healthy subjects and athletes (325), and thus these strategies have been considered potential additions to standard stroke therapies.

The largest trial randomized 121 hemiparetic patients within 6 months of their stroke to receive standard therapy, standard therapy plus twelve 45-minute sessions of structured supervised motor imagery, or standard therapy plus nonmotor imagery practice, but the study found no differences between any of the three groups (326). Action observation as an adjunct has only been evaluated in very small samples so far (327). Thus, although some aspects of neuroscience point toward possible benefits from imagery and observation, the clinical studies carried out so far have not documented any.

Training-Based Therapies to Improve Nonmotor Functions

More recently, some of the practice-based therapy principles that guide motor rehabilitation have been applied to the rehabilitation of cognitive abilities, namely language, attention, memory, and executive function, as well as sensory deficits. Like therapies for motor deficits, these cognitive and sensory therapies are mostly based on the massed practice of specific tasks.

Language. Language impairment, or aphasia, is common after strokes in adults and children and is a cause of significant disability (256,260). Patients with impaired language

following stroke typically receive speech–language therapy (SLT) as the standard of care. A recent systematic review of all available adult trials concluded that SLT improves language outcomes when compared to no intervention (328). However, when comparing SLT to control interventions that provided stimulation or support, such as social activities, SLT has not been shown to be superior. The National Health Service in Britain randomized 170 patients with language impairment 2 weeks after stroke to receive either 18 hours of SLT over the subsequent 13 weeks or 18 hours of social visits (329). This study found no differences in language outcomes between the groups.

Attentional Neglect. Attentional neglect, typically of the left side of the patient's body and visual field, is a common deficit after stroke in adults. It has been hypothesized that a 30-degree visual orientation bias to the right is central to the pathophysiology of left neglect (330). Thus, the use of prism glasses during rehabilitation has produced promising results (331). Patients with left neglect wear right-shifting wedge prisms, making it appear as if all visual objects are shifted to the right. Over time, this leads to a rightward shift of visual orientation, which can persist for hours after a session and for up to five weeks after repeated sessions (332). However, a randomized trial of prism adaptation (333), using a small degree of shift, could not identify any lasting benefits.

Executive Function and Memory Deficits. Practice-based strategies to rehabilitate executive function and working memory deficits are still in their infancy. A systematic review of 10 small trials that evaluated a varied collection of therapies for memory and executive deficits (334) identified some benefits when compared to no intervention. However, it is unclear how well any of these improvements on specific tasks will transfer to real-world scenarios.

Sensory Deficits. Training-based therapies for sensory losses are currently least advanced when compared to motor and cognitive rehabilitation. The majority of studies have simply stimulated the areas of sensory deficit (335). However, a few small-scale studies involved practicing sensory discrimination tasks, more similar to the strategies used in motor rehabilitation. The efficacy of any of these interventions is still unclear.

Damages to early visual cortex seem difficult to restore. Therefore, visual therapies have focused on compensatory strategies, such as scanning to improve reading ability, the efficacy of which is supported by multiple smaller studies (336).

Stimulation of the Nervous System to Improve Stroke Recovery

Neuroimaging and neurophysiological studies have revealed some of the correlates of improved outcomes after stroke. Moreover, other such studies have shown how the functional neuroanatomy of the brain's distributed systems can be reshaped by task practice (196,197,337). Repetitive training on specific tasks clearly improves recovery after stroke, but is very time-consuming. Thus, there is significant interest in directly stimulating specific parts of the nervous system, usually by inducing electrical currents, to bypass or at least enhance the process of task practice.

Stimulation of the Peripheral Nervous System

Fifty years ago, electrical stimulation of peripheral nerves was developed as a functional orthotic or neuroprosthesis. Currently, several devices are available to treat foot drop and hand weakness, therapies termed functional electrical stimulation (FES). Research as to whether FES might enhance motor recovery after stroke typically involves stimulation paradigms that have utilized external or internal EMG electrodes to trigger electrical stimulation tuned to elicit functional movements. A host of small studies have found standard therapy plus FES to be superior to standard therapy alone, but they unfortunately did not control for dose effects (338). Human neuroimaging studies have shown that FES can alter activations in motor systems (339). In healthy volunteers, simultaneous voluntary motor activity and FES led to greater cerebellar activation, launching the hypothesis that the coupling of FES and volitional movements may enhance the formation of cerebellar feed-forward models, so important for normal movement (340). Clearly, further studies are needed to evaluate the utility of FES, but it holds special promise for more severely affected stroke patients who are too weak to move without electrical augmentation.

Brain Stimulation

Directly stimulating or inhibiting specific brain regions electrically moves the level of intervention even closer to the final effectors of stroke recovery. Two methods for providing gentle electrical stimulation either directly (transcranial direct current stimulation—tDCS) or indirectly (repetitive transcranial magnetic stimulation—rTMS) are under investigation as potential treatments for enhancing stroke recovery. These methods have received much attention in recent years because many small studies have shown that they can enhance cognitive, sensory, and motor skills in healthy subjects and stroke patients.

Transcranial Direct Current Stimulation. The basic setup of tDCS requires a cathode, an anode, a reference electrode, and a current source, for which a battery suffices; thus, it is technically straightforward. Currents are too small to elicit cortical action potentials (typically 1–2 mA). During stimulation, cortex underlying the anode becomes relatively more excitable because of a depolarization of the resting membrane potential, whereas cortex under the cathode is relatively inhibited because of a hyperpolarization of the resting membrane potential (341–343). In tDCS, current below 2 mA is typically applied for somewhere between 5 and 15 minutes, but subjects can only feel the current for the first few seconds of a treatment and thus cannot discriminate between full treatment sessions of many minutes and sham control sessions during which the current is turned off again after 30 seconds.

Experiments in animals and humans suggest that anodal tDCS lowers GABAergic tone via $GABA_A$ receptors, inducing a state of heightened neuroplasticity that is conducive to learning (341,343,344). Experiments in mouse brain slices showed that anodal DCS paired with repetitive low-frequency synaptic activation induces NMDA receptor-dependent long-term potentiation, a learning mechanism. These effects depend on BDNF signaling and were abolished in mice with a genetic block in BDNF signaling (345).

Studies in both healthy volunteers and stroke patients have shown a great host of performance improvements when comparing tDCS to sham treatments. Improvements were seen across many cognitive domains, including social cognition (346), memory (347,348), language (349), vision (350), and motor function (351–353). In healthy volunteers, tDCS of primary motor cortex during practice enhanced learning on a difficult novel task, and the effect was still apparent at three-month follow-up (351). However, most other studies of tDCS so far showed persistence of beneficial effects for at least several days, but lacked long-term follow-up.

Prior imaging studies suggest that greater ipsilesional and lesser contralesional neural activity correlates with better motor outcomes in stroke. Thus, several small studies have investigated the effects of tDCS in stroke patients with chronic hemiparesis. One study randomized 20 patients to receive either sham therapy paired with rehabilitation exercises or a combination of inhibitory tDCS contralesionally and excitatory tDCS ipsilesionally, also paired with rehabilitation. The treatment group showed an almost 20% improvement in arm function scores, and these benefits persisted at 1 week follow-up (354). A similar study separately compared ipsilesional excitatory tDCS, contralesional inhibitory tDCS, and sham treatment in chronic motor stroke patients (355). Ipsilesional excitatory tDCS was associated with a 5% to 10% performance improvement as well as increased activations on the ipsilesional side as measured by fMRI. Other small studies demonstrated that contralesional cathodal tDCS enhanced function in mildly paretic patients (356) but worsened it in severely paretic patients, consistent with prior studies showing that severely paretic patients rely more strongly on contralesional activations (357). Studies of the functional connectivity between brain regions within the motor system have shown that tDCS also enhances the coupling between motor regions (358–360). Although tDCS treatment is low cost and very safe, unfortunately it remains largely unstudied in children.

Repetitive Transcranial Magnetic Stimulation. TMS uses rapidly shifting magnetic fields to induce small currents in the underlying brain tissue and induce neurons to fire action potentials; when applied over motor cortex, it can cause muscle movements. Repetitive TMS (rTMS) is similar to tDCS in that it can increase or decrease the excitability of underlying cortex without causing the generation of action potentials. Low-frequency rTMS (1 Hz) diminishes brain excitability, whereas high-frequency rTMS (5–20 Hz) enhances it. Typically, rTMS is applied for about 20 minutes at a time. Modern TMS coils can target small areas of the brain, including deeper-lying structures (361). Repetitive TMS is generally well tolerated; however, there have been some reports of rTMS treatments causing seizures (362).

It is thought that rTMS, similar to tDCS, induces a local state of heightened use-dependent neuroplasticity (343). Yet, rTMS may affect brain plasticity through somewhat different molecular and cellular mechanisms. MR spectroscopy studies in humans, for example, have shown that inhibitory rTMS increases GABA levels locally (344), whereas inhibitory tDCS lowers both GABA and glutamate levels (344).

Neuroimaging studies in humans have shown that rTMS tends to modulate activity throughout the entire functional system that was targeted by the treatments (343,363,364). During post-rTMS task performance, focal brain activations can be altered as well as the relationship between brain regions belonging to the system (e.g., motor system) (343,363,364).

Evidence for the clinical efficacy of rTMS in stroke patients is limited to small-scale studies. A recent double-blinded trial randomized 30 chronic stroke patients with hemiparesis to receive either 25 minutes of inhibitory rTMS (1 Hz) or sham treatment to the contralesional hemisphere twice a day for 10 days. Half the group received treatment prior to 45 minutes of standard therapy and the other half received therapy first followed by rTMS. At 90-day follow-up, the treatment group overall had significantly better motor outcomes. Furthermore, the benefit was significantly greater if the rTMS treatment was followed by therapy and not vice versa (365). A recent meta-analysis of rTMS studies in adult stroke patients suggested that rTMS might be beneficial when added to standard therapy and that contralesional inhibitory rTMS may be more beneficial than ipsilesional excitatory rTMS (366), although patients with larger strokes are less likely to demonstrate positive benefit (367).

In contrast to tDCS, rTMS has been studied in children with chronic paresis after stroke. A total of 10 children who had suffered a subcortical stroke anywhere between the ages of 1 month and 17 years were randomized to receive either contralesional inhibitory rTMS or sham treatment (368). These children received 20 minutes of rTMS daily for 8 days and showed improved grip strength at 17 days after treatment. A follow-up study showed that the treated group had decreased IHI (369). As with tDCS, rTMS has generated some promising results, but more research is needed before it can become a clinical treatment.

Medications to Improve Stroke Recovery

Using medications during the subacute phase to help restore function after stroke represents a separate endeavor from using these same or similar medications to treat persistent symptoms following stroke, such as depression or inattentiveness. Efforts to find such neurorehabilitative medications have focused on compounds shown to improve use-dependent neuroplasticity and learning.

Selective Serotonin Reuptake Inhibitors

Four small clinical trials enrolled a total of 84 patients and each trial showed motor improvements, albeit using different outcome measures and time points and 2 different selective serotonin reuptake inhibitors (SSRIs) (370–373), but each reported a beneficial effect. One trial studied patients with fMRI following a single dose of fluoxetine and found increased ipsilesional motor cortex activation and improved function of the corresponding hand (371).

The fluoxetine for motor recovery after acute ischemic stroke (FLAME) trial was a randomized, placebo-controlled, double-blinded multicenter clinical trial that randomized a total of 118 adults with moderate to severe motor deficits to receive either standard rehabilitative care plus 20 mg of fluoxetine daily, or standard rehabilitative care plus placebo (374). Patients were randomized between 5 to 10 days after stroke and received fluoxetine or placebo for 90 days. Motor outcomes were significantly better in the treatment group, without significant adverse effects. Even though the fluoxetine treatment group had lower levels of depression at 90 days, it seems unlikely that the motor benefits were solely driven by decreases in depression (375). Any patient who developed clinical depression in the treatment or placebo arms was treated with fluoxetine 20 mg, but the data were still analyzed on an intention-to-treat basis.

Although the FLAME trial enrolled only patients between 18 and 85 years, it seems reasonable to extrapolate its findings to include at least teenage patients who have suffered a motor stroke, especially given fluoxetine's safety profile in the pediatric population (376,377).

Stimulant Medications

Stimulant medications have a potent activating effect on the brain and induce the release of norepinephrine, dopamine, and serotonin neurotransmitters. Positive results in animal studies suggested that stimulant medications might be beneficial for human stroke recovery (378). Many studies have shown enhanced poststroke recovery in animals treated with amphetamines, with some of these benefits preserved for up to eight weeks (379,380). A close temporal relationship between stimulant treatment and skill training seemed necessary for lasting improvements. Several studies also reported that the behavioral improvements in stimulant-treated animals were associated with increased axonal sprouting (380–382).

Unfortunately, human trials so far have not replicated the encouraging animal data (383,384). These failures may have been caused by a variety of reasons, such as improper stimulant dosing, incorrect timing of stimulant treatment to rehabilitative therapy, selection of the wrong stroke subpopulations, and inadequate therapy intensity (385,386). Data from pediatric studies are scarce, but stimulants in children actually have a better safety profile than in adults and thus deserve ongoing consideration.

Medications That Increase Dopamine

Similar to animal studies of amphetamines, pharmacologically increasing dopamine also induces neuroplasticity and improves stroke recovery in animal models (387,388). Studies in healthy human volunteers have shown that the administration of levodopamine modulates use-dependent neuroplasticity (389,390) and that it can facilitate motor memory in healthy volunteers (391) and stroke patients (392). In the largest clinical trial of levodopamine in stroke recovery so far (53 adults), those receiving standard therapy plus 100 mg levodopamine daily at 3 weeks to 6 months after stroke had significantly better motor scores when compared to those who were treated with standard therapy plus placebo (393). No data currently exist to determine whether pediatric patients might benefit from levodopamine as an adjunctive therapy during stroke recovery.

Medications That Could Negatively Impact Stroke Recovery

Medications that counteract the neuropharmacological effects of drugs deemed beneficial during stroke recovery could theoretically worsen stroke recovery. There are no human data that speak directly to this point. However, animal studies suggest that increasing GABAergic signaling during the subacute recovery phase, for example, through the use of benzodiazepines, could worsen stroke outcomes (159). Similarly, haloperidol, a neuroleptic that decreases catecholamine release, blocks the benefits of stimulant treatment in rats (378). Thus, it might be prudent to avoid such medications in all patients recovering from stroke, including children, unless absolutely necessary.

CURRENT RESEARCH ON COMPENSATING FOR STROKE DEFICITS

Brain–Computer Interface

Some stroke patients will continue to suffer debilitating deficits despite maximal rehabilitative efforts. For example, adults and children with brainstem strokes often have very poor motor recovery, possibly because important brainstem circuitry is concentrated in a small area and less redundant than circuitry in other parts of the brain (181,182). Despite causing severe motor impairments, brainstem strokes often spare cortical and subcortical motor systems. Thus, though the restoration of typical function may be out of reach for some of these patients, they may benefit from neuroprosthetics controlled by brain–computer interfaces (BCIs). The basic BCI approach is to use the brain's own motor command signals to control a computer-controlled prosthetic device. The prosthetic device can be anything from a cursor on a screen to a complex robotic limb. At least in theory, any type of neural signal can be used to power a neuroprosthetic. BCIs represent a rapidly growing area of research fueled by continued improvements in computing power and algorithms for extracting critical information from extremely large data sets, as well as advances in robot design (394).

Intracortical Multi-Electrode Arrays

Although standard EEG signals recorded from electrodes placed on the scalp can be used to create a BCI (395,396), intracortical recording of neural signals to power BCIs is the more advanced and also the most invasive approach. Multi-electrode arrays that can record extracellular neural signals from many neurons simultaneously are implanted in primary motor cortex. The highly mathematically processed neural-derived signals are then used to control a robotic device. A few tetraplegic human patients have been implanted with electrode arrays in primary motor cortex, which have been used to control a computer cursor (397)—an ability that has remained stable for years (398)—and more recently to move robotic arms in three dimensions, allowing a patient to drink coffee from a bottle (399). Currently, the use of robotic arms is limited to laboratory settings (399) and none have been tested in the pediatric population.

Opportunities and Challenges Specific to Stroke Recovery in Children

Almost all basic research on the molecular, neuronal, and systems-level mechanisms of stroke recovery has been carried out in animal models of adult stroke and adult stroke patients. Similarly, almost all clinical studies of various treatments meant to enhance stroke recovery were carried out in adults. By sheer necessity, much of pediatric stroke rehabilitation has therefore been extrapolated from adult stroke rehabilitation. Thus, it is important to be mindful of the particular opportunities and challenges posed by studying and caring for children during their recovery from stroke.

Children May Have Potential for Better Overall Outcomes

When compared to adult stroke patients, children have better survival rates after stroke (14,400). On average, children who suffered strokes also seem to recover to a greater degree than adults (174,400). In children, many individual cases of complete or near-complete recovery after severe strokes have been highlighted. For example, near-complete recovery from neglect and hemiplegia (401) or major improvements of visual deficits following bilateral occipital stroke (150) have been reported. Children who suffered large left hemisphere strokes perinatally can often develop normal language skills (402,403).

Stroke outcomes are not uniform across age (11). Historically, it had been argued that the youngest stroke patients should have the best outcomes, as their brains were presumed to be the most plastic. However, more recent studies showed that children who suffered a stroke between the ages of 1 to 6 years relatively have the best outcomes (148,404). Stroke outcomes were relatively worse in children younger than 1 year and older than 6 years. Similar to adults, it seems that most of the functional recovery in children occurs in the first three months after stroke (174).

Even though children overall seem to have better outcomes after stroke than adults, the majority of pediatric stroke patients will still have to contend with some neurological deficits for the rest of their lives (139).

Potential Differences in Recovery Mechanisms Between Children and Adults

It often has been argued that the apparently better stroke outcomes in children are at least partly caused by greater neural plasticity. One often-cited example for this is that children who have undergone complete surgical disconnection of one hemisphere commonly show a remarkable recovery of function on the affected side of the body, which by definition can only be supported by the contralesional hemisphere (405). This has led to the hypothesis that recovery of function in children can depend on contralesional activity to a greater degree than in adults. However, a small study of inhibitory contralesional rTMS in children with stroke (mean age 13 years old) showed that it enhanced hand function, just as it does in adults (368). Thus, though children may have better outcomes after functional loss of a whole hemisphere, IHI may still have a negative effect on stroke outcomes in children.

Normal language development following large perinatal lesions of the left hemisphere lesions is also typically attributed to greater neural plasticity in children. Functional MRI studies of language function in such patients documented differences in activation patterns when compared to age-matched controls (402,403). However, the specific differences varied across patients, suggesting that the development of language after stroke differed from child to child.

CONCLUSION

Stroke is an important cause of morbidity and mortality in the pediatric population. The risks and benefits of stroke treatments in children may differ significantly from those in adults, probably because of developmental differences in the cerebrovascular, neurologic, and coagulation systems. The variety of etiologies of pediatric stroke makes it difficult to develop stroke prevention strategies based on adult studies. Despite the fact that the incidence of pediatric stroke is lower than stroke in adults, the consequences of stroke in children can have a lifelong impact on function, families, and use of resources. Lo et al. determined that the median cost for pediatric poststroke care during the first year after diagnosis was $42,338 (7). The cost for stroke care was higher for hemorrhagic stroke than for ischemic stroke. Cost had a significant positive correlation with neurologic impairment.

There is a growing consensus among those who study pediatric stroke that a common terminology is needed to enhance research and multicenter trials (34,151). Increased awareness of unique pediatric stroke subtypes, their clinical presentations, and findings on imaging studies can improve early identification and development of optimal treatment strategies. Furthermore, improved recognition of subtypes may lead to more effective secondary stroke-prevention measures (28).

A pediatric stroke rehabilitation model should be utilized to help parents and the treatment team members embrace the multidisciplinary process for recovery. Encouraging family members to become active participants in the rehabilitation process may help with the advocacy that is necessary in the educational setting. Preconceived notions of what a child may or may not be able to accomplish may interfere with his or her ability to participate fully in athletic and social activities. As is true with all children, it is incumbent on the caregiver to help maximize each child's functional potential. The pediatric rehabilitation team is a resource for families to help accomplish this goal.

Stroke rehabilitation of children and adolescents has improved dramatically over the past two decades. Advances in surgical and medical management and technology have produced a dramatic impact on the mortality/morbidity and quality of life of the acutely affected child. Our understanding of the biologic mechanisms of stroke recovery has accelerated, leading to the hope that this knowledge can be translated into specific therapies that can serve as the basis for restorative rehabilitation. The more immediate need is to upgrade the rehabilitation treatment we provide for our children who survive stroke. Few of the currently employed therapeutic interventions, medications, and physical modalities implemented in the rehabilitation of children and adolescents with stroke have been subjected to rigorous scientific research with appropriate control subjects. Most published investigations involve limited populations with little regard for the impact of normal development on recovery; many fail to recognize that only achievement of functional goals are meaningful and appropriate end points. Objective research investigations with quantifiable, clinically relevant outcomes using double-blinded protocols are essential for the future growth of rehabilitation and improvement in the care given to the survivors of pediatric stroke.

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44

Stroke in Young Adults

Randie M. Black-Schaffer

Approximately 4% of strokes in the United States occur in adults younger than 45 years old (1). Although the 32,000 strokes in this age group are a small fraction of the 795,000 total occurrences in the United States each year, they are a significant source of neurologic impairment in this group. The fact that stroke occurs in those under 45 years old more than twice as frequently as both spinal cord injury (12,000/year for all ages) and multiple sclerosis (12,000/year for all ages) in the United States has not been well recognized (2,3), perhaps because of the tendency to consider young adult stroke in the context of all strokes rather than in the context of all causes of neurologic impairment in the young. In contrast to the United States, in developing countries with younger populations, stroke in adults under the age of 40 accounts for between 19% and 30% of all strokes, leaving no doubt about its significance as a source of neurologic impairment in these societies (4). Numerous investigations over the past 25 years have established important differences in the incidence, epidemiology, etiology, treatment, and outcomes of stroke in young adults compared to older populations. These are discussed in this chapter.

EPIDEMIOLOGY

Incidence

The incidence of stroke in adults under 45 to 50 years of age has been found to range from 8.6 to 26.4 per 100,000 in European and American populations (5–13). Notably higher rates are reported in two studies of African populations (4,14) (see Table 44.1). These numbers contrast with the much higher incidence of stroke in older adults, which, in the United States, ranges between 230 per 100,000 in white females and 660 per 100,000 in black males for those 45 to 84 years old (15).

Not only is the frequency of stroke different in young adults compared to adults of all ages, but the distribution of stroke types differs as well. Among people in the United States of all ages, 87% of strokes are ischemic infarctions and 13% are intracerebral (ICH) or subarachnoid (SAH) hemorrhages (15). In most studies of young adults, there is a higher frequency of hemorrhagic events. The population-based study of young Italians by Marini et al. found 57% infarction and 42% hemorrhages (ICH and SAH) (16). Moreover, Nencini et al. in Florence and Leno et al. in Spain found fewer than 50% infarctions in their young adult stroke populations (5,9). In contrast, studies in Israel and Libya have chronicled rates of 81% and 78% infarction among young adults with stroke (Table 44.2). The reasons for this variation from one population to another are unclear, but may relate to differences in genetic susceptibility, acquired risk factors, or temporal bias.

There is evidence that within the "young stroke" population, incidence increases with age. Under the age of 35, incidence is less than 10/100,000; but between ages 35 and 44, the rate increases to 22–45/100,000/year (17).

A recent investigation using the Nationwide Inpatient Sample (NIS) suggests that the rate of hospitalization for ischemic stroke in young adults in the United States both male and female aged 15 to 44 increased significantly between 1995 and 2007. A second study of the Greater Cincinnati/Northern Kentucky population notes a significant increase in stroke incidence in persons 20 to 54 years old between 1993 and 2005. Both of these studies found a greater increase in ischemic than hemorrhagic events in the studied groups. The extent to which their observed increases are due to improved case ascertainment related to greater use of MRI versus earlier onset of stroke risk factors remains to be clarified. In the Cincinnati study, for example, 18% of stroke patients received an MRI in 1993, compared to 58% in 2005 (18,19).

Location of infarct appears similar in young and older populations, though comparative data are limited. Anterior circulation infarcts comprise 70% of infarcts in older populations and 59% to 64% in two Scandinavian young adult populations (6,10,20).

Gender

Women, as a group, experience an increase in stroke risk during their childbearing years because of the hazards of pregnancy and the puerperium as well as the use of oral contraceptive (OC) medications, particularly in combination with smoking. In many studied populations, young women's incidence of stroke exceeds that of young men. This was the case for all strokes in Rochester, Minnesota, during most of the period from 1955 to 1989 (21); in Denmark from 1977 to

TABLE 44.1 Incidence of Stroke in Young Adults (Population-Based Studies)

STUDY	POPULATION	AGE RANGE	TYPE OF ARTERIAL STROKE	INCIDENCE /100,000
Nencini (1988) (5)	Florence, Italy	15–44	All	8.8
Guidetti (1993) (12)	Northern Italy	15–44	All	13.6
Kristensen (1997) (6)	Northern Sweden	18–44	Infarction	11.3
Lidegaard (1986) (7)	Denmark	15–44	Infarction, TIA	15
Jacobs (2002) (8)	Northern Manhattan	20–44	All	23
Leno (1993) (9)	Cantabria, Spain	16–45	All	12.0
Naess (2002) (10)	Western Norway	15–49	Infarction	11.4
Rozenthul-Sorokin (1996) (11)	Israel	17–49	All	10.4
Radhakrishnan (1986) (4)	Benghazi, Libya	15–40	All	47
Rosman (1986) (14)	Pretoria, South Africa	20–54	Infarction, ICH	33
Gross (1984) (22)	Alabama	20–54	All	Whites: 42
			All	Blacks: 50
Ghandehari (2006) (104)	Southern Khorasan, Iran	15–45	Infarction	8
Corbin (2004) (23)	Barbados	25–34	All	11
		35–44	All	30

1982, where Lidegaard et al. found an increased incidence of cerebral infarction in women aged 15 to 34 compared to men; in Western Norway for those under age 30 (10); in Cantabria, Spain, where strokes were more frequent in women in the 31 to 35 age cohort (9); and in Florence, Italy, where women aged 15 to 34 suffered more strokes than men (5). In southern Alabama, black women in the 20 to 54 age cohort were found to have twice as many strokes as black men and white women. In Barbados, women aged 25 to 44 also exceeded men in the number of strokes (22,23). More recently, this trend was confirmed in an analysis of data from the Helsinki Young Stroke Registry (24).

This trend was not found in the Northern Manhattan study, where men aged 20 to 44 had 1.2 times the risk of stroke and a high proportion of ICH (8). In the African population of Ibadan, Nigeria, the incidence of stroke in those 20 to 29 years old was equal in men and women and higher in men in all other decades (25). Population differences in prevalence of different risk factors in men could account for these differences.

Race and Ethnicity

Population-based studies in American cities have documented a higher incidence of stroke in young blacks compared to whites. In the Greater Cincinnati/Northern Kentucky area, the incidence of stroke was higher for blacks at all ages, but the greatest increase in risk (five-fold) was in young and middle-aged blacks. The risk of first-ever stroke was twice as high for blacks in the less than 35 age group, rising to five-fold higher in those aged 35 to 44 and then declining in succeeding age groups to a 1.3-fold increase in those older than 85. The authors hypothesized that the higher incidence in blacks was related to a higher burden of hypertension and diabetes and to socioeconomic factors (26). A similar trend was seen in the Northern Manhattan study, where the increase in risk of stroke in blacks compared to whites, present in all age cohorts, peaked at nine-fold in those aged 35 to 44 years (27). In southern Alabama, the increase in stroke risk for blacks compared to whites peaked at 2.5-fold in the 55 to 64 age range. In the Baltimore/Washington area, blacks had

TABLE 44.2 Distribution of Stroke Subtypes in Population-Based Studies of Young Adults With Stroke

STUDY	POPULATION	INFARCT %	ICH %	SAH %
Marini (2001) (16)	L'Aquila, Italy	57	20	23
Leno (1993) (9)	Cantabria, Spain	47	27	25
Nencini (1988) (5)	Florence, Italy	38	21	36
Rozenthul-Sorokin (1996) (11)	Israel	81	10	8
Radhakrishnan (1986) (4)	Benghazi, Libya	78	13	10

a 2.1-fold higher risk of ischemic stroke and a 3.1-fold higher risk of ICH compared to whites (22,28). In addition, in 1984, Gross et al. found a higher risk of stroke in black females but not males, compared to their white counterparts aged 20 to 54 in southern Alabama. The actual numbers of strokes in each age and race category in this study were small, and confidence intervals (CI) were not given (22).

These findings corroborate those of the pre-CT era literature (29). Eckstrom et al. in 1965 in Missouri and Heyman et al. in 1971 in Evans County, Georgia, found a higher incidence of stroke in young blacks compared to whites, with young black women showing the highest risk in the latter study (29,30).

The question of black and white racial differences outside of the United States has been less explored. Stewart et al., studying a mixed population in South London, found a higher incidence of stroke in blacks under the age of 45 compared to whites (44 per 100,000 in blacks aged 25 to 34, compared to 5 per 100,000 in whites and 42 per 100,000 in blacks aged 35 to 44 compared to 28 per 100,000 in whites) (31). Whether there are regional differences throughout the world in the susceptibility of different, young black populations to stroke has yet to be investigated.

The Northern Manhattan Stroke Study examined relative risk (RR) of stroke in Hispanics aged 20 to 44 and found a 2.5-fold higher risk compared with whites, whereas blacks showed a RR of 2.4 (8). A population-based study of stroke rates over a 20-year period among New Zealand women found an increasing incidence in Pacific women, a decline in European women, and no change of rate in Maori women. These two studies illustrate the need for further exploration of ethnic and racial differences in stroke incidence around the globe.

ETIOLOGY

An Evolving Spectrum of Causes

More than 60 different disorders causing stroke in young adults were identified in a comprehensive list published in 1983 (32). A few of these, particularly valvular disease caused by rheumatic fever and infectious arteropathies, have diminished in importance in developed nations since that time. However, a number of new potential causes of stroke in young adults have appeared. Prothrombotic states caused by antiphospholipid antibodies (first described in 1978), deficiency of proteins C (1981) and S (1984), Factor V Leiden (FVL) (1993), and the prothrombin 20210A mutation (1996) can increase the risk of arterial stroke as well as venous thrombosis in young adults. Cerebral venous thrombosis (CVT) in young adults has also been characterized (33). Drugs of abuse, including cocaine, heroin, and the ephedra alkaloids, have been recognized as significant causes of stroke at the same time that the risk of stroke from OCs has declined with the advent of lower dosing. The risk of stroke in young adults with HIV/AIDS, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), mitochondrial encephalopathy lactic acidosis and stroke (MELAS), and the reversible cerebral vasoconstriction syndrome have been discovered (34,35). Finally, there is dawning acknowledgment of the role played by our increasing array of medical and surgical interventions in supporting the incidence of stroke in young adults. For example, cervical and brain radiation, transplant surgery, artificial valves, carotid stenting, and chiropractic maneuvers all have an associated risk of stroke, and all tend to be offered to younger patients. The failure of stroke incidence rates in the United States to decline since the 1980s may, in part, reflect an increase in the iatrogenic opportunities for stroke (36–43).

Advances in craniocervical imaging in the past two decades have improved detection of several important causes of stroke in young adults. Magnetic resonance and computed tomography imaging and angiography have greatly enhanced our ability to diagnose large vessel dissection, intracranial vasospasm, vasculitis, and CVT.

Distribution of Causes by Age Subgroup

Although an extensive literature on aspects of stroke in young adults has developed over the past 30 years, the definition of *young* has not been standardized. Case series variably use 30, 40, 45, or 50 as their upper age limit for young adult patients. This fact—and the small sample size of most reported series—have made it difficult to discern natural age subgroups within the broader category of young adult stroke. Nonetheless, it is clear that the distribution of causes of stroke in adults 15 to 35 years of age differs from that in adults 35 to 50 years of age. In the younger group, cardiogenic embolism, drugs (both therapeutic and illicit), migraine, traumatic dissection, prothrombotic states, and premature atherosclerosis caused by inherited conditions such as homocystinuria are prominent factors, whereas in the older subgroup, dissection, antiphospholipid antibodies, and atherosclerosis caused by hypertension and other traditional risk factors are prominent (44–47). Neto et al., using the Trial of ORG 10172 in Acute Stroke Therapy (TOAST) criteria (48), examined the distribution of stroke mechanisms in 106 patients admitted to a university hospital in Sao Paulo with cerebral infarction and found that those aged 15 to 29 had a higher proportion of strokes because of "other determined causes" and the group aged 30 to 40 had more "cardioembolism"-related events (49). The study of larger populations and series will enable further definition of etiology patterns in different decades of adulthood.

Many case series have considered the causes of stroke in young adults. These studies frequently come from tertiary care hospitals, with their attendant bias toward cases of unusual/complex etiology. For this reason, true frequencies of the specific etiologies of stroke in young adults have been difficult to determine. There is fair agreement on broad categories of causation, however, and Hart and Miller's 1983 categories have proven durable, with the addition of drug use, which is an increasing cause of stroke in urban settings in the developed world (50). Hart and Miller attributed stroke in young adults to atherosclerotic disease in 20%;

cardiac emboli in 20%; arteropathies, particularly large vessel dissection, in 10%; coagulopathy in 10%; and peripartum cerebrovascular events in 5%. Another 20% was related to mitral valve prolapse, migraine, and OC use, and 15% remained unexplained after full evaluation (32,47).

Specific etiologies of stroke in young adults described in the literature are listed in Table 44.3. Even though it is beyond the scope of this chapter to discuss all of these in detail, we will review several of the important and controversial causes of stroke in this age group.

Cervicocranial Dissection

After cardioembolic stroke, dissection is the second leading cause of stroke in patients younger than 45 (51). This mechanism accounts for 10% to 25% of strokes in young and middle-aged adults (52). Large vessel dissection is a disorder of midlife; its incidence peaks in the fifth decade. A population-based study from Rochester, Minnesota, found a mean age of 45.8 for dissection cases (53). Both internal carotid and vertebral arteries have segments vulnerable

TABLE 44.3 Causes of Stroke in Young Adults

Cardiac	Congenital anomalies
	Rheumatic valvular disease
	Calcific aortic stenosis
	Mitral valve prolapse
	Patent foramen ovale (PFO)/atrial septal defect with venous thrombosis
	Endocarditis
	Atrial myxoma
	Cardiomyopathy
	Arrhythmias
	Ventricular thrombus
Vascular	Premature atherosclerosis
	Craniocervical dissection
	Infectious vasculitis
	Syphilis, tuberculosis, Lyme disease, HIV
	Moyamoya disease
	Takayasu's disease
	Intracranial aneurysm
	Cerebral arteriovenous malformation
	Susac's syndrome (microangiopathy of brain, ear, retina)
	Reversible cerebral vasoconstriction syndrome
	Buerger's disease
Collagen vascular disease	Systemic lupus erythematosus
	Rheumatoid arthritis
	Sjögren's syndrome
	Polyarteritis nodosa
	Behcet's disease
	Scleroderma
Hematologic	Sickle cell disease
	Hemoglobin SC disease
	Hypercoagulable states
	Antiphospholipid syndrome, Factor V Leiden, PT 20210A, protein C or S deficiency, antithrombin III (AT3) deficiency, elevated factor VIII
	Disseminated intravascular coagulation
	Polycythemia vera
	Idiopathic thrombocytopenic purpura (ITP)

(*continued*)

TABLE 44.3 Causes of Stroke in Young Adults (*continued*)

	Thrombotic thrombocytopenic purpura
	Hemophilia
	Leukemia
Other acquired conditions	Wegener's granulomatosis
	Lymphomatoid granulomatosis
	Cryoglobulinemia
	Sarcoidosis
	Churg–Strauss syndrome
	Inflammatory bowel disease
	Migraine
Inherited conditions	Ehlers Danlos
	Homocystinuria
	Fabry's disease
	Fibromuscular dysplasia
	Pseudoxanthoma elasticum
	CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy)
Pregnancy/Puerperium	ITP
	Eclampsia including HELLP syndrome (hemolysis, elevated liver enzymes, low platelets)
	Postpartum CNS angiopathy
	Cerebral venous thrombosis (CVT)
	Peripartum cardiomyopathy
Drugs	Therapeutic
	Oral contraceptives (OC), sympathomimetics, MAO inhibitors
	L-asparaginase, cytosine arabinoside
	Drugs of abuse
Medical interventions	Craniocervical vascular procedures
	Stents, angioplasty, CEA
	Prosthetic valves
	Surgery
	Radiation-induced arterial injury
	Chiropractic maneuvers

Source: From Refs. (31,33,42,44,49).

to the effects of head and neck movement. In the internal carotid artery (ICA), the distal half of the extracranial segment is most often affected, whereas in the vertebral artery, the V3 segment from C2 to the artery's entrance into the skull and the V1 segment in the neck are commonly involved. The external and common carotid arteries are rarely affected. The mechanism usually involves an intimal tear with dissection of arterial blood between the intimal and medial layers of the arterial wall or rupture of vasa vasorum leading to intramural hematoma. This can cause bulging of the inner arterial wall and stenosis or occlusion of the lumen. The intimal tear can become a nidus for formation and embolization of platelet and/or fibrin thrombi. In some cases, trauma to the artery may instead cause intramural hematoma formation with secondary rupture from the intima into the lumen, or there may be primary intramural hematoma dissecting between arterial layers and causing luminal stenosis or occlusion without rupture into the lumen. Cerebral infarctions resulting from a carotid dissection can thus be small, cortical insults caused by emboli, watershed territory lesions caused by low flow from a sudden carotid stenosis, or major anterior circulation infarction from rapid development of carotid occlusion. The

current belief is that approximately 80% of dissection-related strokes are caused by embolization and 20% by carotid thrombosis.

Carotid dissection has historically been difficult to diagnose. Patients present with pain, often above or behind the eye or along the side of the neck, jaw, and face. They may describe pulsatile tinnitus and transient monocular blindness. They may see scintillating scotomata and have transient cranial nerve dysfunctions, especially of XII, which may be irritated by an expanding ICA in the neck. An important clue in nearly half of patients is a partial Horner's syndrome with miosis and mild ptosis on the side of the pain. This is caused by irritation of the sympathetic plexus carrying oculomotor fibers, which runs along the ICA. Sympathetic fibers supplying the ipsilateral facial sweat glands run along the external carotid artery and are not affected in ICA dissection, hence sweating function remains intact.

The symptoms of vertebral dissection include pain in the posterior neck and face, which typically precedes vertigo, nausea, staggering, and/or dysarthria. Embolization is most often to the PICA territory. Signs of lateral medullary dysfunction, including nystagmus, skew deviation, and first division trigeminal sensory loss, may occur (54–57).

Dissection of a major artery may be related to a variety of diseases and types of trauma, many of them seemingly trivial. The spectrum of these is illustrated in Table 44.4. Symptoms of dissection frequently evolve from migraine-like headache to neurologic deficit over days to weeks, making recognition of the inciting event difficult for the patient and clinician. The diagnosis of dissection can be made by MRI/MRA, ultrasound, or catheter angiography. Axial cuts on MRI/MRA can be helpful in demonstrating a contracted arterial lumen surrounded by clot, and CTA can demonstrate segmental narrowing or rapid tapering of the arterial lumen in sagittal views. Treatment commonly is six months of full-dose Coumadin or aspirin to prevent further embolization, with no significant difference in outcomes or recurrence between the two treatment options demonstrated to date. The risk of recurrent dissection is approximately 1% per year (58).

Pregnancy and Childbirth

Pregnancy and the puerperium are a time of increased risk of stroke for young women. The overall incidence of stroke during this period in the United States in 2000 to 2001 has been calculated at 34.2 per 100,000 deliveries (59). Recent studies suggest that the risk of stroke is less during the first two trimesters and surges in the peri- and postpartum period. In the Baltimore/Washington area, the RR was 5.4 [95% CI 2.9–10] for cerebral infarction and 18.2 (95% CI 8.7–38.1) for ICH during the peripartum weeks (56). A Swedish population-based cohort study found a markedly elevated RR of SAH of 46.9 (95% CI 19.3–98.4), of ICH 95.0 (95% CI 42.1–194.8), and cerebral infarction 33.8 (95% CI 10.5–84.0) from 2 days before to 1 day after delivery, compared to the nonpregnant state (60). Figure 44.1 shows the distribution of stroke risk during pregnancy in this study. The most frequent cause of both ischemic and hemorrhagic stroke in the puerperium is eclampsia, found in 24% to 47% of infarctions and 14% to 44% of ICHs (61,62). Rapid and severe elevation

TABLE 44.4 Associated Factors in Cervicocranial Dissection

Diseases	Ehlers–Danlos syndrome type IV
	Marfan syndrome
	Fibromuscular dysplasia
	Cystic medial necrosis
	Pseudoxanthoma elasticum
	Polycystic kidney disease
	Osteogenesis imperfecta type I
	Alpha-1 antitrypsin deficiency
	Coarctation of the aorta
	Syphilitic arteritis
	Pharyngeal infection
	Sympathomimetic drug use
Trauma	Attempted strangulation
	Blunt trauma to neck (cow's tail, car door, car shoulder seatbelt)
	Sharp trauma to neck (gun, knife injuries)
	Hyperextension of neck (dental chair, beauty parlor stroke, bottoms-up, dissection, painting a ceiling, CPR, roller coaster)
	Head rotation (chiropractic manipulation, shoveling snow, backing up car, yoga, tennis, bow hunter's stroke)
	Forceful head and body rotation (golfer's stroke)
	Vigorous aerobic exercise (treadmill, rowing machine)

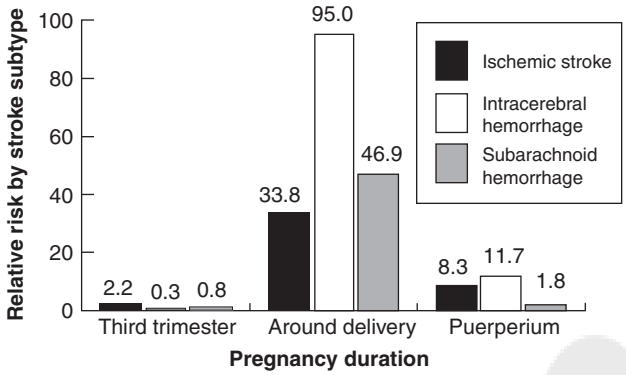

FIGURE 44.1 Risk of stroke in women in the third trimester, peri- and postpartum periods versus risk of nonpregnant women and women in the first two trimesters.

Source: Adapted from Refs. (15,60).

of blood pressure is a likely mechanism, and women with underlying aneurysm, arteriovenous malformation (AVM), or other vasculopathy are particularly vulnerable. Other less common associations with pregnancy-related stroke include amniotic fluid embolism, choriocarcinoma, postpartum cerebral angiopathy, infection, cardiomyopathy, and use of ergot derivatives (59,63). An NIS analysis from the United States using 2000 to 2001 data found a number of factors associated with increased risk with an odds ratio (OR) of six or higher:

- Age older than 35 years
- Migraine
- Thrombophilia
- Pre-existing heart disease or hypertension
- Systemic lupus erythematosus
- Sickle cell disease
- Thrombocytopenia

Regarding race and ethnicity, black women had a higher risk of stroke than Hispanic or white women in this study. Of those who suffer a pregnancy-related stroke, 4% to 15% die, and 10% to 22% of survivors are too impaired to be discharged home from the acute hospital (59).

Cerebral Venous Thrombosis

CVT also occurs in late pregnancy and the postpartum period, as well as in hypercoagulable states of other causes. It may cause ischemic and/or hemorrhagic stroke. Its incidence in a recent U.S. population-based study of pregnancy-related stroke was calculated at 11.6 cases per 100,000 deliveries, nearly as high as the incidence of arterial stroke (13.1 per 100,000). The risk of CVT increases in the presence of an underlying coagulopathy or malignancy, and it is associated with cesarean delivery, infection, and hypertension (64). The initial symptom is most often headache, which may progress after days or weeks to seizures and/or focal neurologic deficits. Sinus thrombosis causes increased intracranial pressure caused by impaired venous drainage. This may progress to venous infarction, usually of superficial cortical veins, often bihemispheric. The superior sagittal, transverse, and straight sinuses are most often involved. MRI, which clearly delineates the venous sinuses, has greatly improved diagnostic accuracy. Treatment in cases without ICH is evolving from anticoagulation with heparin toward targeted thrombolysis, both followed by warfarin for several months. Functional outcome of CVT is usually good, with 75% to 85% achieving full functional recovery (65).

Migraine

Migrainous infarction is a fixed, focal neurologic deficit following an attack of migraine. In population studies, it accounts for 0.5% to 1.5% of all ischemic strokes and 10% to 14% of ischemic strokes in young patients (66). Infarction occurs more often in migraine with aura. The mechanism is thought to involve unusually severe cortical spreading depression with hypoperfusion during the aura and/or the headache. One-third of these infarcts involve the occipital lobe. Common deficits include visual field cuts, perceptual disturbances, and dysphasias. Migraine is a disease of younger adults and is three times more common in women than men. Consistent with this, a recent meta-analysis found the risk of ischemic stroke to be increased 2.7-fold in women younger than 45 years who suffer from migraine headaches (67). That risk rises further in those with migraines who smoke and/or use OC (66,68). Despite this data, the relationship between migraine and cerebral infarction and its true incidence has been difficult to clarify because it is difficult to obtain a detailed and precise headache history from patients during an acute neurologic episode. In addition, the definition of migraine has changed over time in the literature. Finally, some large vessel dissections cause unilateral headache with migraine-like features, but they are not true migraine episodes.

Drugs

A number of drugs of abuse and medications have been linked to stroke in young adults. This section reviews the major drugs of both classes and their relationship to ischemic and hemorrhagic stroke. Illicit drug use is an important risk factor for stroke in urban young adults. It was associated with 12% of strokes in the Baltimore/Washington young adult population and with 2% to 39% of strokes in other published case series (69).

Cocaine

Cocaine is responsible for the majority of strokes caused by illicit drug use and has been most studied. It is a local anesthetic and sympathomimetic alkaloid first extracted from the leaf of *Erythroxylon coca*, a tree native to Peru and Bolivia, in the mid-19th century. For thousands of years in that region, the leaves have been chewed (mixed with lime) or drunk as

tea for their stimulant effects. In the early 1900s, cocaine was a frequent component of medicinal tonics for a variety of ailments in the United States, and it was an ingredient in early cola formulations. Growing recognition of its abuse potential led to its inclusion as a Category II drug in the Controlled Substances Act of 1970. The two chemical forms for illicit use are the hydrochloride salt and the freebase. The hydrochloride salt, or powdered form of cocaine, is water soluble and can be taken intravenously or intranasally. Crack cocaine is a freebase formulation, and, although it is short acting, it is the most concentrated form of cocaine. The smoke of the freebase is inhaled. Cocaine is sold on the street as a fine, white, crystalline powder, known as coke, C, snow, flake, or blow. It is often diluted with cornstarch, talcum powder, sugar, or the active drugs procaine and amphetamine (70). The incidence of new cocaine users in the United States peaked in 1983 at 1.5 million and then declined to 0.5 million in 1992. In 2000, the number of new users had risen again to 0.9 million (71).

Cocaine use is associated with an increased risk of both hemorrhagic and ischemic stroke. In an HMO population in California, young women reporting cocaine or amphetamine use had an OR for stroke of 6.5 (95% CI = 2.5–16.6) compared to those reporting no drug use, with the OR for hemorrhagic stroke at 9.6 (95% CI = 2.7–33.5) and for ischemic stroke at 4.5 (95% CI = 0.9–21.6). Case series have reported 2% to 39% of young stroke patients having associated illicit drug use, predominantly cocaine (72), and the population-based Baltimore/Washington Young Stroke Study found 9.7% of young stroke patients to have a history of recent cocaine use. A number of mechanisms that may lead to hemorrhage have been suggested, such as drug-induced acute hypertension, particularly in individuals with AVM or aneurysm. Other mechanisms include increased platelet aggregation, vasospasm, vasculitis, and apoptosis of cerebral vascular smooth muscle. Complications of cocaine use that can cause stroke include cardiomyopathy leading to arrhythmia or ventricular clot, endocarditis with embolization of septic material, and contaminants in intravenous preparations that embolize to the brain through a pre-existing patent foramen ovale (PFO) or atrial septal defect (ASD).

The plasma half-life of cocaine is 60 to 80 minutes. Smoking provides the fastest route of entry into the cerebral circulation (6–8 seconds), with the intravenous route taking 12 to 16 seconds. The majority of strokes occur within one hour of ingestion. In one series, a positive urine toxicology screen at the time of presentation was associated with more severe stroke (70,73).

Amphetamines have similar sympathomimetic effects and spectrum of potential mechanisms in causing hemorrhagic and ischemic stroke (74). Methamphetamine is most often implicated in stroke cases.

Heroin

Heroin, a derivative of morphine, is usually taken intravenously but can be used by oral, nasal, subcutaneous, or inhalational routes. It has been associated with ischemic stroke, with deficits appearing from immediately to more than 24 hours after use. Hypoxia caused by hypotension or respiratory depression, vasculitis, positional vascular compression, and septic embolization caused by endocarditis have been proposed as mechanisms (70,75).

Clinical studies of the cerebrovascular effects of individual illicit drugs have been hampered by patients' reluctance to admit using drugs, inconsistent toxicology screening, frequent concomitant ingestion of multiple drugs of unknown purity and potency, and patient populations who have, in addition, a substantial burden of traditional risk factors for stroke.

Sympathomimetics

A number of sympathomimetic agents available in the United States without prescription have been associated with stroke. Dietary supplements containing ephedrine and related alkaloids (also known as ma huang) are taken by young women and others to promote weight loss and boost energy. Pseudoephedrine, phenylephrine, phentermine, oxymetazoline, and fenoxazoline are decongestants included in cough and cold preparations. Phenylpropanolamine has both appetite suppressant and decongestant effects and has been used in both types of preparations. These drugs have all been implicated in cases of stroke, primarily hemorrhagic. In a prospective tertiary center series of 2,500 strokes, 2.5% were associated with use of decongestant preparations, and all but one of these were hemorrhagic. A series of 702 hemorrhagic stroke cases in patients 18 to 49 years of age found a significant association between stroke and phenylpropanolamine use (76–78). The mechanism of a causal relationship may include drug-induced hypertension, vasoconstriction and secondary hemorrhage, and/or vasculitis (76,78,79). In 2004, the Food and Drug Administration (FDA) prohibited the use of ephedra in dietary supplements because of health risks (80). Additionally, since March 2006, the FDA has limited the availability of medications containing pseudoephedrine, phenylpropanolamine, and ephedrine to behind-the-counter rather than over-the-counter sales, with quantity limits and purchaser identification required. The Combat Methamphetamine Epidemic Act of 2005 mandated these restrictions, not because of adverse health effects of the agents, but because of their frequent use in the illicit production of methamphetamine (81). Manufacturers of cough and cold preparations have responded by removing them from most formulations.

Cannabis

Despite decades of experience with medical issues related to marijuana use, it is only recently that reports have appeared exploring a possible link between cannabis use and ischemic stroke. Wolff et al. found that within a series of 48 consecutive young strokes, 10 of the 13 cannabis users in this group displayed a similar pattern of multifocal intracranial stenosis on MRI. This pattern partly or completely resolved on repeat imaging at three to six months of all six patients who stopped using, but not in those who continued (82). In a subsequent review, the same author and colleagues note

a preponderance of posterior circulation ischemic stroke in cannabis-associated cases and suggest that these strokes be considered a variant of the reversible cerebral vasoconstriction syndrome (83). Once again, greatly improved imaging techniques will aid case ascertainment and exploration of this link.

Alcohol

In many societies, alcohol consumption begins in adolescence, increases during the young adult period, plateaus during midlife, and decreases in the eighth and ninth decades. The relationship of alcohol consumption to stroke is thus germane to young adults. Although few studies have looked for an association between alcohol and stroke in young adults specifically, many studies of subjects of all adult ages have found that alcohol use increases the risk of ICH and SAH in a linear manner as dose increases. Heavy drinkers, usually defined as persons imbibing more than 40 grams of alcohol per day (3 cans of beer or 15 ounces of wine) have a two- to eleven-fold increase in their risk of hemorrhagic stroke (84,85). The relationship between alcohol consumption and ischemic stroke, in contrast, follows a U- or J-shaped curve, where moderate drinkers have fewer events than either nondrinkers or heavy drinkers. This finding was confirmed specifically in young women in the Baltimore/Washington area (86). However, the definition of *moderate drinking* in this literature has varied from less than once per day to amounts up to two drinks per day, and concern has been expressed that the comparison groups of nondrinkers in some studies may have been self-selected for greater burden of comorbidity (87). The mechanism of the protective effect of moderate alcohol vis-à-vis ischemic stroke is unclear, but may involve raising HDL cholesterol levels, thereby slowing plaque formation (70). A prospective community study of 826 subjects in northern Italy found a slower progression of carotid atherosclerosis over a 5-year period among drinkers of 1 to 50 grams of alcohol per day than among those who drank less or more (87,88). Alcohol also decreases platelet aggregation and fibrinolytic activity, which may play a role both in increasing risk of hemorrhagic stroke and in protecting moderate drinkers from ischemic events (70). The association of alcohol abuse with cardiomyopathy and atrial arrhythmias provides another possible mechanism for ischemic stroke (85). No specific vascular territory or brain structure has been associated with stroke related to alcohol use. Clinical features and treatment are the same as for other strokes, with the caveat that the presence of an overt coagulopathy caused by alcoholism may complicate therapeutic anticoagulation. Chronic heavy drinkers may experience slower and/or less complete recovery because of prior alcohol-induced brain damage.

Oral Contraceptives

OC medications came into use in the United States in the 1960s. It was first suggested that they might increase the risk of cerebrovascular events in 1962. The mechanism of thrombosis from OC medication may involve the elevation of plasma levels of Factors VIIc and XIIc, which occurs in a dose-related fashion in OC users and may promote generation of thrombin (89).

There is convincing evidence that current low-dose OCs (less than 50 mcg estrogen) do not increase the risk of arterial stroke in women without vascular risk factors. However, hypertensive users, as well as smokers and women with migraine headaches, have an increased risk of arterial infarction, and the risk of CVT is increased. In the WHO international study, RR was 10 to 14 for hypertensive OC users and 4.7 for OC users who smoke (90).

Low-dose OCs should be used with caution in women with migraine headaches, who smoke, who are hypertensive, or who have genetic thrombophilic defects, owing to variably increased, though still low, risk of stroke (91).

Thrombophilic States

A number of acquired and inherited thrombophilic states related to stroke in young adults have been described in recent decades. Even though all of them (deficiency of proteins C, S, and antithrombin III [AT3], FVL, prothrombin gene 20210A, and the antiphospholipid antibody syndrome [APS]) are strongly associated with venous thrombosis, only the APS has a strong correlation with arterial stroke. The latter is also the only one of these conditions with distinctive clinical features. First described in 1983, the APS is diagnosed when a patient has had one or more episodes of arterial or venous thrombosis in any organ leading to tissue infarction or fetal loss and when the patient is demonstrated to have antiphospholipid antibodies (lupus anticoagulant [LA] and/or cardiolipin) in plasma on at least two occasions six weeks apart (92). Other frequently associated findings in APS are thrombocytopenia (40%–50%); livedo reticularis, a lacey pattern of microvascular occlusion occurring in the skin of the back and extremities (11%–22%); and hemolytic anemia (14%–23%) (93). The brain is the most common site of arterial thromboembolism, and neurologic manifestations may include TIA, cerebral infarction, CVT, multi-infarct dementia, seizures, encephalopathy, migraines, transverse myelitis, chorea, and mononeuritis multiplex. In situ arterial thrombosis of vessels of all sizes and embolism from cardiac valvular vegetations that occur in approximately 4% of patients are the mechanisms underlying these diverse phenomena. A wide variety of effects involving other organs have been described as well (93).

Primary APS occurs in patients without an autoimmune disease; secondary APS occurs in patients with autoimmune or other disease, most often systemic lupus erythematosus. Treatment recommendations continue to evolve with accumulating evidence. Anticoagulation with warfarin, but not antiplatelet agents, is beneficial in preventing recurrent thrombosis, and the benefit of antiplatelet therapy for asymptomatic individuals with LA or anticardiolipin antibodies is unclear (92–94).

FVL, prothrombin 20210A, and deficiencies of protein C, S, and AT3 cause thrombosis by impairing the normal

modulation of thrombin generation and inactivation. They are strongly associated with venous thrombotic events and variably with arterial stroke. Their frequent clinical expression in the early adult years, with the majority of patients experiencing their first thrombotic event before the age of 45, makes them relevant to our discussion (33).

Resistance to activated protein C is caused by base substitution (adenine for guanine) at position 1691 on the Factor V gene. The resulting mutation is called Factor V Leiden (FVL). This mutation occurs in about 5% of the Caucasian population but is rare in Africans and Asians. Even though its association with increased risk of venous thrombotic disease is clear, its relationship to arterial stroke is less certain. A recent meta-analysis found a modest increase in risk of ischemic stroke primarily among patients less than 55 years of age carrying FVL (33,94,95).

Another substitution of adenine for guanine, at nucleotide 20210 of the prothrombin gene 20210A, has similarly been associated with an increased risk of venous thrombosis at all ages and a modest risk of arterial stroke in younger adults. The greater effect of these two mutations on producing venous rather than arterial thrombosis may relate to the difference in the thrombotic process, with stasis as an important predisposing factor on the venous side and endothelial damage with platelet activation driving arterial clot formation.

In large blood vessels, proteins C, S, and AT3 all act by different mechanisms to control thrombin generation (33). Several case series of stroke in young adults have found approximately 5% of patients with protein C deficiency, though others have seen no increase over the control rate (96). Case reports and series describing stroke associated with deficiency of protein S, which may be inherited or acquired in sepsis or pregnancy or caused by hormonal therapy, are more extensive. Arterial stroke and CVT may occur in the same individual, and the frequency of protein S deficiency appears to be higher in young adult stroke patients than in older groups (94). Evidence linking deficiency of AT3 to arterial stroke is weak, and it appears that this deficiency, which slows thrombin inactivation, is nearly exclusively involved in venous thromboses.

These conditions of modest effect in promoting stroke may be potentiated by the addition of acquired thrombophilic factors, including pregnancy, OCs, smoking, migraine, hypertension, diabetes mellitus, and dyslipidemia. Most experts currently believe that population screening for inherited thrombophilic states is not warranted because of the low incidence of major vascular events. Clinicians treating individual patients must exercise judgment on this point based on the patient's composite of medical and family history as well as acquired risk factors.

Patent Foramen Ovale

PFO is a persistent fetal communication between the right and left atria of the heart. It is present in more than 25% of adults and is associated with ischemic stroke in adults less than 55 years old and less clearly with stroke in older adults. PFOs are thought to cause stroke by allowing paradoxical embolization across the opening from venous to arterial sites, although the possibility of in situ thrombus formation in a tunnel-like PFO or an increased risk of atrial arrhythmia and thrombus because of the presence of the defect has not been excluded. First described in 1877, PFO was difficult to diagnose in vivo until the advent of contrast echocardiography.

The presence of an atrial septal aneurysm with a PFO significantly increases the risk of ischemic stroke. In addition, atrial anatomic variants, including a prominent Eustachian valve or Chiari's network and lower extremity or pelvic venous thrombi or a predisposition to these—caused by presence of the FVL mutation, the prothrombin gene mutation 20210A, an elevated factor VIII level, the APS, or May–Thurner syndrome—can increase the chance of a PFO leading to a stroke. An intriguing association between PFO and migraine with aura has been found in case control studies, and others have noted a decrease in migraine attacks after PFO closure. The mechanism of this association remains speculative, but may involve the presence of a gene modulating both cardiac and vascular development, left to right shunting of an endogenous substance normally metabolized in the lung (such as serotonin) into the systemic arterial circulation, or left to right shunting of microemboli (66,97).

Strokes of Undetermined Cause

An important feature of the literature on stroke in young adults is the high percentage of strokes of undetermined cause in most series. A number of these are summarized in Table 44.5. In addition, Bevan et al., reviewing the literature in 1990, noted that a cause is found in 55% to 93% of the stroke cases in young adults (98). Even though it is reassuring in clinical practice to be able to say to a young stroke patient after an exhaustive workup that no serious disease or defect has been found to explain the stroke, it is at the same time frustrating and worrisome when no cause can be identified. Without a cause, no estimate of risk of recurrence can be made, and no focused plan developed to minimize that risk.

Several definitional issues contribute to the high rate of strokes of unknown etiology. First, the TOAST criteria, a five-category classification of stroke mechanism developed for the TOAST, have been used in a number of young stroke series and also have the advantage of widespread use and familiarity (48). However, the five categories—large artery atherosclerosis, small vessel occlusion, cardioembolism, other determined etiology, and unknown etiology—were designed for an older population with a predominance of atherosclerotic disease. Other than the 10% to 20% caused by large artery atherosclerosis and the 20% of young adult strokes caused by cardioembolism, most strokes in young adults fall into the "other determined etiology" and "undetermined etiology" categories of this classification.

TABLE 44.5 Stroke of Undetermined Cause in Young Adults

AUTHOR	STUDY TYPE	LOCATION	UNDETERMINED CAUSE (%)
Kittner (1998) (50)	Population-based	Baltimore, Maryland	31.8
Adams (1995) (167)	Population-based	Iowa	34.3
Camerlingo (2000) (116)	Hospital series	Bergamo, Italy	21.5
Naess (2004) (115)	Population-based	Western Norway	47.8
Quereshi (1995) (72)	Hospital series	Atlanta, Georgia	26
Lee (2002) (163)	Hospital series	Taiwan	23.5
Putaala (2009) (24)	Hospital series	Helsinki	22.4

Further, these categories are broad and refer to the vascular mechanism rather than the specific etiology of the stroke. Other than TOAST, however, there are no widely recognized classification systems for stroke etiology, and young stroke studies have used a variety of ad hoc instruments, with variable definitions of *unknown* or *cryptogenic, probable cause*, and *possible cause*. Conditions of disputed or unclear etiologic importance—migraine, mitral valve prolapse, PFO, alcohol, and OCs—are classified differently by different authors. An etiologic classification scheme specifically for young adult stroke has been proposed, taking into account our recently acquired ability to diagnose large vessel dissection and CVT reliably via MRI. Hoffman et al. propose the following categories for stroke in young adults:

- Large vessel
- Small vessel
- Cardiogenic
- Dissection
- Prothrombotic states
- Migraine-induced
- CVT
- Vasculitides
- Vasculopathy other
- Miscellaneous
- Unknown (99)

Use of classification schemes such as this one designed for this population segment may help to reduce the number of strokes reported as "unknown cause."

The historical emphasis in American and European medical culture on finding the one unifying cause for an illness or group of symptoms is beginning to yield to the recognition that a constellation of factors—some genetic and some environmental or behavioral—often come together to cause a medical event (100). Many strokes in young adults are likely multifactorial, the result of several mild genetic predispositions or the intersection of genetic predisposition and acquired risk factors. A case control study by Martinelli et al. found women taking OCs to have 13 times the risk of stroke if they also have the FVL and 9 times the risk if they have the prothrombin 20210A mutation, compared to women on OCs without either mutation (101). Smoking and hypertension also appear to increase the risk created by genetic predispositions. Pezzini et al. found that patients with two of four predisposing polymorphisms (prothrombin 20210A, FVL, the TT677 genotype of the methylenetetrahydrofolate reductase [MTHFR] gene, and epsilon-4 carriership of the apolipoprotein gene) had OR for stroke of 3.5 (CI 1.40–9.98), but, if they also smoked, the OR rose to 15.99 (CI 4.01–63.3). If they had two polymorphisms and were hypertensive, the OR for stroke rose to 10.79 (95% CI 1.01–115.4) (100). It may turn out that many of the strokes categorized as "cryptogenic" occur because of alignment of several genetic and acquired risk factors in the individual.

Population Differences

Population-based studies, though superior to case series in gauging the spectrum and distribution of causes of stroke, are subject to the variations among populations studied. In U.S. urban populations, for example, stroke caused by illicit drug use accounts for as many as 12% of young adult cases, whereas, in a Saudi university hospital series, it accounted for 2% and, in the Bern and Zurich stroke registries, just 0.5% of cases (102,103). In Khorasan province in Iran, 54% of infarctions in young adults are of cardioembolic origin, twice the frequency found in American and European populations. Chagas disease, rare or absent as a cause of stroke in most studies, accounted for 4 of 106 young adult stroke cases in a Brazilian series (49,104). As knowledge of stroke in young adults accumulates, our appreciation of its variability over time and from place to place increases.

DIFFERENTIAL DIAGNOSIS OF STROKE IN YOUNG ADULTS

A number of other illnesses can confuse the diagnosis of stroke in young adults. A list of these is provided in Table 44.6. The relative rarity of stroke in young adults predisposes providers to consider first and sometimes exclusively the more routine etiologies of headache, neck pain, ear pain, and dizziness. Reliance on noncontrast head CT

TABLE 44.6 Differential Diagnosis of Stroke in Young Adults

Brain infection
Brain neoplasm
Cranial nerve palsy
Peripheral nerve palsy
Hemiplegic migraine
Demyelinating diseases
Benign positional vertigo
Vestibulitis
Unrecognized seizure with postictal neurologic deficit
Toxic metabolic encephalopathy (hypoglycemia, hepatic encephalopathy)
Brown–Sequard syndrome (hemiplegia and contralateral hemisensory loss)
Conversion disorder
Progressive multifocal leukoencephalopathy (PML)
Subcortical leukoencephalopathy (Binswanger's disease)
Mitochondrial encephalopathy, lactic acidosis and stroke-like episodes (MELAS)

as the sole imaging screen for CNS disease will allow some strokes in young adults to be missed because of CT's limited sensitivity to acute infarction and ischemic territory at risk. In a recent series of 15 misdiagnosed cases of cerebellar infarction, half of the patients were younger than 50 years. A normal head CT and a poorly documented neurologic exam were frequent findings in this series, and incorrect diagnoses included migraine, toxic encephalopathy, gastritis, meningitis, myocardial infarction, and polyneuropathy (105). Younger adults may be more prone to misdiagnosis because of both their lesser frequency of stroke and their higher prevalence of certain easily confused conditions, such as multiple sclerosis and conversion disorder. Increased recognition of the importance of stroke in the younger population and routine availability of more definitive imaging techniques will improve our ability to identify stroke rapidly in this group.

The converse is also true: Patients may be diagnosed with stroke in the emergency room and later be found to have other illnesses. Postictal weakness and confusion, for example, may persist for days to weeks after an unwitnessed seizure, and serial scans, EEG, and further history may be needed to clarify the diagnosis. Brain tumors, multiple sclerosis, and PML may present with neurologic findings, and scan appearances consistent with stroke and the diagnosis may not become clear until deficits progress and/or scans evolve. In an emergency department study of 463 patients given diagnoses of stroke or TIA, 19 were later discharged from the hospital with different diagnoses, including seizure, migraine, peripheral neuropathy, cranial nerve neuropathy, and psychogenic paralysis. The mean age of those misdiagnosed was 55, whereas it was 65 for those correctly diagnosed (106). Conversion disorder with motor symptoms occurs on average at age 39. Symptoms include paralysis, ataxia, tremor, sensory loss, pain, blindness, and dysphonia in patterns consistent with stroke (107). This disorder may be suspected but is infrequently diagnosed early in the patient's hospital course, particularly during the first episode of psychogenic symptoms. Conversion symptoms typically respond well to rehabilitative therapies, though relapse is common.

TREATMENT

Young patients are offered the most advanced and aggressive treatments available for all illnesses more readily than elderly patients. In acute stroke treatment, this tendency is reflected in the use of hemicraniectomy for malignant middle cerebral territory infarction. This procedure is offered to appropriate patients under 50 to 60 years of age because of accumulating evidence that younger patients have better survival and functional outcome (108,109). Younger patients are also offered the most aggressive and technologically advanced rehabilitation treatments because of their lesser burden of comorbidity and prior disability and, therefore, their greater tolerance and lower risk of complications.

OUTCOMES

Survival

The case fatality rate (death within 30 days of the ictus-CFR) for stroke in young adults ranges between 10% and 34% in published series. As in the older population, CFRs are higher in ICH and SAH than infarction. In an epidemiological study evaluating racial differences in CFR in the 1990s, no significant difference between white and black young stroke patients in Cincinnati was found (8,110). Mortality is highest in the first year after stroke, declining in subsequent years (111). Mortality was 1.7% per year among ischemic stroke patients under the age of 45 in the Iowa Registry of Stroke in Young Adults (112), and 86% of these patients were alive at follow-up, a mean of 6 years after the stroke. This last finding was consistent with that of Marini et al., who found an 86.5% 10-year survival rate for ischemic stroke in patients aged 15 to 44 in a multisite series (112,113). As would be expected given these survival rates, the prevalence of young stroke survivors has increased over time. In the United States, there were 590,000 aged 25 to 59 in 1973, growing to 965,000 in 1991 (114). Individual survival, of course, depends on the cause and severity of the stroke and the burden of comorbid conditions.

Function

Global functional outcomes for young adults are generally good. In Western Norway, 80% of young infarction patients achieved a Modified Rankin Scale (mRS) less than or equal to 2 at 3 months after stroke and 78% at long-term follow-up (mean

5.7 years) (10,115). Case series have consistently corroborated this finding, with 96% of the 272 cases studied by Varona et al. achieving mRS less than or equal to 2 at 3 years after stroke (106). Camerlingo et al. found that 91% of their 135 cases evaluated at 1 year had achieved mRS scores less than or equal to 3 (116), and Neau et al. found that 86% of their 65 cases at follow-up (mean 32 months) had RS less than or equal to 3 (117). In the series of Musolino et al., 89% of 54 young patients evaluated a mean of 6.12 years after stroke had mRS less than or equal to 3 (118). Moreover, in a recent large Austrian Stroke Registry analysis of 2223 stroke survivors aged 55 or younger, Knoflach and colleagues found that functional outcome at 3 months varied by decade of age within the under-55 group. Those under 35 years had the highest probability of mRS score less than or equal to 2, whereas this favorable outcome declined by 3% to 4% in each subsequent decade (119).

In population-based studies as well as case series, the great majority of young stroke survivors have achieved good functional outcome in self-care and mobility. Marini et al. in northern Italy recorded 84% achieving a Barthel index of greater than or equal to 90 at the end of follow-up (113). Varona et al. found that 90% of their 272 cases were independent in ADLs and 95% could walk without assistance at follow-up (mean 12 years) (111), and Kappelle et al. noted 92% with Barthel Index scores greater than 90 (112). Poor outcome after stroke in young adults has been associated with a history of diabetes mellitus, severe deficit at presentation, stroke involving the total anterior circulation, and large artery atherosclerosis (103,111,115). There is evidence that functional recovery occurs more quickly in younger than elderly patients in an inpatient rehabilitation setting. In analyzing a large consecutive series of stroke patients stratified into five age subgroups, Black-Schaffer and Winston found that younger patients had significantly higher FIM efficiencies (FIM points gained per day) during inpatient rehabilitation (120). Older patients often enter rehabilitation at a lower level because of prestroke functional limitations and progress more slowly related to a greater burden of comorbid conditions (120–123). Because treating staff feel that young patients have greater functional potential and more complex goals than their elderly counterparts, young adult stroke patients tend to remain in rehabilitation facilities longer than the elderly (120) and are offered the newest and most aggressive rehabilitation regimens.

Community Discharge

In keeping with their higher functional level at discharge, young adult stroke patients are discharged back to the community more often than the elderly. Black-Schaffer and Winston found that, in a cohort of 979 stroke rehabilitation inpatients, 84% of those under age 55 were discharged home, in contrast to 54% of those older than 85 years. Alexander and Granger et al. found the same trend in separate American cohorts of inpatient rehabilitation patients examined a decade earlier (120,124,125). In the United States, skilled nursing facilities are often reluctant to accept young patients because of lack of appropriate programming, further reinforcing this trend.

Return to Work

The ability to perform valued work is central to self-esteem and an important goal for most young stroke patients (126). Between 3% and 84% of patients achieve this goal, with the wide range reported in this literature caused by differing age ranges of patients reported, variable definitions of work, and disability compensation systems with different incentive structures (127). Numerous series have examined the percentage of patients returning to work after the stroke. Those that evaluate patients less than 45 years of age find notably higher percentages of patients returning to work than those that evaluate patients up to the age of 65. These studies are summarized in Table 44.7.

Many case series have been analyzed for factors associated with success in returning to work. Variables cited have included:

- Perceived importance of work (128)
- Pure motor or no hemiparesis (129,130)
- Good self-care and mobility function (115,127,131–133)
- No aphasia or apraxia (117,127,134)
- Advanced education (115,117,135,136)
- Preserved cognition (126,129)
- White-collar job (132,133,135,136; also 128)
- Higher income (137)
- Married status or social supports (115,128)
- Younger age (115,131,133,138)

Variables identified as barriers to successful vocational rehabilitation include, in addition to the reverse of these factors:

- Visual/perceptual impairment (129)
- Depression (117,129)
- Economic disincentives related to disability and retirement benefits (132,139)

Of those returning to work after a stroke, about two-thirds reduce hours and/or duties (126,140). The rehabilitation physician is often asked to certify that the young stroke patient is "medically cleared" to return to work. This may mean certifying only that the patient has sufficient cardiovascular capacity to perform the job, but, more often, it is a request for a detailed evaluation of the patient's cognitive, physical, and psychological capacity as they relate to specific job requirements. This assessment is complex and ideally is accomplished with the assistance of a coordinated multidisciplinary team, including physical, occupational, speech therapist, neuropsychologist, and vocational rehabilitation counselor (139).

Patients who are able to resume work after a stroke on average do so within the first six months. In the United States, the 1990 Americans with Disabilities Act had a positive impact on employers' responsiveness to the requests of stroke survivors for accommodations on their prestroke job, not only regarding physical access and equipment but also for personal assistance, schedule flexibility, and task modification (139). However, employers' concerns regarding possible costs associated with stroke survivors as new hires may, in some cases, make it hard for survivors to change to a different job.

TABLE 44.7 Return to Work After Stroke

STUDIES OF PATIENTS UNDER THE AGE OF 46					
AUTHOR	YEAR	N	RTW	AGES	WORK
Adunsky et al. (158)	1992	30	81%	20–45	FT, other
Bogousslavsky and Regli (134)	1987	41	81%	<30	FT
Camerlingo et al. (116)	2000	135	62%	16–45	Unspecified
Ferro and Crespo (160)	1994	140	73%	<46	FT, PT, HM, S
Hindfelt and Nilsson (162)	1977	52	84%	16–40	FT, PT
Kappelle et al. (112)	1994	274	42%	15–44	Unspecified
Leys et al. (155)	2002	265	60%	15–45	Unspecified
Marini et al. (113)	1999	330	56%	15–44	Unspecified
Musolino et al. (118)	2003	60	69%	17–45	FT, PT
Naess et al. (115)	2004	134	68%	15–44	Unspecified
Neau et al. (117)	1998	63	73%	15–45	FT, PT, HM, S
Varona et al. (111)	2004	240	53%	15–44	Unspecified
STUDIES OF PATIENTS UNDER THE AGE OF 65					
AUTHORS	YEAR	N	RTW	AGES	WORK
Black-Schaffer and Osberg (127)	1990	79	49%	21–65	FT, PT, HM, S
Coughlan and Humphrey (159)	1982	170	33%	<65	FT, PT
Fugl-Meyer et al. (161)	1975	83	41%	<65	FT, PT, HM
Kotila et al. (129)	1984	58	55%	<65	CE, HM, S
Mackay and Nias (164)	1979	45	38%	<65	Unspecified
Saeki et al. (165)	1993	230	58%	<65	FT, PT, HM, S
Weisbroth et al. (166)	1971	62	37%	<65	CE
Wozniak et al. (138)	1999	109	53%	mean 55	FT, PT

Abbreviations: CE, competitive employment; FT, full-time; HM, homemaking; PT, part-time; S, student.

Driving

Throughout the developed world, a return to driving has become a necessary step to resuming a normal lifestyle and avoiding social isolation. In many locations, it is a prerequisite for returning to gainful employment. It has been estimated that half of stroke survivors in the United States return to driving without advice or reevaluation of their fitness to drive (141). Of those who do seek reevaluation, approximately half are successful in passing driving evaluations (142,143). In the United States, many rehabilitation clinics offer written tests of driving ability. These can be useful for screening out patients with significant perceptual or cognitive problems who would be unsafe in a road test setting. In one study, two commonly used tests, the Motor Free Visual Perception Test and the Trail Making B test, were found to correlate closely with on-the-road driving performance (144). Computerized driving simulators also hold promise both as screening tools and training devices (145,146), though their adoption in clinical rehabilitation settings has been slow. In the published case series on this topic, a number of factors have been associated with driving performance after stroke:

- Right hemisphere location of stroke (143,147,148)
- Visual perceptual deficits (144,149)
- Reduced sustained and selective attention (150,151)
- Impulsivity or poor judgment (143,149)
- Lack of organizational skills (151)

All correlate with poor performance behind the wheel. Aphasia, though it may negatively impact performance on written and road tests because of compromised processing of verbal or written instructions, does not always interfere with self-directed driving (141,149,152). And physical impairment alone does not increase the risk of accidents or traffic violations (143). Physicians are often consulted about a patient's readiness to resume driving, and, though visual perception can be readily screened, the evaluation of attention, judgment, and organizational ability is more complex and benefits from involvement of a neurologic rehabilitation team (153). An on-the-road test performed either by a driving instructor or by a state licensing agency remains the gold standard for assessing driving ability.

Parenting

The young adult stroke survivor who needs to return to parenting faces physical as well as cognitive and perceptual challenges in the performance of child bathing, dressing, feeding, and transporting tasks. Fortunately, many helpful items of equipment are readily available. Disposable diapers with adhesive tabs require less dexterity than cloth diapers with pin closures. Microwaves make heating bottles of formula easier and safer than warming them in a pan of boiling water. Baby tub inserts help to stabilize an infant for bathing, and so on. Other adult family members, home care occupational therapists, and/or hired childcare assistants can provide valuable assistance to the stroke survivor in problem-solving performance of these tasks. When the survivor requires physical assistance to accomplish a childcare activity, he or she should be encouraged to assume the supervisory role whenever possible.

Even more challenging, potentially, is the establishment and maintenance of a loving and effective relationship between a disabled parent and a growing child, because children's needs and perceptions of their parents evolve as psychosocial development proceeds. The child's second parent, or another adult important to the child, can play an important role in helping both parties negotiate this relationship over time.

RECURRENCE

The likelihood of a second stroke increases as young patients' vascular disease risk factors multiply. In Hordaland County, Norway, risk of recurrence ranged from 2.1% during the mean 6-year follow-up period for those young adult stroke survivors without hypertension, diabetes, hypercholesterolemia, smoking, angina, myocardial infarction, or intermittent claudication to 67% recurrence for those with five of these risk factors (150). In the Helsinki Young Stroke Registry, the overall 5-year cumulative recurrence rate for ischemic stroke in those aged 15 to 49 was 9.4%. Survivors with diabetes, atherosclerosis, heart failure, and prior TIA were at increased risk (154). Recurrence rates are highest in the first year after ischemic stroke, ranging from 1% to 3% (111,113,155). For certain nonatherosclerotic stroke etiologies, recurrence risk is well defined. After carotid dissection, recurrences occur in approximately 10% at the rate of 1% per year, and they are usually in a different artery. Recurrences are more common in those with first dissection under age 45 (52). CVT carries an overall recurrence rate of 11%, which may reflect comorbid conditions such as cancer with continuing thrombophilia (65). Risk of recurrence after a drug- or pregnancy-induced stroke depends on whether intake of the drug is resumed or pregnancy is again undertaken.

It is important for the young stroke survivor and his or her physician to review the etiology of the patient's stroke, identify modifiable risk factors for recurrence, and jointly develop a plan to minimize those factors. The patient's motivation to comply with treatment for hypertension and diabetes, develop a habit of compliance with newly prescribed anticoagulation therapy, quit smoking, avoid excessive alcohol intake, and turn away from the use of street drugs will be maximal in the months following the stroke. Close medical follow-up to reinforce the risk reduction plan and monitor its effects will improve the likelihood of success. Young adult survivors with stroke of unknown etiology face unavoidable uncertainty regarding the risk of recurrence. It is not clear whether empiric prescribing of preventive medications for these individuals, in the absence of corresponding risk factors, is beneficial; though sometimes it is an attractive way to deal with the natural desire to do something (156). Recent evidence suggests that even for stroke of undetermined etiology in young adults, a statin for secondary prevention is associated with lower rates of new vascular events in an average follow-up of nine years after the stroke (157). Significant progress has been made in elucidating components of the stroke of unknown etiology category in recent years, and we can anticipate that future research will shed further light on this area.

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45

Stroke in Older Adults

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Stroke is the fourth leading cause of death and a foremost cause of serious, long-term disability in the United States (1). As cardiovascular and metabolic disease incidences rise with age, so does the risk of stroke; and clinical and functional consequences may be compounded by other conditions associated with aging. However, stroke is not an inevitable consequence of aging. By identifying and modifying risk factors in older people, there are opportunities to reduce the incidence and mortality of this condition (2) and improve function, independence, and quality of life after stroke. Recent advances in emergency medical care have reduced mortality and stroke severity, resulting in greater numbers of older adults who survive strokes (3). Although stroke incidence in America appears stable and stroke mortality is slowly declining, the absolute magnitude of stroke is likely to grow over the next 30 years. With aging of the population, the number of older stroke survivors is likely to increase substantially (1). The very old are expected to become a growing part of the stroke survivor population (4).

This chapter presents a discussion of special considerations in the management of stroke recovery and rehabilitation for older adults. We describe the incidence, prevalence, and economic impact of stroke in the aging population. We discuss the management of common risk factors for recurrent stroke. We address challenges to successful rehabilitation in older adults with stroke, and suggest strategies to overcome barriers and optimize outcomes.

INCIDENCE, PREVALENCE AND ECONOMIC IMPACT

Age is the single most important risk factor for stroke. For each successive 10 years after age 55, the stroke rate more than doubles in both men and women (5). Nearly three-quarters of all strokes occur in people over the age of 65. Stroke incidence rates are 1.25 times greater in men, but because women tend to live longer than men, more women than men die of stroke each year (1).

Not only are they more likely to have strokes, but the physical, psychological, and social consequences may be more severe for older adults. The burden of stroke is heterogeneous and is greatest among the elderly, men, and African Americans (1). Furthermore, age is an independent predictor of outcome after an ischemic stroke. Older patients, especially those over 80 years old, are more likely to die in the hospital after stroke and less likely to make a favorable long-term recovery (4). Other factors, such as onset stroke severity, preexisting disability, and atrial fibrillation (AF), are also significant age-related independent predictors of prognosis after stroke (4).

Many stroke survivors (50%–70%) regain functional independence, but 15% to 30% are permanently disabled and 20% require institutional care at 3 months after onset (1). Effective rehabilitation interventions initiated early after stroke can enhance the recovery process and minimize functional disability (6). Stroke rehabilitation begins during the acute hospitalization, as soon as the diagnosis of stroke is established and life-threatening problems are under control. The highest priorities during this early phase are to prevent recurrent stroke and complications, manage comorbid illness, promote mobility and self-care activities, and provide emotional support to the patient and family (6). Poststroke guidelines recommend transfer to a stroke-specific rehabilitation unit as soon as possible to ensure early mobilization; availability of speech, physical, and occupational therapy; rehabilitation psychology; and the social support derived from interaction with other stroke survivors (6). There is a body of evidence indicating that patients do better with an organized, multidisciplinary approach to postacute rehabilitation after a stroke (7,8).

The economic impact of stroke has been and will continue to be substantial. Based on estimated incidence data from the Centers for Disease Control, the direct costs to the health care system associated with stroke are estimated to total approximately $70 billion by 2025 (8). As many older adults leave active employment, indirect costs such as those associated with premature mortality and lost productivity are lower, but are still estimated to approach an additional $38.9 billion. Both these estimates are calculated in 2008 dollars (8).

A recent literature review indicated that most studies on economic impact of stroke emphasize the short-term costs associated with hospital and ICU care. However, long-term ambulatory care and nursing home care also account for substantial portion of direct costs, at 35% and 17% respectively (9). Brown and colleagues projected the U.S. costs of ischemic stroke from 2005 to 2050 (in 2005 dollars) to be

approximately $2.2 trillion: $1.52 trillion for non-Hispanic whites, $313 billion for Hispanics, and $379 billion for African Americans (10). The proposed figures likely underestimate the true economic burden of stroke, because the estimates do not take into account the rise in salaries and treatment costs, growth among minority populations, and the increase in risk factors for stroke such as obesity, diabetes, and heart disease (9–11).

Uncontrolled risk factors dramatically increase costs associated with stroke. An analysis of data from the National Health and Nutrition Examination Survey (NHANES) II study examining cost data from short-term hospitalization and estimated first-year loss of productivity or premature death concluded that the annual costs of one undermanaged cardiovascular risk factor for subjects who had already suffered an MI or stroke are estimated between $3.2 and $11.1 billion (11). Among persons with previous MI or stroke, two or more inadequately controlled risk factors accounted for incurred cost ranging between $4.1 to $12.2 billion (11). Estimates using the same data for years of life lost due to uncontrolled risk factors range from 7.5 years for one uncontrolled risk factor to 8.9 years for 2 or more (11).

Still, stroke risk factors remain suboptimally managed in the poststroke population at large. In a group of 364 community-dwelling chronic stroke survivors, who were assessed by basic history and physical and laboratory analysis of a fasting sample, 99% had at least one suboptimally controlled risk factor. Ninety-one percent had two or more risk factors inadequately treated. Eighty percent of the participants had prehypertension or hypertension, 67% were overweight or obese, 60% had suboptimal low density lipoprotein (LDL) levels, 45% had impaired fasting glucose, 34% had low high-density lipoprotein (HDL) levels, and 14% were current smokers, despite the fact that all were reportedly receiving routine medical care (12). Clearly, in addition to public health efforts to educate all Americans about stroke risk and recognition of signs and symptoms, risk factors that persist must be managed as aggressively as possible.

Managing Common Risk Factors for Recurrent Stroke in Older Adults

Risk factors and the incidence of stroke peak in individuals 75 years old or older. Patients with the highest risk benefit the most from effective risk-reduction therapy (13). For this reason, all strategies of demonstrated value in stroke prevention are pertinent in the care of older adults. Control of hypertension, treatment of dyslipidemia, management of diabetes mellitus, anticoagulation for AF, promotion of exercise and healthy diet, and cessation of cigarette smoking are obligatory at all ages, but are of particular importance in older adults (13).

Management of Hypertension

High blood pressure, once believed to represent a normal and progressive component of the aging process, is now recognized as a sign of structural and physiologic abnormalities of vascular function (14). Elevated blood pressure is a significant determinant of the long-term risk of stroke (15). Casual systolic hypertension is a prevalent finding in older adults (50% of women over the age of 80 have casual systolic blood pressures >160 mmHg (16). Isolated systolic hypertension, defined as a systolic blood pressure greater than or equal to 140 mmHg with a diastolic blood pressure less than 90 mmHg, affects most individuals aged 60 years and older (14).

Antihypertensive treatment has established efficacy in the primary prevention of fatal or nonfatal stroke in hypertensive and high-risk patients who are more than 60 years of age, particularly through treatment of systolic hypertension (17). In a summary of 17 treatment trials of hypertension throughout the world involving nearly 50,000 patients, investigators found a 38% reduction in all stroke and a 40% reduction in fatal stroke resulting from systematic treatment of hypertension (18). Treatment was also highly effective in preventing stroke in individuals older than 65 years with systolic hypertension (18). Importantly, there was no less impact on stroke prevention above age 80, with incidence reduced by 40% (17).

The initial antihypertensive drug should be started at the lowest dose and gradually increased, depending on the blood pressure response to the maximum tolerated dose and following a stepwise approach as recommended in the JNC-7 guidelines (19). Before adding new antihypertensive drugs, possible reasons for inadequate blood pressure response should be examined. These include noncompliance, volume overload, and drug interactions (e.g., use of NSAIDs, caffeine, antidepressants, nasal decongestants containing sympathomimetics). Causes of secondary hypertension should be identified and treated (19). Altered pharmacodynamics resulting from changes in body composition due to aging, or organ function due to pathophysiology, should also be considered.

Polypharmacy and potential drug interactions are a greater concern in the elderly than in younger patients. The average elderly patient is taking three to five prescription drugs daily (20). Medications likely to be used in the elderly that increase BP include NSAIDS, corticosteroids, erythropoietin, amphetamines, ergotamine, and anabolic steroids.

The general recommended blood pressure goal in persons with uncomplicated hypertension is less than 140/90 mmHg. However, this target for elderly patients with hypertension is based on expert opinion rather than on data from randomized controlled trials (RCTs), and it is unclear whether the target systolic blood pressure (SBP) should be the same in 65- to 79-year-olds versus older patients (21). The HYVET study (22) results provide evidence that blood pressure lowering is associated with definite cardiovascular benefits in patients 80 years of age or older, including a decrease in mortality and a prolongation of life (22). This finding is highly relevant for public health because subjects 80 years of age and older represent the fastest growing segment of the population (21). Optimal clinical management accounts for specific aspects of pathophysiology and metabolic characteristics of older adults. Treatment should be initiated with lower doses of antihypertensive agents, bringing pressure down slowly, while monitoring for orthostatic hypotension, impaired cognition, and electrolyte abnormalities (14).

Management of Dyslipidemia

Elevated cholesterol levels are not uncommon in older adults. Sixty-one percent of women aged between 65 and 74 are reported to have total cholesterol levels over 240 mg/dL (23). Elevated total cholesterol and decreased HDL levels predispose older adults to ischemic stroke (23).

Possible benefits from lipid-lowering therapy are particularly relevant for the older population at high risk for stroke (23). Though associations are relatively weak, epidemiological evidence indicates that elevated total cholesterol and subfractions increase stroke risk (23). Lowering high serum cholesterol with HMG-CoA reductase inhibitors (statins) has been beneficial in the primary and secondary prevention of myocardial infarction, but further research is needed to determine the effect of lipid lowering on stroke occurrence (23). Few large-scale studies have investigated the specific effect of statins on stroke prevention in older individuals. To date, the largest trials suggest a beneficial effect for stroke prevention with statins in high-risk elderly subjects 82 years of age or less (17).

Indirect evidence suggests that the reduction in the stroke risk with statins is larger than would be expected with reduction of serum cholesterol level alone. Antioxidant and endothelium-stabilizing properties of statins may contribute to reducing the risk of stroke by protecting vascular walls (23). Although the relative risk (RR) of stroke associated with elevated lipids is only moderate, its population-attributable risk is high, given the increase in the elderly population worldwide (23). It is important to note that elevated serum cholesterol seldom occurs in isolation from other cardiovascular risk factors.

Recently published guidelines identify four groups of primary- and secondary-prevention patients on whom clinicians should focus their efforts to reduce cardiovascular events (24). In these four patient groups, the new guidelines make recommendations regarding the appropriate "intensity" of statin therapy in order to achieve relative reductions in LDL cholesterol.

The four major primary- and secondary-prevention patient groups who should be treated with statins were identified on the basis of randomized controlled clinical trials showing that the benefit of treatment outweighed the risk of adverse events. The four treatment groups include (24):

- Individuals with clinical atherosclerotic cardiovascular disease
- Individuals with LDL cholesterol levels greater than or equal to 190 mg/dL, such as those with familial hypercholesterolemia
- Individuals 40 to 75 years old with diabetes and with LDL cholesterol levels between 70 and 189 mg/dL and without evidence of atherosclerotic cardiovascular disease
- Individuals without evidence of cardiovascular disease or diabetes but who have LDL cholesterol levels between 70 and 189 mg/dL and a 10-year risk of atherosclerotic cardiovascular disease of 7.5% or higher

In those with atherosclerotic cardiovascular disease, high-intensity statin therapy should be used to achieve at least a 50% reduction in LDL cholesterol unless otherwise contraindicated or when statin-associated adverse events are present (24). In that case, clinicians should use a moderate-intensity statin. Similarly, for those with LDL cholesterol levels greater than or equal to 190 mg/dL, a high-intensity statin should be used with the goal of achieving at least a 50% reduction in LDL cholesterol levels (24).

For those 40 to 75 years old with diabetes, a moderate-intensity statin, defined as a drug that lowers LDL cholesterol 30% to 49%, should be used, whereas a high-intensity statin is a reasonable choice if the patient also has a 10-year risk of atherosclerotic cardiovascular disease exceeding 7.5% (24). For the individual 40 to 75 years old without cardiovascular disease or diabetes but who has a 10-year risk of clinical events greater than 7.5% and an LDL cholesterol level anywhere from 70 to 189 mg/dL, the panel recommends treatment with a moderate- or high-intensity statin (24).

Management of Diabetes

There is an age-related increase in total body fat and visceral adiposity that often is accompanied by diabetes or impaired glucose tolerance. The prevalence of type 2 diabetes increases progressively with age, peaking at 16.5% in men and 12.8% in women at age 75 to 84 years. Over age 65, glucose intolerance or diabetes was present in 30% to 40% of Framingham Study subjects (25). In a recent report, 80 chronic hemiparetic stroke patients were evaluated by fasting plasma glucose and oral glucose tolerance test to assess the utility of screening for abnormalities using fasting plasma glucose alone. Seventy-five of the 216 (35%) had type 2 diabetes by medical history. Another 70 were either diabetic (n = 11) or had impaired fasting glucose (n = 59) based on a single blood draw at the time of screening. Fasting plasma glucose among nondiabetic stroke patients had a sensitivity of 49% for predicting abnormalities in the 2-hour glucose level during oral glucose tolerance test. Cumulative results identify 77% as abnormal (impaired or diabetic) on the basis of medical history, fasting plasma glucose, and/or 2-hour glucose level, reflecting a very high prevalence of diabetic states in these chronic stroke survivors (26).

Type 2 diabetes and obesity are both associated with a clustering of atherogenic risk factors. Diabetes, often associated with high blood pressure, contributes to increased frequency and severity of cerebral vascular events (27). The risk of macrovascular disease is actually increased before glucose levels reach the diagnostic threshold for diabetes, and 25% of newly diagnosed diabetics already have overt cardiovascular disease (25). Diabetes, and related complications including untreated or poorly treated hypertension, may lead to premature arterial stiffening. The resulting stiffening and hypertrophy of the left ventricle yield a predisposition to coronary heart disease, heart failure, stroke, and other conditions (28). Other aspects of glucose metabolism may play a role in stroke risk, specifically hyperinsulinemia

and increased insulin resistance. Both were shown to be associated with ischemic stroke risk even among subjects with normal glucose status by laboratory values (26).

The risk of cardiovascular sequelae in diabetics is variable. The majority of events occur in those with two or more additional risk factors. Comprehensive stroke risk reduction in older adults should include not only normalization of the blood sugar, but also weight reduction, dietary fat restriction, strict blood pressure and lipid control, exercise, and avoidance of tobacco (25).

Atrial Fibrillation Management

AF is the most common clinically relevant arrhythmia in persons aged more than 75 years, and is strongly associated with ischemic stroke and other adverse outcomes. AF is also the most treatable cardiac precursor of stroke (29). The incidence and prevalence of AF increase with age (30). Data from the Framingham Study and hospital discharges suggest that the prevalence of AF in the U.S. population is increasing (15). More than 2.2 million Americans currently have AF, and this number is expected to increase by at least 2.5-fold over the next 50 years (29).

Stroke is the most feared complication of AF. Multiple clinical trials have shown that warfarin sodium anticoagulation therapy is effective in reducing the risk of stroke in older adults (31). However, the complex pharmacokinetics and narrow therapeutic window of warfarin make its use challenging. An adjusted dose of warfarin with a target international normalized ratio (INR) of between 2 to 3 prevents ischemic stroke in elderly patients with an acceptable hemorrhagic risk, but is still largely underprescribed (31).

Newer therapies for anticoagulation have been introduced in recent years, but evidence is limited by the small number of studies and lack of direct comparisons of novel anticoagulants (32). A comparative effectiveness analysis of relevant studies found that a factor IIa inhibitor (dabigatran 150 mg) was superior to warfarin in reducing the incidence of stroke (including hemorrhagic) or systemic embolism (RR 0.66; 95% CI 0.53 to 0.82) with no significant difference in the occurrence of major bleeding (RR 0.93; 95% CI 0.81 to 1.07) (32). The Xa inhibitor rivaroxaban was noninferior to warfarin in preventing stroke or systemic embolism and showed similar rates of major bleeding and death (32). The Xa inhibitor apixaban was superior to warfarin in reducing the incidence of stroke or systemic embolism (hazard ratio [HR] 0.79; 95% CI 0.66 to 0.95), major bleeding (HR 0.69; 95% CI 0.60 to 0.80), and all-cause mortality (HR 0.89; 95% CI 0.80 to 0.998) (32). Apixaban was also superior to aspirin in reducing the incidence of stroke or systemic embolism (HR 0.45; 95% CI 0.32 to 0.62) with similar hemorrhagic events, including major bleeding (HR 1.13; 95% CI 0.74 to 1.75), in patients who are not suitable for oral anticoagulation (32). However, no studies have as yet directly compared the new therapies to one another.

Carotid Stenosis Treatment

Carotid stenosis refers to the buildup of atherosclerotic materials within the carotid arteries, leading to occlusion of vital circulation to the brain. Management of carotid stenosis must take into account individual patient considerations and surgical risk. Carotid endarterectomy (CEA) has been the standard of care for years for severe carotid artery stenosis, but for less severe lesions, carotid angioplasty and stenting (CAS) have emerged as a therapeutic alternative and data suggest success and complication rates comparable to those for CEA (33). The advantages of CAS are its less invasive nature, decreased patient discomfort, and a shorter recuperation period, but its durability remains unproven, so CAS is mainly offered to those patients considered at high risk for open endarterectomy (33). Current recommendations for management depend on the degree of stenosis, surgical risk, and optimal medical therapy. This includes antiplatelet therapy, statin therapy, and risk factor modification, and is recommended for all patients with carotid artery stenosis (33).

Antiplatelet Therapy in Stroke Prevention

Finally, for most patients with noncardioembolic stroke, daily treatment with an antiplatelet agent is recommended. Four antiplatelet drugs are approved by the FDA for prevention of vascular events among patients with a stroke or TIA: aspirin, combination aspirin/dipyridamole, clopidogrel, and ticlopidine. On average, these agents reduce the RR of stroke, MI, or death by about 22%, but important differences exist between agents that have direct implications for therapeutic selection, including tolerance of specific agents, cost, comorbidities, safety, adverse event profiles, and patient preference (33). Aspirin is by far the least expensive agent, and ticlopidine is associated with thrombotic thrombocytopenic purpura and should be used only cautiously in patients who cannot tolerate other agents (33).

CHALLENGES TO SUCCESSFUL REHABILITATION

Even with identical stroke severity, increasing age is associated with greater disability in activities of daily living (ADLs) and mobility. Patients older than 85 years are nearly 10 times as likely to show a low response to rehabilitation in ADLs, and nearly 6 times as likely to show low response to mobility as younger patients (34). Nevertheless, rehabilitation treatment is still valuable in patients older than 85 years, because even small changes in function can improve independence and quality of life. Though possibly less effective than for younger patients, inpatient rehabilitation is still substantially helpful for older patients (34).

Rehabilitation and gerontology care professionals share a function-based assessment and management paradigm. Clinical challenges after stroke therefore should be considered within the context of age and any pre-existing disability.

Biological Changes With Aging

Visual Changes

Visual loss is usually defined as less than 20/40 in the better eye and is associated with functional consequences. Blindness is traditionally defined as vision less than 20/200 in

the better eye. Blindness or low vision affects 3.3 million Americans age 40 and over, or 1 in 28, and this figure is projected to reach 5.5 million by the year 2020. Low vision and blindness increase significantly with age, particularly in people over age 65 (35). *Presbyopia*, the loss of accommodative ability, is the major age-associated ocular change leading to low vision. It begins at approximately age 40 and progresses, so that by the seventh decade, little ability to accommodate remains. Other changes with senescence include increased light absorption by the lens, cornea, and vitreous humour, leaving less to reach the retina, resulting in decrease in sharpness of vision and the need for more light for certain activities, such as reading and driving. The prevalence of common ophthalmologic diseases also dramatically rises with advancing age, with those over 80 years of age suffering an increase in cataract (68%), age-related macular degeneration (35%), and open-angle glaucoma (7.7%; 35).

Consequences of stroke may also manifest in visual disturbances, such as homonymous hemianopsia, visual field defects, visual neglect, disturbances in color vision, or paralysis of conjugate gaze. Ocular motility disturbances may produce diplopia, vertigo, oscillopsia, or visual distortions. All of these visual disturbances have potential to complicate or hinder the progress of rehabilitation. For example, visual deficits may make it difficult for an older adult to orient to new surroundings, to follow directions, or to receive feedback and cues for mobility and self-care activities. Visual deficits may contribute to fear of falling, and impede progress in ambulatory activities. All stroke survivors should be screened for visual impairment as soon as they are medically stable, conscious, and communicative enough to participate in the examination, and an individualized plan should be formulated by the rehabilitation team to compensate for any losses.

Auditory Changes

Hearing loss is one of the most prevalent chronic conditions in the elderly population, affecting 31% of people over the age of 65, and 40% to 50% of persons over the age of 75. It is defined as the inability to hear a pure tone softer than 40 decibels (dB) at more than one frequency in one or both ears (36). The most common cause of hearing loss in the elderly is presbycusis, which is a sensorineural loss marked by difficulty hearing high-frequency tones, and by impaired speech comprehension. Other common causes of hearing loss in the elderly include cerumen plugs, otosclerosis, ototoxicity, tinnitus, Ménière's disease, and acoustic neuromas (36).

Again, stroke may impose comprehension or communication deficits that may compound hearing loss and negatively affect rehabilitation, such as aphasia, dysarthria, and apraxia of speech. Individuals with stroke are usually assessed for these problems, but all stroke survivors, especially the elderly, should also be screened for hearing loss and referred for treatment or adaptive strategies as needed. Adequate auditory acuity is critical for stroke survivors to understand the rehabilitation team's instructions, to participate in problem assessment and decision making, and to communicate effectively with family and members of the rehabilitation team, thereby improving chances for successful rehabilitation.

Body Composition

A potential confounder to reaching physical therapy goals for older stroke patients may be sarcopenia (age-related loss of muscle mass), commonly seen in older adults (37,38). Between 50 and 80 years of age, the number of fibers in the large thigh muscle, the vastus lateralis, of men decreased by 50%. Although a comparable study has not been undertaken for women, the age-related changes in muscle mass suggest that similar, if not identical, changes occur. The loss of type 2 muscle fibers appears to be immutable, but the impact of the fiber loss on muscle mass depends to a substantial degree on the regularity and intensity of the physical activity in which elderly people are engaged (38). Loss of skeletal muscle fibers is a major contributing factor to sarcopenia, but other factors, including decreased physical activity, altered hormonal status, decreased total caloric and protein intake, inflammatory mediators, and factors contributing to protein synthesis are also involved, and together may contribute to functional decline (39). Interventions targeted at combating sarcopenia of aging have included testosterone replacement, growth hormone replacement, and resistive strength training. Of these, only strength training has been shown to be an effective means of increasing muscle mass and strength in healthy older adults (41).

The additional loss of muscle in the hemiparetic limb(s) creates further difficulties for stroke survivors as they attempt to mobilize again following stroke. A recent study examining 30 chronic stroke survivors showed that lean mass of the paretic leg and thigh were 4% and 3% lower than the nonaffected leg; arm lean mass of the paretic side was 7% lower than the nonaffected side; and midthigh muscle area was 20% lower in the paretic limb than in the nonaffected leg (41). The mechanism of muscle atrophy following stroke is not well understood at this time, nor is the time frame over which the atrophy occurs. However, it appears that the sarcopenia associated with aging, combined with the disability of stroke, may conspire to place the survivor at a disadvantage from a rehabilitation perspective. Most stroke patients are carefully assessed for muscle strength throughout the rehabilitation course, and more research is needed to identify specific strength training recommendations for these patients.

Comorbidities

Early exercise rehabilitation is critical to maximizing functional outcomes following stroke (42). However, sedentary older adults with stroke often suffer from comorbidities that may limit their ability to fully participate or maximize physical therapy in the subacute and chronic phases of stroke recovery.

Disorders of the cardiovascular system can potentially impact rehabilitation therapy by limiting exercise tolerance, and are very common in older adults. With age, pre-existing coronary artery disease (often seen coincident with cerebrovascular disease), congestive heart failure, valvular dysfunction, and arrhythmias increase in prevalence (1). Chronic obstructive pulmonary disease, emphysema, and chronic bronchitis are also more prevalent in older adults. Stroke survivors with these and similar comorbid illnesses are likely to face additional challenges with rehabilitation and life beyond. These individuals may experience severe limitations in activity tolerance and progress more slowly toward their rehabilitation goals. It is likely that comorbid cardiovascular or pulmonary problems played a role in dictating a previously sedentary lifestyle that precipitated the stroke.

Rehabilitation may also be challenged by musculoskeletal disorders (osteoarthritis, rheumatoid arthritis, history of muscle or bone injury). Careful evaluations of pre-existing disability, the extent of neurological deficit, and motor control are critical to developing a realistic exercise prescription. Identifying and addressing barriers to mobilization (medication prior to physical therapy appointments, braces/orthotics for support, appropriate assistive devices, and environmental modifications) will maximize chances of success in reaching therapeutic goals.

Cognitive impairment is another potential barrier to successful rehabilitation. Stroke survivors are likely to have long-standing hypertension and other cardiovascular risk factors that can lead to vascular-related cognition impairments or dementia, and cognition may be further impaired by the stroke itself. In an observational study of 645 first-ever stroke survivors, 38% were judged cognitively impaired (Folstein Mini Mental State Exam score of <24) at 3 months after stroke. Those with cognitive impairment were matched with cognitively intact stroke survivors and outcomes were compared over time. Cognitive impairment was associated with advanced age (75 and older), ethnicity (Caribbean/African and Asian), lower socioeconomic class, left hemispheric lesion, visual field defect, and urinary incontinence. It is associated with poor long-term outcomes, including survival and disability, up to four years after stroke (43). These problems are very likely to impact the course of rehabilitation therapy and are discussed more comprehensively elsewhere in this text, but all older stroke survivors should be carefully screened in these domains of cognition to maximize therapeutic intervention.

Access to Care

Older adults in general face more barriers in accessing health care services than their younger counterparts. Older disabled stroke survivors face even more hurdles in their quest for both restorative and preventive health care services. Many older adults are dependent on Medicare benefits to pay for health care services, and may or may not carry an additional group or private gap coverage policy. The Medicare insurance system was developed to ensure that the older workers had insurance for health care expenses, and many have used it for incidental care only (44), as coverage for preventive services has been added incrementally over time. In a recent study of 46,659 respondents aged 65 years and older, 93% reported having a regular care provider, 98% had a regular place of care, and 98% were able to obtain needed medical care (45). Those with a regular care provider or a regular place of care were more likely to receive clinical preventive services than those without either of these. Reasons given for not obtaining needed medical care were cost (27%), too long a wait for an appointment (20%), distance or unavailability of transportation (9%), office not open when the individual could get there (8%), and other reasons (32%) (45). Another large study of older adults revealed that a perceived lack of responsiveness to patient concerns, cost, transportation, and street safety were substantial barriers for many older adults (46). Some older adults in the United States have no health care coverage at all, and therefore experience significant cost barriers to care, and do not regularly receive annual checkups or preventive health screenings (47).

For stroke survivors, economic barriers are only the beginning of the battle. As noted earlier, transportation becomes problematic, as driving ability is frequently lost because of disabilities resulting from the stroke. Independent older adults are forced to rely on family, neighbors, or public transportation to access health care services. Those who provide transportation for the stroke survivors must adjust schedules to accommodate primary and subspecialty physician appointments and multiple weekly physical occupational and/or speech therapy appointments throughout the subacute rehabilitation period. These barriers have potential to significantly reduce the ability of stroke survivors to access the care necessary to optimize recovery. Health care providers should remember to query stroke survivors regarding these potential barriers, and be sensitive to the multiple demands placed on survivors and caregivers.

Behavioral Barriers

Lack of physical activity is an important contributor to many of the most important chronic diseases for older Americans, including heart disease, diabetes, colon cancer, and high blood pressure. Few older adults achieve the minimum recommended 30 or more minutes of moderate physical activity on 5 or more days per week. Data from the Centers for Disease Control and Prevention (CDC) indicate that 35% to 44% of adults aged 75 or older are inactive, meaning they engage in no leisure-time physical activity. National data indicate that few older persons engage in regular physical activity. Only 31% of individuals aged 65 to 74 report participating in 20 minutes of moderate physical activity 3 or more days per week, and even fewer (16%) report 30 minutes of moderate activity 5 or more days per week (48). For those aged 75 and older, levels of activity are even lower: 23% engage in moderate activity for 20 minutes 3 or more days per week and only 12% participate in such activity for 30 minutes 5 or more days per week (48).

The tendency for older adults to be sedentary places them at risk in multiple ways. Inactive lifestyles alone, or in combination with other inadequately controlled risk factors (hypertension, hyperlipidemia, diabetes, smoking, imprudent diet) create a scenario that makes a stroke more likely. After stroke, an inactive lifestyle not only inhibits optimal recovery, but also accelerates the muscle atrophy and resultant cellular changes that raise the risk of recurrent stroke (26). Further, older adults who have been sedentary may be reluctant to adopt active lifestyles due to affective disorders, fear, or fatigue.

A substantial proportion of individuals with stroke (ranging from 39%–76%) report significant and persistent fatigue affecting their daily lives (49–51). The frequency of self-reported fatigue is about twice as high in individuals with stroke as in age-matched controls (51). Self-reported fatigue has been identified as an independent predictor for having to move into an institutional setting after stroke (49). For further discussion of fatigue after stroke, refer to Chapter 32.

OVERCOMING BARRIERS

Common poststroke problems include cardiovascular deconditioning, impairments in gait and balance, diminished muscle tone and weakness, alterations in glucose metabolism, and persistent cardiovascular disease risk factors. Because it is more difficult to get around and requires more energy to do so, survivors of stroke often become sedentary. Without regular physical activity, cardiovascular fitness may be lost, further compounding the imbalance of energy resources and expenditure. Add to the mix fatigue, loss of confidence, and social isolation, and a cyclical pattern emerges that negatively affects function, independence, and quality of life.

With effective interventions, many of these problems are remediable, if not reversible. The potential for recovery is not time limited, and relatively simple task-oriented activity programs can induce meaningful physiologic changes in function, fitness, metabolism, and brain activity.

The Role of Exercise

Conventional rehabilitation care typically provides little or no structured therapeutic exercise beyond the subacute stroke recovery period. Evidence now firmly indicates that task-oriented exercise has the potential to improve both upper- and lower-extremity motor function regardless of the time since stroke (53–56). Low-intensity treadmill training 3 times per week has been demonstrated to improve motor and gait function in 12 weeks, even in distant chronic stroke survivors (55,56). Repetitive task training was also trialed in 14 chronic hemiparetic stroke survivors who trained on a custom arm extension machine. They gained significant strength in elbow and wrist flexion and extension on the paretic side after six weeks of training three times per week (53,54). The task-oriented exercises referenced in these studies were conducted under close medical supervision, and studies are under way to identify appropriate training protocols for use in community settings.

Following stroke, regular exercise can facilitate motor recovery, and also help control the common comorbidities that influence recurrent stroke risk. Exercise can reduce hypertension, enhance glucose regulation, improve blood lipid profiles, and reduce body fat. Many older adults with stroke have never been advised by a health care professional to engage in a regular exercise or walking program (57), yet generalized recommendations have been formalized to promote physical activity following stroke (42). The field of poststroke exercise rehabilitation is still developing. Constraint-induced movement therapy (CIMT), body-weight-supported gait training, functional electrical stimulation (FES), robotic-assisted therapies, cognitive disorders interacting with movement (CDIM), constraint-induced language therapy, and noninvasive brain stimulation are some examples of the paradigms that are actively under investigation to identify the best singular and combination approaches to maximize functional recovery following stroke (58). All stroke survivors should be questioned regularly about physical activity and exercise patterns, habits, and beliefs. If a stroke survivor reports little to no physical activity, and he or she is capable of performing physical activity safely, each office visit is an opportunity to educate and prescribe daily exercise activity.

Role of Self-Efficacy in Behavior Change

Many of the cardiovascular risk factors associated with stroke require changes in health behaviors, such as choosing a healthier diet, losing weight, beginning an exercise program, and stopping smoking, or adhering to a medication regimen (59). Social cognitive theory indicates that specific efficacy expectations affect behavior, motivational level, thought patterns, and emotional reactions to any situation (60). Perceptions and beliefs affecting behavior include self-efficacy (i.e., an individual's judgment of his or her capabilities to perform a specific action) and outcome expectations (i.e., beliefs that if a certain behavior is performed, there will be a specific outcome or benefit). These beliefs are essential to the adoption and maintenance of self-care ADL after stroke (61) and exercise following stroke (57). Bolstering self-efficacy to make significant lifestyle modifications is accomplished through the following four steps: (a) educate and encourage, (b) provide specific tasks to accomplish and directions to complete the task, (c) identify and address barriers to compliance, and (d) cue with role-modeling or self-modeling. Finally, education regarding expected benefits may provide further incentive and motivation to change behaviors (62,63). Helping an older adult to begin an exercise program, choose a healthier diet, or adhere to a medication regimen requires time, care, and encouragement, and discussing these and other behavior modification goals should be a routine part of routine assessment and surveillance.

Evaluation and Activation of Support Systems

For many older adults, particularly those affected by stroke, support systems can make the difference between returning

to home in the community or life in an assisted living or skilled nursing facility. The support system of older adults is comprised of three components: the informal network, the formal support system, and semiformal supports (64). Informal supports provided by family and friends are based on long-standing relationships and form the basis for the older adult's social network. Neighbors who see the older adult on a daily basis to perform chores or errands, or offer to shop, are examples of informal support. Formal supports are those paid for and provided by Social Security, Medicare, Medicaid, other service providers, and social welfare agencies. Home-based therapists, home health nurses, and personal care aides are examples of formal supports. Semiformal supports are those provided by local or neighborhood organizations, churches, or senior centers. The local stroke support group may be another example of a semiformal support.

It is critically important to identify and mobilize social supports and resources as quickly as possible in order to smooth the transition to home and begin community reintegration. Identification of the informal and semiformal resources allows for an inventory of persons or services that can be called upon while waiting for formal supports to become available, such as applying for transportation service for the disabled. Similarly, home-based therapies and nursing/personal care assistance may be prescribed immediately upon discharge to home to allow the stroke survivor the additional time necessary to become independent with ADLs, or to allow identification of an informal or semiformal support that will take up care provision when formal services end.

Care providers should routinely inquire about support systems and changes in available supports for stroke survivors over time. In particular, providers should inquire about the well-being of the primary caregiver for the stroke survivor. Multiple studies have indicated that primary caregivers experience strain that is described as mild to severe in the first year following a stroke (65,66), and the chronic strain on caregivers over the long term takes a toll on health in higher levels of emotional and physical distress (67). Respite resources should be identified and used as needed to preserve the health and well-being of the primary caregiver.

Continuing Patient/Family Education: Recognizing Signs and Symptoms

Of the more than 795,000 strokes that occur each year, 185,000 are recurrent (1). About 25% of people who recover from their first stroke will have another stroke within 5 years. Unless specific interventions are directed toward modifying stroke risk factors, the potential for recurrence persists. Stroke survivors should be monitored regularly for recurrent stroke risk, and they and their families educated to self-monitor as well.

To minimize impact from stroke, early recognition of signs and symptoms and immediate initiation of evaluation and treatment are imperative. Quantitative estimates of the rate of neural circuitry loss in ischemic stroke emphasize the urgency of timely and definitive care. The adage that "time lost is brain lost" takes on added significance when one realizes that the typical patient loses 1.9 million neurons each minute during which stroke goes untreated (68).

Older adults often do not associate new-onset symptoms with acute stroke, but rather attribute them to other illnesses (arthritis, weakness, headaches, or fatigue) and fail to take immediate action. The American Stroke Association has launched a campaign to educate the general public about the signs and symptoms of stroke. The name of the campaign is FAST, which is an acronym for (a) Face Drooping, (b) Arm Weakness, (c) Speech Difficulty and (d) Time to call 9-1-1. Although the program was launched more recently in the United States and evaluation results are not yet available, similar programs in Australia and the United Kingdom have demonstrated limited success. A recent report of semistructured interviews conducted with 19 stroke survivors and 26 witnesses in the United Kingdom suggested that most participants were aware of the "Act FAST" campaign, but the majority reported no impact on their actions during the stroke event (69). In Australia, interviews were conducted with either stroke patients or a key bystander for consecutive eligible cases admitted to two metropolitan hospitals between August 2006 and April 2008. Of the 100 patients and 70 bystanders interviewed, only 12% were aware of the FAST campaign, and of these few (19%) were able to recall all FAST symptoms, with only one bystander using the FAST assessments to identify stroke. Awareness of the FAST and Signs of Stroke campaigns was low, with poor recall and little use of the FAST assessments (70).

A report of the Reasons for Geographic and Racial Differences in Stroke Study (REGARDS) indicated that 18% of more than 18,000 participants had no history of diagnosed stroke or TIA, but reported having had at least one stroke symptom, most reporting unilateral numbness, weakness, or sudden visual disturbance. Symptoms were more prevalent among African Americans compared with white participants and among those with lower income, lower educational level, and fair to poor perceived health status, indicating that continued educational efforts are required (71). Multiple public health organizations and researchers have developed and trialed programs, but an effective public education campaign to raise awareness of stroke symptoms and guides to action when symptoms are witnessed or experienced remains elusive.

CONCLUSION

There are nearly 5 million persons in the United States aging with the chronic disability of stroke, and with advancing age the risk for first-time stroke increases (1). Older adults often have age-associated factors that compound the risk for stroke and can potentially affect recovery trajectories. Rehabilitation therapies are effective at any age if comorbidities and functional changes associated with aging are taken into account. Careful, comprehensive assessment of the older stroke survivor, along with that person's family and support network, is necessary to design a customized, progressive exercise program to maximize recovery.

Example: Self-Efficacy Based Intervention to Encourage Exercise in Older Adults

ASSESSMENT/PLAN	EXAMPLE
Analyze risk factor profile for primary prevention	Comorbidities (diabetes, high blood pressure, hyperlipidemia) Medication regimen Lifestyle influences (smoking, poor diet, physical inactivity)
Consider deficit profile for stroke survivor	Hemiparesis, cognitive, language deficits, depression are common in survivors of stroke
Intervention	
Educate and encourage	Provide education on influences of comorbidities on risk for first or second stroke, and encourage patient to make changes in behavior to minimize risk.
Provide explicit direction and verify ability to perform activity	Give patient (and family, if available) clear instructions on self-monitoring, prescribed medication regimen, and symptom management. In conjunction with primary health care provider, provide detailed, customized activity program and calendar to mark off days as activity is accomplished. If an exercise program is warranted, a physical therapist or exercise physiologist may be consulted.
Identify barriers, physiological feedback	Pain, fatigue, and anxiety are some examples of physiological barriers. Depression may influence perceived ability to carry out activities. Age-related sensory changes may influence ability to perform tasks. Transportation and finances may be also identified as barriers to adherence to prescribed regimens.
Cuing and role modeling, self-modeling	Patients derive confidence in their own ability to perform any activity by watching others who are similar to themselves performing the same activity or seeing themselves successfully performing the activity. A photograph may be helpful as cue.
Evaluation	
Provide routine surveillance of risk factors/profile	Review risk factor profile at every visit.
Revise prescribed regimens as needed.	Medications, physical activity programs should be modified as needed in collaboration with primary provider.
Routinely provide encouragement to reach patient goals	Continue positive reinforcement for work accomplished. Behavior change is hard. Continue gentle reminders for healthy behaviors yet to be adopted.
Continue education as needed	Routine review of comorbidities, symptoms, new diagnoses as needed.

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VIII

PSYCHOSOCIAL AND COMMUNITY REINTEGRATION

46

Ethical Issues in the Care of Stroke Survivors

Lynne C. Brady Wagner, Megan A. Morris, and Kristi L. Kirschner

> I wanted to communicate: Yelling louder does not help me understand you any better! . . . Speak more slowly. Enunciate more clearly. Again! Please try again! S-l-o-w down . . . See that I am a wounded animal, not a stupid animal. I am vulnerable and confused. (1)

Suddenly and without warning, 37-year-old neuroanatomist Jill Bolte Taylor sustained a large, left hemispheric intracranial hemorrhage from an arteriovenous malformation. After several years of rehabilitation, she wrote an account of her stroke experience and recovery, *My Stroke of Insight: A Brain Scientist's Personal Journey* (1). Embedded in her recollections and fragmented memories are examples of the moral dilemmas that are familiar to health care professionals who work with people after strokes. Questions that commonly confront the clinician working with stroke patients and the families of stroke survivors include:

- Does the stroke survivor have decision-making capacity (DMC)?
- How does one evaluate DMC when there is an obvious language disorder?
- Is the patient the "same person" with the same values as before, or is he or she forever altered? Should this matter?
- Should life-sustaining medical treatments be initiated or continued in the face of sometimes devastating neurologic impairment?

These questions are just a few of the common ethical issues that are frequently encountered after stroke. This chapter is intended to provide some guidance for health care professionals navigating these uncertain waters. There are no easy answers. There are only some ethical principles and guidelines that can help clarify the range of acceptable choices. The rapid pace of change in this field compounds the complexity of these ethical dilemmas. As new research is produced, new stroke treatments and technologies become clinically available, and the equations change related to the potential benefits and burdens of existing treatment choices. Individual outcomes are often uncertain, not only in terms of level of impairment, but also in those of disability and life satisfaction as well. Patients and families frequently feel overwhelmed and daunted by the decisions that must be made—often within a constrained time frame—about the most routine to the more complicated interventions and procedures. The lack of societal and financial resources to support people who need care after stroke can add a layer of complexity and create ripple effects on family members, friends, and others in the environment. Stroke, though an individual medical event, affects a community of people.

This chapter addresses a range of potential ethical issues faced by patients, family members, and various individuals who are part of the health care team. One of the most common ethical issues encountered in the care of stroke survivors is questions regarding decision-making ability. Because stroke can result in a host of neuropsychologic impairments that may affect a person's cognitive–communication skills, questions regarding the stroke survivor's level of ability to participate in decision making after stroke are familiar to all clinicians caring for this population. Other common dilemmas include issues related to personhood, social justice, and restrictions people face in choices of where and how to live, the role of the family and surrogate decision makers (2,3), the use of therapies and technologies that have limited evidence of effectiveness, and controversies that arise when patients need alternative nutrition and hydration caused by dysphagia (4–6).

We use excerpts from patient narratives about the lived experience of stroke to illustrate how the ethical problems may present to clinicians. Rehabilitation clinicians have stated that they face a number of clinical ethical issues in their daily practice (7); these are often recognizable as situations in which values are in conflict and the right course of action is not clear. Differentiating the clinical questions or options from the ethical questions or duties can often be accomplished by considering how the question should be phrased. Clinical questions begin with the phrase "Can we?" Can we achieve the medical goals for this patient by applying this treatment approach or technology? For example, "Can we place a feeding tube in Mr. Jones? Is it medically feasible and reasonable?" Ethical questions begin with the phrase "Should we?" Should this particular outcome be a goal for this person at this time? For example, "Given that Mr. Jones values the pleasure of eating above his nutritional status, should we insert a gastrostomy tube for this purpose?" An additional question could be "Should we

proceed with the use of technologies or therapies such as electrical stimulation for swallowing in light of conflicting or limited evidence of its benefit?"

INFORMED CONSENT

> Later in the morning, it was time for me to have an angiogram that would outline the blood vessels in my brain . . . Although, I thought it absolutely absurd that anyone would ask me to sign a form of consent while in this condition, I realized that policy is policy! How do we define "of sound mind and body" anyway? (1)

The first and most pressing issue that commonly arises after a stroke is to what degree the patient is able to understand and make important medical decisions. From the time the person enters the emergency room through the course of rehabilitation, the medical team will need to engage in an evaluative process to decide if the person has the requisite capacity to make informed decisions (8). The ethical principle of respect for autonomy demands that medical decisions be a result of a shared communication process between the health care professional(s) and the patient whenever possible (9,10). As a conceptual framework, the terminology of informed consent is fairly recent and did not become fully integrated into medical care in the United States until the 1970s (9).

Though the initial emphasis for obtaining informed consent focused on the obligations of the health care professional or researcher to disclose the appropriate information, the process of assessing the patient's or subject's comprehension and ability to make an uncoerced choice quickly became of paramount interest. For this reason, some bioethicists began to use the terminology *valid consent* rather than *informed consent* to emphasize the interactional nature of the process. In his classic textbook, *Ethical Issues in Neurology*, neurologist and bioethicist James L. Bernat identifies three critical elements for valid consent:

> (1) physicians must convey adequate information to their patients; (2) consent must be obtained without coercion (or be "voluntary"); and (3) patients must be competent to consent or refuse. (11)

"Adequate information" is further clarified to include the basic facts about the available medical therapies, including their risks and benefits, the risk of no treatment at all, the course of treatment recommended by the health care professional, and the rationale thereof (11).

Assessment of Decision Making Capacity (DMC)

As one of the three criteria required for valid consent, assessing competence, or DMC, is a critical skill for all health care professionals. In the hospital setting, people who were previously competent may become temporarily or permanently compromised in their ability to make decisions on their own behalf. Reasons include a direct injury to the brain (as in stroke) or secondary factors such as medications, metabolic abnormalities, hypoxia, or psychiatric conditions (12–14).

In the health care setting, competency is more accurately referred to as DMC. The distinction is not merely a matter of semantics. In our society, adults age 18 or older are presumed to be competent and able to make their own decisions. Only a court of law can declare someone "incompetent," and the specific areas of incompetence must be delineated in the court decision. For example, a person may be declared incompetent to manage his financial affairs, but be deemed competent to participate in medical decisions (15,16). Usually, a guardian is appointed by the court to oversee the areas in which the person has been judged incompetent.

It is important to note that the assessment of DMC is not a global concept, but is assessed in the context of the question at hand. In other words, it is a situation- or question-specific assessment. In the classic model for assessing decision making, as articulated by Appelbaum and Grisso (15,16), the person must in some way—either verbally or behaviorally—be able to communicate a choice. Thus, adequate consciousness and a method of reliable communication are essential. The person must also be able to understand relevant information, such as the nature and rationale of the treatment and its risks and benefits, as well as alternatives to the proposed treatment. Applying this information to his or her particular circumstances, which requires insight and appreciation of one's own medical condition, is the next critical capacity. Finally, the person should be able to demonstrate a logical process of reasoning.

Various tools have been developed to assist clinicians in assessing DMC in the health care setting, including the Aid to Capacity Exam (ACE) developed by the University of Toronto Joint Centre of Bioethics (see http://jointcentreforbioethics.ca/tools/ace.shtml) (14,17). In addition to providing training and a framework for the assessment of DMC, a series of suggested questions and a scoring system allow the evaluator to tabulate a total score. The determination of capacity thus falls along a continuum, acknowledging that capacity is not an all-or-none phenomenon. Depending on the score, at that specific point in time, the person may be considered:

- Definitely capable
- Probably capable
- Probably incapable
- Definitely incapable

The circumstances of the assessment are noted, as are any factors that might be interfering with DMC so that these issues can be addressed medically, if possible. Ideally, a final determination of DMC will be deferred until such confounders are corrected (17).

It is possible for patients to have DMC for some medical decisions and not others. For example, a patient may not be able to decide if the benefits of a carotid endarterectomy are worth the risks, but the same person may be

able to tell clinicians who he or she wants to speak for him or her if there are important medical questions to be addressed. The issue here is the congruence between the complexity of the information involved in the decision and the person's capabilities. It is also possible that, for decisions that involve greater risks (for example, a patient's refusal of life-sustaining treatment), a higher level of evidence may be required than for decisions with less consequence, such as whether to wear a splint or what to eat (9,14,16–18). It is not the outcome that is at issue here, that is, whether the health care team agrees with the decision or not. It is the evidence that the process the person used to arrive at the decision is sound. This concept is also known as the sliding scale for standards of evidence in the assessment of DMC (9).

A sliding scale also exists for the extent to which a patient physically participates in decisions about his or her care. Even when a patient lacks the capacity to make informed choices, he or she can be included in the decision-making process (19). One model that captures this continuum is the shared decision-making model (20). This is a process in which the provider, patient, and, at times, the family member or caregiver actively contribute to and collaborate in making medical decisions. It is not a substitute for informed consent, but a broader concept that includes communication about medical options and the patient's values and preferences (20). The extent to which each of these stakeholders contributes may differ based on patient need and the decision at hand. This allows for customized participation of patients with impaired DMC. To facilitate the patient's involvement and to ensure that his or her wishes are included in the decision, the health care team may need to provide accommodations. These modifications can vary and might even be as simple as having the discussion in the patient's presence. It may be appropriate to include a speech–language pathologist (SLP) in the decision-making process, as SLPs have been increasingly involved in facilitating these discussions for persons with communication disability (19). The SLP can serve multiple functions, such as developing a communication tool for the patient to use or physically assisting the patient during the actual discussion. Whatever method is used, it is paramount that the health care team attempt to discover the patient's values and preferences related to the decision at hand.

The Effects of Stroke on DMC

> To someone looking on, I may have been judged as less than what I had been before because I could not process information like a normal person. I was saddened by the inability of the medical community to know how to communicate with someone in my condition . . . I wanted my doctors to focus on how my brain was working rather than on whether it worked according to their criteria or timetable. I still knew volumes of information and I was simply going to have to figure out how to access it again. (1)

When patients make choices that are compatible with the team's recommendations, there is typically little concern about DMC. It is when decisions are contrary to the team's recommendations or when certain medical conditions occur, such as brain diseases or injuries, that clinicians raise the question of DMC. Decisional processes, after all, involve a complex integration of neurologic systems and processes (12). A neurologic condition such as a stroke has the potential to affect the patient's ability to understand, contemplate, and communicate a choice—all critical skills for decision making (21–23).

The process of shared decision making requires the patient to possess basic comprehension and expression skills, verbal or nonverbal (21,23). Persons with impaired communication skills are at risk for unnecessary exclusion from this process (23,24). A stroke can result in a myriad of problems, including dysarthria, aphasia, dyslexia, agraphia, dysphonia, abulia, and other cognitive–communication impairments. Patients with these impairments may be especially vulnerable to judgments that their participation in the informed consent process would be invalid because they may not be able to communicate without accommodation or facilitation from a trained assistant (either a clinician, family member, or volunteer) (21,23,25). In general, poststroke deficits that can affect DMC fall into four general categories: disorders of consciousness, communication, insight and awareness of one's condition, and mood. Freedman et al. have further classified that the cognitive processes fundamental to decision making include attention, language, memory, and frontal lobe function (12).

DMC and Disorders of Attention

Attention can be considered the sine qua non for all other cognitive neurologic processes (26), without which encoding, problem solving, and essentially all other cognitive functions cannot optimally operate. It is also highly distributed in the brain, from the brainstem/reticular activating system to the thalamus and bilateral frontal and nondominant parietal lobes.

In the context of such a neurologic model, it is easy to see how attentional mechanisms may be disrupted when a stroke occurs. Patients who have had strokes may have attentional problems from both the brain lesions as well as from seizures, or toxic-metabolic factors such as medications, hypoxia, infectious processes, or electrolyte abnormalities that can result in acute confusional states (26). Patients who are unconscious are de facto unable to participate in decision making until they regain consciousness. If attention is fluctuating or drifting, capacities may be emerging, but they are often not adequate for in-depth discussions and assessments about medical decisions (12). Patients need to be able to attend to information long enough to decode information, apply the information to their circumstances, and reason.

Another interesting attentional problem occurs with lesions in the nondominant hemisphere, resulting in neglect syndromes. For example, there are well-described syndromes

that result in disruptions of the internal template of the body (26), such as anosognosia, as well as syndromes that disrupt the exploratory motor components. Such lesions can result in disconnection syndromes in which patients can verbally comprehend information, but have difficulty applying this information to their particular circumstances. Such verbal–behavioral disconnections pose particular difficulties for clinicians when assessing DMC (12,27), as the assessments tend to be heavily weighted to the verbal realm. It is possible for patients to verbally demonstrate an accurate understanding of information, but be unable to apply this information to their own particular circumstances. Such defects in intrapersonal awareness or perception can pose serious challenges to DMC.

DMC and Aphasia

> "Answer this, squeeze that, sign here!" they demanded of my semiconsciousness, and I thought, How absurd! Can't you see I've got a problem here? What's the matter with you people? Slow down! I can't understand you! Be patient! Hold still! That hurts! What is this chaos? . . . They couldn't hear me because they couldn't read my mind. (1)

Aphasia is an acquired disorder of the language system that can result from a stroke or other damage to the language centers of the brain (28,29). Linguistic or verbal (language) ability is critical to decision making. As noted earlier by Appelbaum and Grisso, among the requisite skills for DMC is that the person must in some way—either vocally or behaviorally—be able to consistently communicate a choice. Furthermore, the person must also be able to understand relevant information, such as the nature and rationale of the treatment and its risks and benefits, as well as alternatives to the proposed treatment. The complexity of the decision will thus determine the level of detail required for accurate communication.

Under the diagnosis of aphasia, many taxonomies exist (29). Relative to the area and size of the neurologic lesion, diastasis, and an individual's premorbid linguistic capabilities, aphasia can present a number of challenges for a stroke survivor. The most recognizable form of this impairment presents as problems with word finding that can range from the very mild (minimally affecting a person's word choice and fluency) to the very profound (resulting in absence of the ability to produce or communicate words). The situation may be further complicated by the fact that the person with an aphasia affecting verbal expression and others who interact with him or her may not be fully aware of the extent of any accompanying impairment of comprehension, raising the risk of incorrectly assuming accurate communication (23,30).

Unfortunately, health care professionals receive little or no formal training specifically in methods to facilitate and accommodate communication with patients who are aphasic and who have communication impairments (31,32). Kagan (33) demonstrated that, even without objective improvement in the linguistic abilities of a person with aphasia, training medical professionals and other caregivers who work with persons with aphasia can lead to more successful communication outcomes. The presence of aphasia should not preclude attempts to involve the patient in making decisions, with appropriate accommodations as needed. Indeed, it would be an injustice to the patient to exclude him or her a priori (12,25,33). When a patient has a way to demonstrate that he or she can comprehend the information provided and make or contribute to a choice regarding treatment, a very significant measure of respect for individual self-determination is fulfilled.

When patients with communication impairments have the ability to participate in decision making but are denied the opportunity because of lack of either awareness or of training on the part of their health care providers or family members, their autonomy is usurped. The opposite can also occur. Linguistic representation in the brain is complex, and one's ability to recognize and convey nonverbal communication can be preserved while the ability to encode specific words and concepts may be severely limited. Because of this, persons with some language impairments may communicate by responding to head nods, tone of voice, or gestures and might therefore be assumed to understand information that they do not. In this example, DMC may be assumed when it is not present, and the stroke survivor is denied the protection and involvement of a surrogate (21,23). When possible, a detailed assessment of language abilities by a SLP is critical if questions of DMC arise in the context of aphasia. Not only can the SLP clarify the type and extent of aphasia, but he or she can also provide guidance for compensatory strategies in many cases. For example, communication with a patient who has comprehension impairments may be more successful if information is presented visually, in shortened segments, or accompanied by diagrams, rather than through lengthy auditory presentations (32).

DMC and Disorders of Speech

> So I usually have the skimpiest arsenal of facial expressions, winks, and nods to ask people to shut the door, loosen a faucet, lower the volume on the TV, or fluff up a pillow. I do not succeed every time. As the weeks go by, this forced solitude has allowed me to acquire a certain stoicism and to realize that the hospital staff are of two kinds: the majority, who would not dream of leaving the room without first attempting to decipher my SOS messages; and the less conscientious minority, who make their getaway pretending not to notice my distress signals. (34)

In his book, *The Diving Bell and the Butterfly* (34), Jean-Dominique Bauby described the devastating loss of his communication abilities following a stroke at the age of 43. He became "locked in" as a result of a massive stroke affecting his brainstem. Though his cognition was intact, he

TABLE 46.1 Strategies for Maximizing Communication When a Patient Requires Increased Time to Interact

1. Partner with the patient to develop strategies together so he or she knows you are purposefully attempting to optimize communication.
2. Be thoughtful about scheduling. For nonurgent discussions, try to schedule meetings when you are not rushed to get to another appointment.
3. Encourage the patient to record questions or statements ahead of time. If the patient has computer access, he or she can email the questions before the appointment or may be able to work with an assistant who can write down the questions ahead of time. These can either be sent to you or read at the appointment.
4. Physicians and other team members may call on the SLP or other trained individuals to assist by asking the patient specific questions. The physician can then schedule time to be there at the end of the appointment, and the information gathered can be shared. The trained facilitator can then assist in facilitating a discussion about the particular issue.
5. If you cannot understand the message and do not have more time to stay with the patient, let the patient know that you will return to this question at a later time or use one of the above strategies.

was paralyzed and unable to phonate or articulate (anarthria). His only preserved movement was blinking his left eye. It was through this movement that Bauby communicated, meticulously and tediously blinking in response to the presentation of letters from the alphabet to spell out his thoughts, needs, wishes, and feelings. Indeed, his book is a remarkable product of such efforts. It provides a distressing perspective on the health care system, in which a man with a rich inner life is considered by some to be a vegetable or treated as an object with his only interaction with staff through the provision of tube feedings, baths, and repositioning. This is in striking contrast with the many care providers and friends who invested the time to learn the laborious communication strategies and facilitate Bauby's connection with humanity.

Though a number of authors have addressed the various ethical issues that are a consequence of aphasia (21,23,31,33), less has been written about the issues involved in the face of speech disabilities (25,35,36). Yet, the impact of motor impairments of speech on DMC can be devastating. A person like Bauby, who clearly has the ability to make decisions when given the opportunity to do so with appropriate facilitation, can easily be discounted or prevented from doing so. Even health care professionals may have limited understanding of the association between cognitive abilities and one's ability to speak, often presuming that a person who is unable to articulate well has related difficulty with the ability to understand and think. The importance of a careful neurologic evaluation and frequent reevaluations by trained professionals cannot be overstated; furthermore, once the appropriate methods and techniques for facilitated communication are identified, all staff and contacts with the person need to be trained in their use (25,35).

Augmentative and alternative communication (AAC) techniques have been used successfully to assist in the decision-making process for persons with neurologic disease or disorders that have severely affected motor control of speech (25). The aid of a knowledgeable facilitator and the necessary high-tech (for example, electronic or computerized equipment) or low-tech (e.g., alphabet boards and picture books) device(s) can reveal the decisional abilities of persons whose profound communication difficulties may lead clinicians and families to believe that the patient cannot possibly participate. SLPs and occupational therapists with experience in the use of these strategies are invaluable resources for the physician, nurses, family, and all other team members (25) and should be involved early after the stroke.

AAC solutions are frequently not easy to implement. Their use often requires a great deal of time on the part of both the patient and facilitator (see Table 46.1 for suggestions to maximize communication). Allowing patients to participate fully in discussions contributes to respect for individual autonomy and fosters clinician understanding of the patient's authentic wishes. An additional challenge to allowing patients with severe motor output impairment to participate in medical choices is the lack of trained personnel, as well as the availability and funding for AAC devices (37). Even though some individuals who need this kind of equipment are able to obtain insurance coverage of higher-tech and expensive systems, other insurers fail to accept the medical necessity of this equipment. In light of increasing health care costs, devices or therapies deemed to have limited medical import are often not reimbursable (37). The onus is often on the clinician to advocate for the patient and appeal such adverse funding decisions, arguing that accurate and timely communication is essential for good, safe, medical care. In other instances, even when insurers cover the cost of an AAC device, they do so at such a low rate that the equipment is still unattainable for many people. Clinicians are then required to use low-cost alternative or turn to cheaper commercially available devices.

DMC and Mood Disorders

> My own mood seesawed wildly—at times I felt almost euphoric with relief and at the satisfaction of being alive, and other times almost suicidally depressed (38).

In his book *My Year Off: Recovering Life after a Stroke*, British editor Robert McCrum, 42 years old and newly married at

the time of his cerebral hemorrhage, describes his experience of emotional turmoil after his stroke. Neuropsychologic processes involved in mood regulation can be both caused and affected by the presence of stroke (39–42). Even though an affective disorder may be transitory and fluctuating, depression and anxiety can limit a stroke survivor's ability to engage fully in the process of deliberating about daily problems and considering future events and issues.

Depression and anxiety can impede two critical elements of DMC. First, a person may be unable to fully appreciate or remember information conveyed by others and therefore may be unable to comprehend various treatment choices presented. Additionally, the patient who is depressed or anxious may experience interference in the cognitive processes typically referred to as *executive functioning* (40), that is, the ability to identify problems, generate possible solutions, remember factors of these solutions, and weigh them against one another and select a reasonable approach to the challenge. In this situation, a patient may be unable to fully deliberate on the options presented in making a medical choice. Treatment for the underlying depression and/or anxiety may not only alleviate the patient's suffering, but may also help the patient imagine possibilities and process information in a more balanced fashion.

When a Patient Lacks DMC: The Role of a Surrogate

> Honestly, I didn't really understand all of the details about what they were proposing to do—partly because the cells in my brain that understood language were swimming in a pool of blood and partly because of the sheer speed of their conversation . . . In my condition, I thought I understood that they were planning on passing a suction instrument up through my femoral artery into my brain to suck out the excess blood and threatening tangle of vessels. I was aghast when I realized it was their plan to cut my head open! . . . I made it perfectly clear to everyone that under no circumstances would I ever agree to permit them to open my head . . . The meeting ended with the craniotomy option temporarily tabled, and though it was clear to everyone (except me) that it was G.G.'s job to convince me to have the surgery. (1)

When a determination is made that a person lacks the capacity to make a particular decision—even with the proper supports, compensatory strategies, and facilitation—then a proxy or surrogate decision maker is required (Figure 46.1). The least common, but most straightforward, situation for naming the surrogate is when the patient had previously

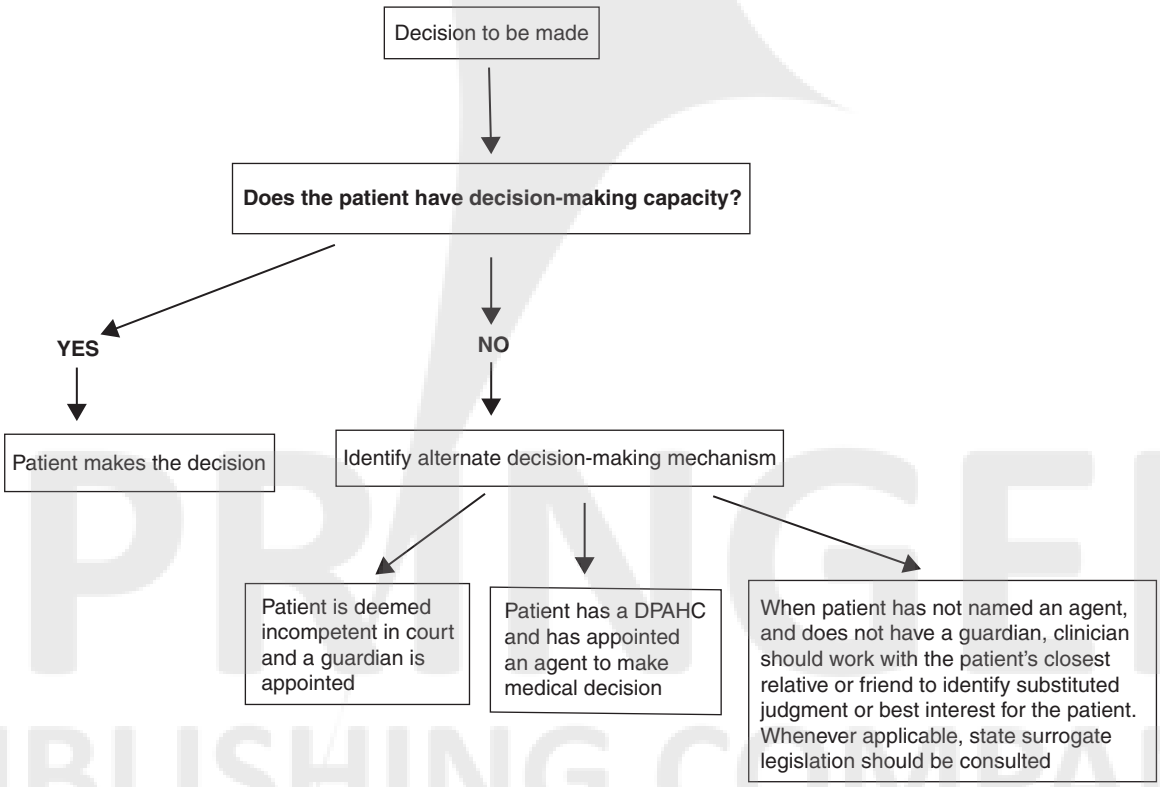

FIGURE 46.1 Who is the decision maker?

Source: Adapted from Ref. (16). Kothari S, Kirschner K. Decision-making capacity after TBI: clinical assessment and ethical implications. In: Zasler ND, Katz DI, Zafonte RD, eds. *Brain Injury Medicine*. New York, NY: Demos Medical Publishing; 2007:1205–1222.

executed an advance directive naming the individual he or she would want to act on his or her behalf in the event of incapacity. At present, it is estimated that only about 18% to 36% (43) of the population have completed advance directives, though this percentage varies widely by geographic region, socioeconomic background, ethnicity, and other factors (43–47).

The Patient Self-Determination Act of 1990 requires that all hospitals and health care facilities query patients upon admission about whether they have an advance directive and, if not, whether they wish to complete one (48).

There are two general types of advance directives: instructional documents such as the living will, and proxy directives such as the durable power of attorney for health care (DPAHC) (9). There are also a growing number of hybrid documents, such as the physicians' orders for life-sustaining treatment paradigm (POLST; www.ohsu.edu/ethics/polst) and Five Wishes (www.agingwithdignity.org/5wishes.html). The level of legal recognition each state gives to these documents varies, and it is therefore imperative to know the law in the state in which you reside.

The living will is the earliest form of an advance directive. It became prominent in the 1970s after the case of Karen Ann Quinlan (49) as a tool for allowing a person to exercise autonomy into states of future incompetence (50). The early living will was typically effective only when a person became terminally ill and unable to make his or her own decisions, and included instructions that allowed the physician to withhold death-delaying treatments. Unfortunately, these documents do not provide guidance for situations in which a person may become temporarily or permanently incapable of making health care decisions, but is not terminally ill, such as in the case of a stroke or brain injury. In general, living wills also do not include provisions for withholding artificial nutrition and hydration. After the case of Nancy Cruzan (51), a woman with a traumatic brain injury in a state of persistent unconsciousness whose father petitioned the courts to allow her feeding tube to be removed, the DPAHC became of greater interest. With a DPAHC, a person can name an individual to speak on his or her behalf (a *proxy*) if he or she becomes temporarily or permanently unable to participate in medical decision making. It is thus a more powerful and flexible document than a living will. Both the living will and DPAHC must be executed while an individual is considered to be competent in order to be legally recognized.

If a person has not completed an advance directive and is not able to make health care decisions, then the health care team must identify a surrogate. As of 2007, 38 states and the District of Columbia have formal state surrogate statutes that provide guidance on naming the appropriate surrogate decision maker (52). Usually, this follows a next-of-kin hierarchy, and the person highest on the list who is available and willing to serve in this capacity is the default legal surrogate. As opposed to the DPAHC, in which proxies can make any health care decision that the patient could (unless the patient restricted the proxy's authority in some way), the state surrogate laws typically establish some limits and restrictions on the types of decisions the surrogate can make, particularly when it comes to withdrawing or withholding life-sustaining treatments. Again, it is best to know the specific standards for the state in which one practices, as these laws vary from state to state (43,52). In the absence of a formal state surrogate law, health care providers will usually ask the next of kin to serve in this capacity. As with any situation, if there is concern about the appropriateness of the surrogate, conflict within the family, or the magnitude and extent of the decisions, the courts can be asked to appoint a guardian.

Some organizations, such as the Gunderson Lutheran Respecting Choices Program (www.gundluth.org/AdvanceCare), have attempted to assist patients and families by training health care professionals to facilitate the difficult conversations involved in making choices for medical treatment. The concept of advance care planning focuses on helping people identify aspects of life that they value most in order to guide a surrogate decision maker in selecting the most respectful choice for the loved one (53).

Whether a proxy is named by a DPAHC or via a state law, the surrogate is first and foremost asked to make the same decision that he or she believes the patient would have if he or she were capable. This principle is known as *substituted judgment* (9). Written directions are one source of information that can be referenced. Conversations and, in some instances, even lifestyle decisions have also been considered (16). In the absence of knowledge of a person's wishes, the surrogate is counseled to make a decision based upon what he or she believes to be in the best interest of the patient (9). This involves weighing the benefits and burdens of a treatment decision in the context of the person's condition. In theory, both substituted judgment and best-interest standards have great appeal, but they can be difficult to implement in practice. There is growing literature that questions whether it is ever really possible to put one's beliefs, values, and needs aside to make decisions on behalf of another (50,54).

Adjustment to Disability and the Concept of Personhood

> [Stroke] is an event that goes to the core of who and what you are, the You-ness of you. First of all, the event happens in your brain which is, without becoming unduly philosophical the command centre of the self. Your brain is you: your moods, your skills, your character, your intelligence, your emotions, your self-expression, your self. (38)

One of the thorniest problems with substituted judgment as a heuristic is the issue of personhood. Simply put, who is the person for whom the decision is being made (16)? The name, social security number, birth date, and even genealogy and personal history as defining characteristics of personhood are clear and unchanging. What is not clear, however, is whether somehow the survivor is literally a changed person

after the stroke, with different personality characteristics, values, interests, and capacities. Grieving the loss of the old self is commonplace after stroke. Grieving occurs not only by the person who experiences the stroke but also by his or her network of close family and friends. How then does a proxy take these issues into consideration when making decisions?

A rich and layered debate on this topic exists without a clear consensus (55–57). That being said, there are some general guidelines that can be offered (50). Patients who have very strong feelings about personhood are more likely to have made an advance directive and put their future care wishes in writing. Indeed, the advance directive is the best way for a person to maintain control of his or her treatment into states of future incompetence and should therefore be taken very seriously. It is also possible that the person may be temporarily incapacitated and, with time, may recover to the point where he or she can resume making personal health care decisions. People who are not fully capable may still be able to indicate wishes and preferences in such a way that their proxies and health care team can use this information to guide decisions. In the end, knowledge that people frequently change their minds when their circumstances change is relevant to decision making, and must be a part of an informed consent discussion about future treatment decisions (50,58).

Balancing the Patient's "Best Interests" in the Context of a Family

> But today we spend the whole of the symbolic day together, affirming that even a rough sketch, a shadow, a tiny fragment of a dad is still a dad. I am torn between joy at seeing them living, moving, laughing, or crying for a few hours, and fear that the sight of all these sufferings—beginning with mine—is not the ideal entertainment for a boy of ten and his 8-year-old sister. (34)

Though substituted judgment and best-interest standards have been extensively discussed in the ethics literature and are widely accepted, these standards are not without controversy. Some ethicists advocate considering the interests of the family, not just the patient, when decisions must be made, particularly when those decisions will have a substantial impact on others. A decision to place a feeding tube in a person with a severe brain injury may have financial repercussions, for example, or create an unspoken expectation that the family will take the person home and provide substantial care, usually without compensation (2,3,59,60). Some studies have found that, even if it is theoretically desirable, it is probably not truly possible to stand in another's shoes and put one's perspectives and wishes aside in making a decision on behalf of another (47,55). Interestingly, despite this observation, studies have also shown that many patients, even when told that their identified surrogate does not understand and make decisions as he or she would want, would still want a family member, rather than a stranger, to make these decisions (61).

In general, despite the limitations of surrogate decision making, the health care team should respect the choices made by a proxy unless there is evidence that the proxy is not acting in the best interest of his or her loved one. Disagreement among members of the patient's family or between the family and the patient's care team can lead to unresolved conflicts and has occasionally led to the need for legal adjudication of these matters (62,63). When reviewing questions regarding a surrogate's ability to authorize removal of life-sustaining treatments, the courts have affirmed that the state can stipulate the level of evidence required to support such decisions as being reflective of the patient's desires/wishes. Many states require the criterion of clear and convincing evidence based on a reasonable person standard. That is, would the evidence convince a reasonable person that the allegation is so? This standard is used in Missouri and other states. However, there has been some movement to accept a less stringent standard—for example, after the Wendland case in California (64).

When Conflicts Occur

Conflicts often arise because of fractured or incomplete communication (61,65). Ethics services in health care institutions promote education related to ethical distress and dilemmas in addition to providing ethics consultation when requested (66). This education gives team members a process and framework for understanding the ethical principles involved, such as autonomy, beneficence, nonmaleficence, justice, and virtue. One important goal for ethics consultation is to assist the team in prioritizing and balancing the principles and values in conflict and, ultimately, to achieve an ethically acceptable outcome in an individual case. Varied methods can be found in the literature (9,10,67,68) (Table 46.2) as well as in approaches developed by individual institutions. The Joint Commission mandates that all accredited hospitals provide a mechanism for resolving ethics conflicts in the medical setting (69).

Caregiver Burdens and Lack of Resources: When Patient and Family Interests Conflict

Very often, when a conflict regarding a medical decision occurs, the parties involved hope to identify the course of action that is ethically correct. In most ethics cases, there is no single right answer. More often, a range of ethically acceptable options can be identified as well as those that might be impermissible. Because the stroke survivor may have a temporary or permanent disability that requires the care of another person, the interests of the patient are frequently intertwined with those of his or her involved family members.

In many ethics cases, clinicians are taught that the interests and wishes of the patient supersede those of family members. Several authors caution, however, that dealing

TABLE 46.2 Selected Paradigms for Case-Based, Ethical Decision Making

Jonsen, Siegler, and Winslade (2006) (10): The Four-Box Model

Consideration of four coexisting factors (medical indications, patient preferences, quality of life, and contextual features) present in the shared decision-making process. Primary focus is on the patient–clinician relationship acknowledging potential conflict between "Medical Recommendations" [beneficence] with "Patient Preferences" [autonomy]

McCormick-Gendzel and Jurchak (2006) (67): FESOR

Facts: Collect the facts of the case

Ethics: Identify and apply the appropriate ethical principles

Stakeholders: Ensure that all stakeholders are involved in the process

Options: Identifying and implementing the ethically acceptable options

Results: Evaluating the outcome of the ethical analysis and decision for all stakeholders

Miller, Fletcher, and Fins (1997) (69): Clinical Pragmatism

Detailed ethical decision-making model in outline/checklist format that gathers information for a moral diagnosis. Reflective analysis is used to develop approaches for managing similar situations in the future.

Purtilo (2005) (68): Six-Step Process of Ethical Decision Making

1. Getting the story straight: gather relevant information
2. Identify type of ethical problem (e.g., ethical distress, ethical dilemma, question of locus of authority)
3. Use ethics theories or approaches to analyze the problem(s)
4. Explore the practical alternatives
5. Complete the action
6. Evaluate the process and outcome

with the family issues and interests should not be an afterthought (2,3). Instead, clinicians should partner with families to optimize the choices for the patient. Indeed, when patients need care and/or supervision following a stroke, the patient's ability to recover may be directly related with the health of the family system. Family caregivers give assistance to loved ones who are ill or have disabilities. This care would otherwise cost tens to hundreds of thousands of dollars annually if the patient hired a third party to provide it. Some families may not be physically or psychologically equipped to participate in the care of their loved one. Others may lack the financial resources or flexibility to reduce work hours or leave a job to care for a relative/close friend.

Brashler (2) recommends a family-focused team approach to identifying, recognizing, and addressing conflicts between the interests of patients and those of their family members. Central to this approach is the understanding that the recovery and success of a person following stroke may be substantially dependent on the involvement of family members and their willingness to assist the patient, so their interests are inseparable. The key considerations in Brashler's model include bringing all family stakeholders into the discussion, dealing directly and openly with competing interests, and developing shared goals to create a family discharge plan (Table 46.3).

TABLE 46.3 Family-Focused Team Approach

Deal with family conflict and competing interests in the care of a stroke survivor by addressing the following:

1. Recognize all family members with standing
2. Identify family-focused goals
3. Communicate a commitment to the whole family
4. Address competing interests
5. Identify and protect vulnerable family members
6. Construct family discharge plans

Source: Adapted from Ref. (2). Brashler R. Ethics, family caregivers, and stroke. *Top Stroke Rehabil*. 2006;13(4):11–17.

Management of Dysphagia: A Predictable Ethical Challenge After Stroke

In the past 8 months I have swallowed nothing save a few drops of lemon-flavored water and a half-teaspoon of yogurt, which gurgled noisily down my windpipe. The feeding test—as they grandly called this banquet—was not a success. But no call for alarm; I haven't starved. By means of a tube threaded into my stomach, two or three bags of a brownish fluid provide my daily caloric needs. For pleasure, I have to turn to the vivid memory of tastes and smells, an inexhaustible reservoir of sensations. Once, I was a master at recycling leftovers. Now I cultivate the art of simmering memories . . . . (34)

Dysphagia is a common consequence of stroke, and may lead to inadequate food and/or liquid intake, or aspiration pneumonia. The use of dysphagia screening as a means of mitigating this risk is recommended or required for stroke specialty care in several countries (70).

Dysphagia is the impairment of one's ability to chew and swallow food and liquid safely and efficiently (taking in enough calories in a given time frame) to sustain life. It is estimated that anywhere from 64% to 78% of all persons surviving stroke develop at least some degree of dysphagia (71,72). The severity of problems following dysphagia can range from a mild condition in which the person requires extra time to complete a meal to very severe, in which an individual cannot manage his or her secretions safely and requires a tracheostomy tube to protect the airway. In cases of severe dysphagia, an alternative method of nutrition and hydration may be recommended and initiated in the acute phase of the illness (73).

Clinicians, patients, and family members may disagree over treatment when severe dysphagia is diagnosed. Clinicians may recommend alternative nutrition and hydration with the goal of avoiding aspiration and its complications while maintaining sustenance. The issue of food and nutrition often raises strong emotions for patients and families. Food has high symbolic value and is not simply a health necessity. It is an issue rooted in social habits and cultural values and patients often associate this with a higher quality of life. Even though various ethical issues arise in the treatment of dysphagia, including questioning the continuation of a life-sustaining treatment, perhaps the most challenging for many clinicians is balancing a patient's desire to eat, regardless of the hazard posed, when the clinical team believes that an alternative feeding approach is lower risk. The conflict between a clinician's sense of beneficence and the patient's preferences or desires frequently causes considerable ethical distress for the clinician.

Beneficence and autonomy are two of the cornerstones of Western bioethics principles. Beauchamp and Childress (9) state that *beneficence* is the obligation of the health care provider to do good for patients, based on what he or she believes to be in the patient's best interest. The principle of *autonomy* is the duty of the health professional to respect, support, and facilitate the patient's ability to make an authentic medical choice without coercion. When clinicians find themselves in a situation where these two principles directly conflict, the ethical distress can be high. Further complicating this issue is the active role that the health care team plays in assisting stroke patients with dysphagia. Thus, a patient who is deemed unsafe to take oral nutrition, but insists on receiving this feeding nonetheless, may require assistance by the nurse or SLP in eating. Health care professionals are trained to make recommendations that promote health. When a patient or a proxy makes a decision that appears to place a person at risk for a poor health outcome, and the health care team's participation is required, some clinicians are inclined to view such a decision as unethical based upon the principle of nonmaleficence—that is, "Do no harm."

Sharp and Genesen (74) describe how a case-based model of clinical ethical analysis can be useful in managing the ethical challenges inherent in such conflicts. Use of this model, based on Jonsen, Siegler, and Winslade (10) (Table 46.2), can assist clinicians and others in identifying ethically acceptable options. The primary challenge is balancing respect for a patient's autonomous wishes related to use of feeding tubes and oral intake after carefully weighing the risks and benefits of eating and drinking when one has dysphagia. As with all other medical decisions, recommendations related to dysphagia should occur in the context of an informed consent and shared decision-making process.

When such values conflicts arise in the clinical care of a patient after stroke, some health care providers wonder if they should continue to be involved in the care of that patient, even if they fundamentally agree with the principle that patients have the right to reject medical recommendations. We believe this consideration is based on two concerns:

1. The treating clinician will be complicit in a "bad decision" that may result in harm to the patient.
2. The clinician may be liable from a legal perspective if the patient experiences a bad outcome.

Clinicians are highly immersed in a medical culture that promotes improving health, and find participation in a treatment plan that may result in "avoidable" medical complications uncomfortable at best. These situations can be very difficult to negotiate. Even though in most scenarios professionals have the right to withdraw from a clinical case where they feel that care is in conflict with their own ethical values (a conscientious objection clause of sorts), it is critical to avoid abandoning the patient in the process. Because we recognize that people have the right to accept our recommendations, they also have the correlate right to refuse them. If a clinical recommendation is rejected, patients still may benefit from clinical interventions to mitigate potential harms. Additionally, patients may refuse recommendations for many reasons (Table 46.4). Without coercing or usurping a patient's right to make his or her own choices, clinicians should investigate the reasons behind a patient's refusal to accept treatment recommendations and to aid him or her in attaining as complete an understanding of the issues as feasible to ensure that this is an informed choice.

The degree of uncertainty regarding the outcome of a particular medical treatment (or foregoing that treatment) may guide the options and decisions made by patients, proxies, and health care providers. When the benefits of a certain treatment outweigh the risks—for example, an otherwise healthy person taking antibiotics for pneumonia—clinicians may try to assure or persuade patients through further education and discussion to accept the recommended treatment. In other cases, such as the treatment of dysphagia, the degree of uncertainty of the likelihood of a poor outcome (e.g., development of aspiration pneumonia) can be quite high (75). The clinical consequences of aspiration or risk of aspiration are not fully understood. In a

TABLE 46.4 Reasons for Patient/Surrogate Refusal of Medical Recommendations

1. Personal values and preferences (may include religious beliefs)
2. Desire to continue current behaviors (e.g., refusal to stop smoking, refusal to change diet). Patient values the behavior above the health-related concern (quality-of-life judgment)
3. Concern that the intervention will be painful or uncomfortable
4. Fear of the potential for negative outcome from the procedure (e.g., mortality risk in some surgeries)
5. Lack of full understanding of the recommendations (e.g., language barrier, belief that the treatment is something other than described, not yet realized lack of DMC)
6. Conflicting recommendations from various health care professionals
7. Cultural differences (e.g., family members helping persons with disabilities instead of facilitating independence in ADL)
8. Negative personal experience (self, family member, or friend) with the recommended treatment plan
9. Lack of understanding of the potential for recovery or possibility of a positive quality of life given the patient's current condition
10. Family conflict
11. Lack of insurance benefit (e.g., personal payment for the treatment would drain personal and family resources)
12. Lack of trust in the clinician or in medical personnel in general
13. Depression or thought disorder

medical record review of nursing home residents, Langmore et al. (75) concluded that, even though dysphagia was a risk factor for the development of aspiration pneumonia, it was not a leading determinant. The fact that an individual was dependent upon another person for feeding or had poor dental and oral hygiene were stronger predictors of the development of aspiration pneumonia.

Time-Limited Trials

Clinical ethicists have promoted the use of a time-limited trial of treatment in order to assist decision making and cooperation in cases of disagreement or uncertainty about the best course of action (76,77). For example, the use of an alternative method of nutrition and hydration is often recommended when a patient experiences moderate or severe dysphagia. The goal of using enteral or parenteral feeding is to reduce the risk of prandial aspiration by bypassing the oral route altogether. It is also to ensure adequate caloric and nutritional intake and hydration to foster recovery and avoid malnourishment. There is growing literature that questions these assumptions for certain patient populations, in particular persons with advanced dementia (78,79). Some studies (80) have found that the risk of aspiration of gastric reflux actually increases when feeding tubes are placed.

In a time-limited trial of treatment, the patient agrees to try a treatment for a limited period of time, followed by a period of reassessment and renegotiation. The patient will then either continue the trial treatment or change course (81). The following clinical vignette illustrates this concept:

> Mrs. E was admitted to a rehabilitation hospital after a pontine stroke. She presented with moderate to severe dysphagia and had a percutaneous endoscopic gastrostomy (PEG) placed in the acute care hospital. Several days after Mrs. E arrived, she told her SLP that she no longer wished to use the feeding tube and she wanted to eat and drink, despite her treatment team's strong recommendation that she continue to rely on tube feedings for the present time. After much discussion, Mrs. E and her team agreed to a time-limited trial of continuation of the PEG feedings and intensive swallowing therapy to target and remediate her difficulties. At the agreed reevaluation point 2 weeks later, the patient's swallowing was much improved. She was able to begin eating pureed solids at that time, consistent with the SLP's recommendations.

Another version of this time-limited trial scenario is as follows:

> Mrs. E was admitted to a rehabilitation hospital after a pontine stroke. She communicated to the staff via a letterboard that she would like to discontinue use of her PEG tube. Despite discussion and further education, the patient was not dissuaded from this decision, even though she was aspirating. Mrs. E agreed to begin eating a diet that had been deemed to be the safest and to use swallowing techniques taught her by her SLP for a period of 2 weeks. After this trial period, the patient had not developed any respiratory complications, and, indeed, her swallowing function had improved. The SLP upgraded her diet further.

Use of time-limited trials can be extremely valuable in many cases by clarifying what the goals and measurable risks are for a particular patient.

Combination Treatment

Another strategy for balancing conflicting values is to combine a therapy that has been recommended by the clinician with a high-priority desire of the patient that also has some risk (81). This vignette provides an example:

> Mr. B was a 46-year-old gentleman who sustained a right hemisphere stroke and now had left-sided paralysis, visual neglect, and severe dysphagia. Although he

demonstrated mild cognitive–communication impairments, he was felt to have adequate DMC regarding his feeding choices. Because of aspiration on all consistencies, Mr. B's physician recommended a feeding tube. After a thorough discussion about the risks, benefits, and alternatives, Mr. B refused. Though he wanted to get better, he placed higher value on eating and drinking orally and accepted the risk of aspiration pneumonia. The SLP considered removing herself from his case because of her discomfort with his decision. After discussing her concerns with the patient's physician and a clinical ethicist in the hospital, she was able to accept his decision as informed and authentic. She chose to stay involved and attempt to mitigate potential harms by educating Mr. B on a diet and techniques that were safest while carefully documenting all discussions and the process of decision making in the case. (Table 46.5)

Using combination therapy allows clinicians to engage in providing patients with needed expertise and care while acknowledging and supporting the person's informed choice to refuse a particular medical treatment.

The use of feeding tubes is perhaps one of the most widely discussed life-sustaining treatments in the field of medical ethics, as evidenced by the controversies surrounding Terry Schiavo (63). Differing conceptual frameworks for the meaning of a feeding tube seem to underlie at least some of the debate (82). A traditional medical ethics perspective is that a feeding tube is a form of medical treatment, similar to a ventilator, and can be withheld or withdrawn as such. A second perspective is that a feeding tube provides basic humane care of food and fluids without which a person cannot survive, so they should always be continued. A third perspective would be that a feeding tube is a disability accommodation. Just as a person uses a wheelchair for a mobility impairment, a person uses a feeding tube for a swallowing impairment. Understanding the perspective of the various parties involved when a discussion arises about withdrawing or withholding food and fluid can help in negotiating difficult conversations (82).

TABLE 46.5 Critical Documentation of the Shared Decision-Making Process

1. The clinical situation and recommendation(s)
2. Whether or not the patient has DMC to participate in the decision
3. If the patient is not the decision maker, indicate who is
4. Report information shared with patient and/or the surrogate
5. The response of the patient or proxy
6. If the response was a rejection of the clinical recommendations, state the reasons given
7. Further information provided to the patient and/or surrogate to address questions or concerns that may have been raised
8. The agreed-upon plan
9. Plan for monitoring the intervention

In general and importantly, documentation should consistently reflect who the decision maker is and that questions about care are appropriately directed to that person.

Decisions to withhold or withdraw a life-sustaining treatment are very emotionally charged because they are in most cases, by definition, final decisions.

Withdrawal or Withholding of Life-Sustaining Treatment

We make a distinction here between withholding and withdrawal of treatment and withholding and withdrawal of care. Medical and basic care is/should always be provided to a patient, but, in all but the most exceptional of circumstances, the withholding and withdrawal of medical treatment is the personal preference of an autonomous patient or his or her surrogate. *Withholding* life-sustaining treatment is a term applied to a situation in which a medical treatment is not initiated. *Withdrawal* of life-sustaining treatment is the discontinuation of a medical treatment after it has been started (9).

Withholding and withdrawing life-sustaining treatment are often within the purview of a proxy decision maker, just as they are for a patient (50,83), though the circumstances may be limited by a patient's advance directive or state law. Based on the presumed right to privacy, that is, to be free of unwanted medical treatment, case law in the United States recognizes this personal choice as a defensible construct (49). Ethical study also supports this as a correlate for the respect for patient autonomy. Both legal and ethical frameworks hold that there is no moral difference between withdrawing or withholding life-sustaining treatments (84,85), though clinicians do not always agree. Within the context of a clinical case, some clinicians feel that withdrawing life-sustaining medical treatment feels psychologically as if they have a direct responsibility for the patient's death (84,86).

Therapies and Technologies: Evidence and Resource Allocation

The economic climate is continually changing in the field of health care and unfortunately often results in reduced reimbursement for rehabilitation services. Health care teams face the dilemma of creating treatment plans that maximize effectiveness and can be implemented in a constrained time frame (87). Complicating these situations is an increasing number of new, expensive, and unproven technologies developed to help enhance function after stroke. Where research does exist on some interventions, the protocols may not have included significant number of participants with stroke. Patients and families may ask for or insist on receiving the newest technologies and therapy methods. Clinicians may then face dilemmas of determining the most appropriate treatment for the patient while considering the request (or demand) and any resource restrictions that may exist.

Consider Ms. K and Mr. G:

Ms. K recently had her second stroke which resulted in severe dysphagia requiring the placement of a PEG tube. After discharge from the hospital, Ms. K began therapy at an outpatient center. Her insurance company

allows only 10 speech therapy visits per year. Ms. K read an advertisement for electrical stimulation of the swallow musculature and is eager to try it during her SLP sessions. The patient's therapist is concerned that devoting all Ms. K's sessions to this intervention will limit her progress and that there are other impairments that require attention. Additionally, the SLP knows that evidence for the effectiveness of electrical stimulation for swallowing after stroke is inconclusive.

The SLP shares this information with and discusses her thoughts with Ms. K and together they develop a treatment plan in which all Ms. K's therapy goals are addressed.

Mr. G is a 63-year-old gentleman who survived a right hemisphere stroke. He participated in inpatient rehabilitation and has been discharged home with 2 caregivers who assist him 24 hours daily for safety and mobility. Mr. G has dense left hemiplegia and left inattention. Mr. G has personal wealth and is a celebrity in the community. While an inpatient, Mr. G completed a trial treatment on the hospital's robotic body-weight-assisted ambulation device. He feels he made improvement after using this device; however, he has not shown any functional increase in his ability to walk.

Mr. G tells his outpatient physical therapist (PT) that he would like to supplement his regular treatment sessions with use of the hospital's robotic ambulation device three times per week. The PT tells Mr. G that she does not recommend this treatment now. Mr. G tells the PT that he understands that using the device may not yet result in functional change, but that he knows it is helping him and he wants to have the feeling of walking again. Mr. G talks to the outpatient supervisor about paying privately for the use of this technology. The PT and her supervisor are concerned—they do not want Mr. G to waste his money on a treatment that may not be clinically beneficial; they do not want to schedule Mr. G to use the device when there are other patients who could benefit from the treatment and may need the appointment slot; they do not want to jeopardize a positive relationship with a prominent person; and they also do not want to diminish Mr. G's motivation by limiting an activity he takes such pleasure in.

Mr. G's therapist consults with colleagues and proposes trial use of a standing wheelchair. With assistance, this device allows Mr. G to rise to a standing position to participate in many daily functional and leisure activities. The PT promised to continue to monitor Mr. G's progress for clinical indications that an additional trial of the robotic ambulation device might be warranted.

Team Conflicts: Goals of Rehabilitation

The biggest lesson I learned that morning was that when it came to my rehabilitation, I was ultimately the one in control of the success or failure of those caring for me. It was my decision to show up or not. I chose to show up for those professionals who brought me energy by connecting with me, touching me gently and appropriately, making direct eye contact with me, and speaking to me calmly. I responded positively to positive treatment. The professionals who did not connect with me sapped my energy, so I protected myself by ignoring their requests. (1)

The literature has suggested that team-based care, as is the model for rehabilitation, may inherently predispose individuals to conflict (65,66,88). As previously stated, conflicts often arise when a clinician's professional recommendation is at odds with a patient's choice. Sharp (88) delineates an often-experienced process of individuals coming together to form a team. She indicates that the way people come together and begin to make joint decisions may not be smooth. Often, groups test each other before they trust the judgment and recommendations of other group members. Teams then ideally reach a place where they can challenge one another safely and reach consensus for the best approach to a particular patient. Dowdy and his colleagues (89) demonstrated that challenging issues are predictable in certain clinical contexts and that use of a preemptive ethical consultation aided team members in feeling that they were each involved in the process of decision making. Bringing clinical teams, patients, and families together to discuss problems and issues is often a very effective means of navigating and resolving conflict (65,66,90,91).

The patient and family (2) are part of this team as well. They face adjustment challenges to team interaction and communication similar to those faced by clinicians. However, at the end of the day, the patient and, in many cases, the family have the most at stake in any scenario. Having direct conversations with patients to learn and focus on their specific goals can aid interdisciplinary teams in avoiding unnecessary discord and in allowing patients' wishes to direct the plan of care to the greatest degree possible.

SUMMARY

I think that one of the problems with stroke is that, as a condition, it offers a moving target. Compared to, say, cancer, stroke is not a degenerative condition. If you survive the initial crisis you are—with luck—constantly and imperceptibly getting better. I had to learn to adjust, and also to wait. (38)

Ethical issues are common in the clinical care of persons who survive a stroke, in part because different individuals in an interdisciplinary team, including patients and families, can experience conflicting values; and in part because the experience and sequelae of stroke may change a person's abilities and concept of himself or herself. This shift in perspective

that stroke survivors commonly experience may require a period of reflection and redefinition for the stroke survivor to clarify his or her new vantage point. Stroke can result in cognitive and communication impairments that affect a survivor's ability to participate in both the routine and the complex decisions about medical care faced in the first hours, days, and even years following the event. Additionally, some potentially life-threatening medical conditions, such as dysphagia, require balanced consideration of the risks and benefits of common and sometimes invasive interventions.

This chapter has presented an overview of the kinds of ethical issues faced by health care providers, patients, and families in the care of stroke survivors. Understanding and use of ethical paradigms and principles will guide clinicians and clinical teams in identifying ethically acceptable options in difficult circumstances. Keeping the wishes of the patient paramount and supporting participation of patients who demonstrate significant communication impairment are critical in reaching optimal outcomes.

Illness can create defining moments in one's life. Clinicians have a role in fostering and facilitating self-actualized choices for the stroke survivor. In the face of great change (either temporary or lasting), patients can still maintain dignity and self-fulfillment with a considered and ethical approach to patient interaction and care.

As Marc Black Sings in "When You Get Back," ". . . you never get back to where you've been, always get back to where you're going on down the line" (92).

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47

Stroke and the Family

Tamilyn Bakas and Lisa Scarton

Families are an integral part of stroke recovery and rehabilitation. A family caregiver can be a relative, partner, personal friend, or neighbor who provides assistance to an older person or adult with a chronic or disabling condition (1). Roughly 68% to 74% of stroke survivors are discharged home under the care of family members (2,3). Stroke is different from other chronic conditions in that stroke caregivers must suddenly assume the caregiving role after a stroke event, whereas, for example, dementia caregivers typically assume the caregiving role gradually over time (4). Family caregivers must quickly learn how to help stroke survivors live with a variety of stroke-related impairments (i.e., motor, sensory, visual, language, cognitive, and affective impairments) (5,6) while also trying to adapt to the changes in their own lives that have resulted from providing care (7–11). Studies have shown that family caregivers are at risk for depression, psychosocial impairments, and mortality as a result of providing care (12–14). To make matters worse, family caregivers of stroke survivors are commonly neglected by health care providers in the practice setting (7,13). In a study of 116 stroke caregivers, 11.7% reported that communication with health professionals was very or extremely difficult (15). Stroke affects the entire family, not just the stroke survivor and his or her caregiver. The survivor's children, siblings, parents, extended family, and friends are also affected. The purpose of this chapter is to provide a general overview of the impact of stroke on the family and to explore existing literature regarding stroke caregiver interventions, which are designed to support families of stroke survivors through recovery and rehabilitation.

IMPACT OF STROKE ON FAMILY MEMBERS

Family caregivers have a variety of needs and concerns related to stroke care and also experience negative outcomes such as depression, declining health, and other life changes such as social and financial problems. Other family members may experience conflict, psychological distress, and other negative outcomes. The literature regarding these topics is reviewed in the following sections.

Caregiver Needs and Concerns

The assessment of caregiver needs and concerns from the caregivers' perspective and culture is important across inpatient, outpatient, and community-based settings (1,7,16–20). The caregiver needs and concerns checklist (CNCC) is one instrument with which health care providers can assess caregivers in the context of stroke care (Figure 47.1) (7). The CNCC, originally developed based on qualitative comments from stroke caregivers, addresses five main areas of needs and concerns:

1. Information
2. Emotions and behaviors
3. Physical care
4. Instrumental care
5. Personal responses to caregiving

Information

Finding information about stroke is especially important for families because spouses and other family members are commonly the initiators of emergency care for stroke survivors (21). Of the estimated 700,000 strokes that occur each year in the United States, 200,000 are recurrent strokes (5). Moreover, 14% of persons experiencing a stroke or a transient ischemic attack (TIA) for the first time will have a reoccurrence within 1 year (5). Family caregivers of stroke survivors have expressed concerns about whether they would be able to recognize a second stroke, and they want more information from health professionals about stroke warning signs (7,22). For example, one caregiver reported that she thought her father was drunk when he was actually suffering a stroke. She was concerned that she might not be able to recognize signs of another stroke (7). Stroke warning signs can be difficult to distinguish from other conditions, particularly when a stroke survivor already has some residual deficits from the initial stroke. It is imperative that health professionals assess and reinforce knowledge of stroke warning signs in both patients and caregivers during follow-up visits.

Stroke caregivers also have needs and concerns about recommended lifestyle changes and risk factors for recurrent stroke. One caregiver reported that she had only received

Information: At this time, I would like more infomation about . . .
(Check all that apply.)
- ☐ the warning signs of another stroke.
- ☐ recommended lifestyle changes after stroke (e.g., eating a healthy diet, being physically active, stopping smoking, getting regular checkups).
- ☐ risk factors for stroke (e.g., controlling high blood pressure, diabetes).
- ☐ the stroke survivor's medications (e.g., drug name, what it's for, dosage, possible side effects).
- ☐ the stroke survivor's condition or what to expect before going home.
- ☐ how to manage specific problems the stroke survivor may have (e.g., constipation, bowel or bladder incontinence, dizziness, fatigue, pain).
- ☐ which health professionals to call for advice (e.g., doctor, nurse, physical therapist, occupational therapist, speech therapist, social worker).
- ☐ where to find books or written materials, support groups, or organizations that can help.
- ☐ where I can go for my health care needs.

Emotions and behaviors: At this time, I need help . . .
(Check all that apply.)
- ☐ dealing with the stroke survivor's emotions (e.g., mood fluctuations, anxiety, nervousness, anger, depression, poor future outlook).
- ☐ dealing with the stroke survivor's feelings about himself or herself (e.g., feelings of dependency, feelings of being a burden on others, worthlessness).
- ☐ keeping the stroke survivor socially active (e.g., keeping in touch with friends, holding an interest in others, finding someone to talk to who's had a stroke).
- ☐ communicating with the stroke survivor (e.g., trying to understand him or her, getting him or her to understand me, using the telephone, dealing with the frustration of communication).
- ☐ dealing with the stroke survivor's changed personality from the stroke.
- ☐ dealing with the stroke survivor's problems with thinking (e.g., loses or forgets things, has poor judgment, can't make decisions, confusion).
- ☐ dealing with the stroke survivor's difficult behaviors (e.g., cries easily, acts childlike, loses temper, uses foul language, waits for others to do things, doesn't appreciate caregiver).

Physical care: At this time, I need help . . .
(Check all that apply.)
- ☐ getting the stroke survivor to take medications on time.
- ☐ getting the stroke survivor to do prescribed exercises.
- ☐ learning how to help the stroke survivor walk, transfer to a wheelchair, move about, or avoid falls.
- ☐ getting the stroke survivor to eat (e.g., forgets to eat, refuses to eat, or has trouble swallowing).
- ☐ assising the stroke survivor with bathing, dressing, or going to the bathroom.

Instrumental care: At this time, I need help . . .
(Check all that apply.)
- ☐ learning how to manage checkbooks, bills, forms, or finances related to the stroke survivor's health care.
- ☐ trying to cover the cost of the stroke survivor's health care (e.g., medications, glasses, adult day care, therapy, services).
- ☐ transporting the stroke survivors places, going public with the wheelchair, or driving.
- ☐ finding care for the stroke survivor while I am away.

Personal responses to caregiving: At this time, I need help . . .
(Check all that apply.)
- ☐ dealing with my own emotions while providing care (e.g., mood fluctuations, anxiety, nervousness, anger, depression, poor future outlook, feelings of loss).
- ☐ with new responsibilities that I am not used to (e.g., taking on unfamiliar household tasks or things the stroke survivor used to do).
- ☐ finding the best way to ask family and friends for help with the stroke survivor's care.
- ☐ dealing with other things in my life (e.g., balancing work with caregiving, caring for other family members).
- ☐ taking care of my own health.
- ☐ keeping my energy level up.
- ☐ keeping my own social life going (e.g., getting out with friends and family, attending church, having free time for myself).

FIGURE 47.1 Caregiver needs and concerns checklist.

Source: From Ref. (7). Bakas T, Austin JK, Okonkwo KF, et al. Needs, concerns, strategies, and advice of stroke caregivers the first six months after discharge. *J Neurosci Nurs.* 2002;34(5):245. Copyright 2002 by American Association of Neuroscience Nurses. Reprinted with permission.

information about her husband's diet and speech therapy and commented that, if he had had a heart attack, she would have received more information on smoking, exercise, and other lifestyle changes (7). Another study reported that only 40% of stroke caregivers remembered receiving any information about stroke prevention (16). Providing information for stroke survivors and families regarding lifestyle changes and risk factors for recurrent stroke is critical for secondary stroke prevention. Current guidelines recommend management of hypertension, diabetes, and cholesterol in stroke survivors, along with counseling to avoid smoking, heavy alcohol consumption, and obesity (17–20,23). Stroke survivors should also undergo a supervised therapeutic exercise regimen that includes a pre-exercise evaluation (17–20,23,24).

Family caregivers need information about these recommendations so they can encourage and reinforce prescribed healthy behaviors and lifestyle changes throughout stroke recovery and rehabilitation.

Additional areas of stroke caregiver informational needs and concerns relate to:

- Medication management
- The survivor's condition and treatment plans
- Management of specific symptoms or problems that the survivor may have (for example, constipation, bowel or bladder incontinence, dizziness, fatigue, and pain)
- Which health professionals to call for advice
- Where to find books or written materials, support groups, or organizations that can help (7,17–20)

Stroke organizations, such as the American Stroke Association (www.strokeassociation.org; 1-888-478-7653), the National Stroke Association (www.stroke.org; 1-800-787-6537), or the National Institute for Neurological Disorders and Stroke (http://www.ninds.nih.gov/disorders/stroke/stroke.htm; 1-800-352-9424), can be valuable resources for stroke survivors and their families. They offer written information on a variety of stroke-related topics, monthly magazine subscriptions addressing the latest issues in stroke care, websites for stroke survivors and caregivers, and lists of stroke support groups for specific geographical areas. Informational needs may not be the same for each caregiver, so individualization is often indicated. This can be challenging given the limited time that health professionals usually have with family members. In fact, caregivers often report that health professionals ignore them (7,13). Nevertheless, caregivers recommend trying to get as much information as possible before the survivor is discharged home; asking for names of health professionals they can call for advice; attending therapy sessions; talking with other stroke survivors and caregivers; and looking for books or written materials, stroke support groups, home health care, financial counseling, and other resources that may assist them in providing care (7,16–20).

Emotions and Behaviors

Managing emotional and behavioral reactions of the stroke survivor are among the most stressful aspects of providing care for family caregivers (5,10,15,16,19,25–30). Gonzalez and Bakas (30) found that male stroke survivors exhibited significantly more bothersome behaviors as identified by their family caregivers. This finding could be attributed to female caregivers being more likely to provide care for more impaired male family members (31). After controlling for survivor gender, 35% of difficult or bothersome behaviors were explained by the family caregiver's depressive symptoms, task difficulty, life changes, and threat appraisal (30). Some studies have also described caregiver unawareness that difficult behaviors might be stroke related and therefore responded with either anger or excessive sympathy (32,33). Emotional and behavioral problems experienced by stroke survivors that caregivers typically face include depressive symptoms and other emotional reactions to stroke, changed personality or cognitive impairment resulting in disruptive behaviors, and communication deficits, including aphasia.

Studies have documented that approximately one-third of ischemic stroke survivors suffer from poststroke depression, a condition that is often misdiagnosed, undertreated, and associated with poor outcomes and increased mortality (34–37). Dealing with poststroke depression is a primary concern for family caregivers, particularly because, although physical deficits are usually recognized in the hospital environment, cognitive behavioral deficits may not become apparent until after discharge (4). Clark and colleagues (26) reported that 74% of their sample of 130 stroke caregivers indicated that their survivor appeared sad or depressed, and this was the most frequent memory or behavior change found in their study. Pierce and Steiner (38) reported in their qualitative study that male caregivers were most concerned about how to deal with their wives' depression and irritability. Although screening for depressive symptoms in stroke survivors using the PHQ-9 Depression Severity Scale is gaining attention in the literature (19,39), information provided to stroke caregivers on how to screen and seek treatment for poststroke depressive symptoms is lacking (19). Caregiver communication with health care providers regarding survivor depressive symptoms can be challenging at times. For example, one caregiver reported that during a clinic visit she tried to inform the physician about her spouse's feelings of worthlessness and negative attitudes, but the survivor displayed a more positive attitude in the presence of doctors, making assessment and treatment for the depression difficult (7).

Additional survivor emotions and behaviors that are troublesome for stroke caregivers to manage include such things as (7,10,15,26,28,29,33,38,40,41):

- Feelings of worthlessness or being a burden on others
- Moodiness or irritability
- Anger, frustration, loss of temper, or negative interpersonal exchanges
- Cognitive difficulties, memory loss, or confusion
- Personality changes or emotional dependency
- Indifference or inertia
- Waiting for others to do things the survivor can do
- Lack of participation in social activities
- Communication difficulties

Providing care to a stroke survivor who has aphasia has been associated with more negative caregiver outcomes and difficulties with tasks compared with caregivers of nonaphasic stroke survivors (10). In a sample of 42 family caregivers of aphasic stroke survivors, communication with the survivor, closely followed by managing behaviors, were rated as the most difficult tasks caregivers faced (10). The challenges that caregivers have in communicating with aphasic survivors have been found in other studies as well (42,43). Helping aphasic survivors and their family caregivers develop effective communication techniques prior to discharge and across the care continuum is strongly recommended by current patient care guidelines (19,20). One stroke caregiver intervention

found in the literature focused on improving communication in the context of aphasia (44). Caregivers receiving the intervention had significant reductions in stress; however, these results were not maintained at three-month follow-up (44). There were no significant effects on communication skills or burden.

Unfortunately, no reported stroke caregiver intervention studies have specifically addressed how to help caregivers manage the emotional and behavioral reactions displayed by stroke survivors, other than the Telephone Assessment and Skill-Building Kit (TASK) (45,46). Stroke caregivers in the TASK program, who identify managing emotions and behaviors as a priority need, are trained how to assess the survivor for depressive symptoms and how to intervene using skill-building strategies that focus on stress management, problem solving, and communicating with health professionals (45). Not all caregivers have to deal with the same types of survivor emotions and behaviors; therefore, there is no one-size-fits-all solution to this problem. Nevertheless, supporting caregivers in their role of managing these difficult emotions and behaviors is paramount. Including the family caregiver in the assessment of stroke survivor depressive symptoms and other emotions and behaviors is a starting point where health professionals may begin to quickly identify areas for treatment or referral (17–20). Simply asking family caregivers about the emotions and behaviors they are dealing with and how they are communicating with the survivor may uncover serious barriers to stroke recovery and rehabilitation that may be amenable to treatment or psychological counseling for the survivor and his or her caregiver.

Physical Care

Physical care provided by stroke caregivers may include such things as assisting the survivor with bathing, toileting, getting dressed, walking, mobility, exercises, meals, managing symptoms and deficits, and medication management. Studies have shown that caregivers do have concerns about managing stroke-related symptoms and deficits as well as providing basic stroke care (7,15,17–20,29). Although the provision of personal care (i.e., bathing, toileting, getting dressed, and feeding) and assisting with mobility and exercises were not among the most difficult tasks on average in a sample of 116 stroke caregivers, 9.1% found personal care to be very or extremely difficult, and 14.3% found assisting with mobility to be very or extremely difficult (15). In a qualitative study of 14 stroke caregivers within 6 months after discharge, getting survivors to take their medications and exercise were major concerns, as were getting survivors to eat; assisting with bathing, dressing, or toileting; and avoiding falls (7). Caregivers suggested such things as using pill boxes for medications, taking the survivor to the mall for exercise, avoiding clutter to prevent falls, taking advantage of resources like Meals on Wheels, following a bladder and bowel regimen, and encouraging the survivor to do as much self-care as possible (7). Health professionals are encouraged to assist caregivers in providing personal care by encouraging them to attend therapy sessions with the survivor to learn transfer techniques and how to assist with activities of daily living (19,20). Medication instruction for stroke survivors should also include the family caregiver, especially if the stroke survivor has trouble reading or has poor sensory perception or cognitive deficits (47). Health professionals should encourage caregivers to ask questions about the survivor's medications, symptoms, and other stroke-related care issues (17–20,47).

Instrumental Care

Instrumental care provided by stroke caregivers include such things as dealing with financial issues, providing transportation, assisting with household tasks (i.e., laundry, cooking, cleaning, yard work, and home repairs), shopping, running errands, managing services and resources, as well as finding someone to care for the survivor while away. In one study of 116 stroke caregivers, household tasks and managing finances were among the top four most difficult tasks, with approximately 17% to 18% finding these activities to be very or extremely difficult (15). Providing transportation (14.2%), finding respite care while away (15.3%), and finding resources (9.1%) were rated as very or extremely difficult as well (15). In another study, six caregivers shared their concerns regarding finances, with one caregiver fearing she would run out of money, which would result in institutionalization of the stroke survivor. Financial management was also a concern for caregivers in another study across all time periods up to two years after stroke (16). These are only a few examples of the needs and concerns that family caregivers have in providing instrumental care. Referral of stroke caregivers to a social worker to assist them in dealing with financial problems and finding appropriate community resources are clearly areas where health professionals may better serve families of stroke survivors (17–20).

Personal Responses to Caregiving

Caregivers will often share their needs and concerns about their stroke survivors before they will share their own personal needs and concerns (7). However, in one qualitative study, caregivers reported needs and concerns about their own emotions while providing care, shouldering new responsibilities, balancing caregiving with existing responsibilities (i.e., employment and care of other family members), asking friends and family members for help, keeping their own social life going, as well as keeping their energy level up and taking care of their own health (7). It was evident from the findings of this study that caregivers experienced great stress while providing care (7). One caregiver stated she would cry late at night at home, but would try to hold up for her sister. Another caregiver mentioned how she and the survivor used to have frequent gatherings and cookouts, but that had stopped since the stroke. Another caregiver was assertive enough to ask the doctor why everyone always asked how her husband was doing, but never asked her how she was doing. This caregiver felt neglected by the health professionals involved in her husband's care and was reaching out for help. In a similar study (16), a wife indicated she wanted more attention from health professionals and they did not have anything for caregivers. In a more recent

intervention study, a caregiver stated, "I was a superwoman and I was going to do it even if it killed me . . . and it almost killed me . . . What I like about it is that you not only deal with the issues of the person with stroke, but you also deal with the health issues and things of the caregiver" (45, p. 372). The most difficult times for caregivers have been reported to occur during hospitalization and the first few months after the patient is discharged home, which underscores the need for early caregiver assessment followed by individualized caregiver interventions during these critical time periods following stroke (16,45). The next section provides a review of literature about negative caregiver outcomes, including depression, poor health, decreased social functioning, and other negative outcomes of providing care.

Caregiver Outcomes

Caregiver Depression

Studies have explored caregiver psychological distress and depression as well as the many factors associated with these outcomes. Estimates of the prevalence of depression in stroke caregivers have ranged between 30% and 52% (12,40,48), with poorest mental health when the stroke survivors were discharged home early (49). In fact, some studies have reported higher depression rates in caregivers than in the stroke survivors for whom they provided care (48,50). The treatment of stroke caregiver depression is important because caregiver stress has been found to be a leading cause of long-term institutionalization of stroke survivors (12). In one landmark prospective study, family caregivers experiencing strain had a 63% higher risk of mortality compared with noncaregiving controls (14).

Factors directly associated with caregiver psychological distress and depression have included:

- Difficulty with caregiving tasks (15,51)
- Burden (52)
- Lack of social support (50,52,53)
- Poorer family functioning (50)
- Concern for future care (54,55)
- Negative caregiver appraisal of the situation (51,56)
- Lower life satisfaction (53)
- Self-losses (53)

Positive factors that tend to be associated with lower caregiver depression and psychological distress include:

- Hope and meaningfulness (57)
- Optimism (54,55)
- Self-esteem (51,58)
- Resiliency (56)

Survivor characteristics such as stroke severity, physical impairment, depression, and negative personality characteristics have also been associated with caregiver depression (48,53,54,57,59,60). Other studies, interestingly, have found that physical disability of the stroke survivor is often unrelated to caregiver depression (12,13). Some studies have shown that Caucasian caregivers, as opposed to African American caregivers, and those providing care for older stroke survivors were at greater risk for developing depression (48,52). Pinquart and Sorensen (61) conducted a meta-analysis of 228 caregiver studies involving informal caregivers of older adults. They found that care recipient behaviors were more strongly associated with caregiver burden and depression than care recipient physical limitations or cognitive status. Perceived benefits of caregiving, such as feeling useful or feeling closeness with the care recipient, were associated with decreased burden and depression in caregivers. Pinquart and Sorensen (61) recommended that caregiver interventions be focused on reducing care recipient problem behaviors, improving caregiver skills in the management of problem behaviors, and promoting positive perceptions of providing care. Screening for depressive symptoms in stroke survivors using the PHQ-9 Depression Severity Scale has been recommended (19,39); however, the use of the PHQ-9 to screen for depression in stroke caregivers might also help to identify caregivers in need of antidepressant therapy or counseling (10,19).

Caregiver Health

The research agenda for stroke caregiving must move beyond psychological distress and depression to explore the general health of family caregivers (12,13,19). Researchers have noted that attention to the health status and health promotion activities of family caregivers is lacking in both descriptive and intervention studies (62,63). More studies are needed to determine predictors of health outcomes. For example, Bakas and Burgener (51) found that low household income and appraisals of threat were significant predictors of self-perceptions of poorer general health in stroke caregivers. Tooth and colleagues (64) found that only patient characteristics, such as cognitive function and mental health and caregiver employment, were predictive of caregiver SF-36 mental and physical component scores. Many studies have used global health measures in stroke caregivers, such as the SF-36 Health Survey. Some reported scores close to published general population norms (49,65,66), whereas others reported lower scores (64,67,68). Bakas and Champion (8) found that, although stroke caregiver SF-36 general health scores were close to published norms, caregivers perceived that their physical health had changed for the worse as a result of providing care. Other studies have also found that stroke caregiver perceptions of their own health worsen as a result of providing care (58,69). Although more research is needed to identify key indicators of stroke caregiver health, clinicians are urged to ask caregivers about their health, encourage them to seek regular checkups, and practice health promotion activities while providing care (19).

Other Caregiver Outcomes

Quality of life issues associated with providing care other than depression, psychological distress, and health deserve more attention in research studies (13,70). White and colleagues (70) described the lack of clarity regarding the term

quality of life in a review of stroke caregiver literature and asserted that quality of life involved not only health, but such things as participation in social and recreational activities, leisure, social relationships, family life, sexual life, ability to manage self-care, vocation, finances, and satisfaction with life as a whole. In an earlier review of the stroke caregiver literature, Low and colleagues (13) found that only 2 out of 31 studies had focused on the social health of stroke caregivers (40,71), noting that, although social measures were most often used as variables associated with depression or psychological distress, they were rarely explored as outcomes (13).

Bakas and colleagues (8,9) noted that, although a number of generic quality-of-life measures were used in stroke caregivers, there was a need for an instrument that measured changes in caregivers' lives, specifically as a result of providing care. Based on Lazarus and colleagues' (72,74) definition of adaptational outcomes, the Bakas Caregiving Outcomes Scale (BCOS) was developed to measure changes in social functioning, subjective well-being, and health, specifically as a result of providing care (Figure 47.2) (8,9). Extensive psychometric testing of the BCOS has found acceptable evidence for its reliability and validity in stroke caregivers (8,9). Two comprehensive reviews of caregiver measures have recommended the BCOS because of its extensive psychometric testing compared with other measures (75) and because it had the highest rate of agreement among the authors for seven different factors considered to be important for stroke caregivers (76). The BCOS has also been used to describe the impact of stroke caregiving in a population-based study in Auckland, New Zealand (77). The most current 15-item BCOS (9) consists of a comprehensive list of caregiver life changes rated on a scale from –3 (changed for the worst) to +3 (changed for the best), with 0 meaning no change. Life changes relate to such things as time for social and family activities, relationships with family and friends, relationship with the stroke survivor, roles in life, financial well-being, emotional well-being, ability to cope with stress, self-esteem, future outlook, level of energy, physical functioning, and general health. Unlike many other measures, an added benefit for the BCOS is the fact that it allows caregivers to rate these life changes as either negative or positive

This group of questions is about the possible changes in your life from providing care for the stroke survivor. For each possible change listed, circle one number indicating the degree of change. The numbers indicating the degree of change range from **–3 "Changed for the Worst"** to **+3 "Changed for the Best."** The number **0 means "Did Not Change."**

	Changed for the Worst			Did Not Change		Changed for the Best	
As a result of providing care for the stroke survivor:							
1. My self-esteem	–3	–2	–1	0	+1	+2	+3
2. My physical health	–3	–2	–1	0	+1	+2	+3
3. My time for family activities	–3	–2	–1	0	+1	+2	+3
4. My ability to cope with stress	–3	–2	–1	0	+1	+2	+3
5. My relationship with friends	–3	–2	–1	0	+1	+2	+3
6. My future outlook	–3	–2	–1	0	+1	+2	+3
7. My level of energy	–3	–2	–1	0	+1	+2	+3
8. My emotional well-being	–3	–2	–1	0	+1	+2	+3
9. My roles in life	–3	–2	–1	0	+1	+2	+3
10. My time for social activities with friends	–3	–2	–1	0	+1	+2	+3
11. My relationship with my family	–3	–2	–1	0	+1	+2	+3
12. My financial well-being	–3	–2	–1	0	+1	+2	+3
13. My relationship with the stroke survivor	–3	–2	–1	0	+1	+2	+3
14. My physical functioning	–3	–2	–1	0	+1	+2	+3
15. My general health	–3	–2	–1	0	+1	+2	+3
16. In general, how has your life changed as a result of taking care of the stroke survivor?	–3	–2	–1	0	+1	+2	+3
If there are any other changes in your life as a result of providing care for the stroke survivor, please write them below and rate them accordingly.							
17.	–3	–2	–1	0	+1	+2	+3
18.	–3	–2	–1	0	+1	+2	+3
19.	–3	–2	–1	0	+1	+2	+3

FIGURE 47.2 Bakas Caregiving Outcomes Scale (BCOS).

or having no change at all. Stroke caregiver studies using the BCOS have shown that the worst life changes were caregivers' time for family and social activities, relationship with friends, financial well-being, emotional well-being, level of energy, and physical health. Areas that changed for the better on average were relationship with the stroke survivor and self-esteem (8,9). Factors found to be associated with total BCOS scores have included threat appraisal (8,9,51), difficulty with tasks (8,9,15), emotional distress (8,51), or depressive symptoms (9,10). The BCOS has been shown to be a valuable measure in stroke caregiver research (8–10,75,76) and might also serve as an assessment tool to determine deteriorating aspects of caregivers' lives so that individualized interventions or referrals can be made (8–10).

Impact of Stroke on Other Family Members

Although literature regarding the effect of stroke on family caregivers has grown substantially in recent years, very little research has focused on the effects of stroke on other family members such as minor children, spouses of adult child caregivers, siblings, and other relatives who may be involved in the care of stroke survivors (78). Even rarer are studies that document the effect of stroke on parents, most likely because pediatric stroke is an infrequent occurrence (17,18,79). Nevertheless, family caregiver education across the continuum of care is important in the context of both adult and pediatric stroke (17,18). Two studies have focused on the effect of a parent's stroke on minor children (80,81). Visser-Meiley and colleagues (81) interviewed 82 children (ages 4–18; average of 13 years) of 55 parents who had suffered a stroke and were admitted to a rehabilitation center in the Netherlands. Shortly after admission, 54% of the children showed at least one behavioral problem or depression; 21% of those scored in the clinical range. Although these behavior problems and depression significantly improved by two months after discharge ($P < .001$), trends for increasing internalizing behavior problems and decreasing health status in the children were noted between two months and one year after their parent's discharge. Significant predictors of child depression scores at one year were the child's baseline depression scores, child's gender, and physical functioning of the parent at admission. Significant predictors of child's health status at one year were baseline health status, spouse depression, and spouse perception of marital relationship at the time of admission. These findings underscore the need to screen for children's functioning, spouse depression, and the quality of the marital relationship during rehabilitation for a more family-centered approach to care (81). Lackey and Gates (80) conducted a retrospective study of 51 adults who had been 3 to 19 years old at the time of their parent's stroke or diagnosis of other types of chronic conditions such as cancer, cardiovascular disease, amyotrophic lateral sclerosis, respiratory disease, diabetes, or arthritis. Providing personal care was most difficult. Household tasks were most time-consuming, and family life, school, and time with friends were most negatively affected by the caregiving situation.

Palmer and Glass (78) urged researchers and clinicians to consider the entire family system, not just stroke survivor–caregiver dyads, in trying to understand the ripple effect of stroke on families. Family roles, responsibilities, and patterns of emotional support and communication must be reconfigured to accommodate the recovery process for stroke survivors. This reconfiguration can pose challenges to pre-existing family relationships as well as family functioning in general (78). Current research is limited in studying family systems in the context of stroke, largely because of inadequate measures and the complexity of developing and studying family intervention methods. The limited research that exists provides some evidence that family functioning is associated with discharge disposition, treatment adherence, rehospitalization, and poststroke depression (78). Although stroke caregiver intervention research is on the rise, very few studies have focused on psychosocial interventions for whole-family systems (78). The next section provides a review of existing stroke caregiver intervention research, followed by a section on recommendations for future research and practice that urges researchers and clinicians to consider a family systems approach to care.

STROKE CAREGIVER INTERVENTION RESEARCH

According to current stroke rehabilitation clinical practice guidelines (17–20,82), health care providers should involve family caregivers in decision making and treatment planning for survivors, be alert to the stress and support needs of caregivers, and provide information on community resources and services, as well as provide patient and family caregiver education about stroke and potential complications. Despite these recommendations, research has not produced sufficient evidence regarding the effectiveness of stroke caregiver interventions that can be easily incorporated into practice, although several recommendations have been provided (12,13,17–20,83–85).

Stroke Caregiver Clinical Trials

Visser-Meiley and colleagues (85) identified 22 studies from January 1966 to March 2003 (14 from Europe, 5 from the United States, 1 from Australia, 1 from New Zealand, and 1 from Canada). From March 2003 to August 2006, an additional three European studies were found (86–88). There was a broad range of outcomes and measures, making comparison of findings difficult, and many other limitations were identified. Only 10 of the 22 studies reviewed improved on one or more outcomes, meaning that 12 (54.5%) studies found no significant intervention effects (85). Potential reasons for the nonsignificant findings included insufficient interventions, incorrect timing of interventions, the use of measures that lacked sensitivity to detect relevant changes, and samples that included different mixtures of spouse and adult child caregivers (85). Of the 10 studies that reported positive outcomes on one or more measures:

- Two reported reduced depression
- One reduced burden
- Five improved knowledge
- One improved satisfaction with care
- One improved family functioning
- Three improved quality of life
- Two enhanced problem-solving skills
- Three improved social activities and support (85)

Legg and colleagues (89) conducted a more recent systematic review of randomized controlled clinical trials published from January 1950 to August 2010 and found that only eight met their inclusion criteria of nonpharmacological interventions that involved stroke survivors and caregivers randomized as a dyad. Only one single-centre study reported significant improvements in outcomes (86). This study involved 300 stroke caregivers randomized to caregiver training or conventional care during inpatient rehabilitation. Outcomes included lower costs, reduced caregiver burden, lower anxiety and depression scores, and improved quality of life for caregivers in the intervention group one year after the intervention (86). Patients of caregivers in the intervention group also reported less depression and anxiety and improved quality of life (86). The caregiver training in this study consisted of three to five sessions of hands-on caregiver training on:

- How to handle stroke problems and complications
- How to prevent future strokes
- Information about local benefits and services
- Training in lifting and mobility techniques, assistance with activities of daily living, and communication tailored to the needs of the stroke patients (86)

However, these interventions were not tailored to the needs of caregivers (85,86). Caregiver intervention studies that better target the needs and concerns of family caregivers, rather than only the needs of stroke patients, have been strongly recommended (1,7,16,17–20,85).

Bakas and collegues (45,46,90) reported findings from a pilot study that tested content validity, satisfaction, effect sizes, and costs of delivery for the TASK intervention. Using the CNCC (7), the TASK program enabled stroke caregivers to self-identify their own needs and concerns regarding care for the survivor, as well as care for themselves as caregivers. Individualized interventions were then delivered based on caregiver self-identified needs. Content tip sheets were provided in five main areas (45):

- Information about stroke
- Managing emotions and behaviors
- Providing physical care
- Providing instrumental care
- Taking care of oneself as a caregiver

Skill-building tip sheets that addressed the following were also provided (45):

- Strengthening existing skills
- Screening for depressive symptoms
- Maintaining realistic expectations
- Problem solving
- Communicating with health professionals
- Stress management workbook for survivors and caregivers

Compared to an Information, Support, and Referral (ISR) group (n = 19), caregivers in the TASK group (n = 21) had significantly higher satisfaction, higher optimism, lower task difficulty, and lower threat appraisal regarding their future ability to provide care (45,46). Subgroup analyses revealed medium to large effect sizes for depressive symptoms for caregivers who screened positive for at least mild depressive symptoms (PHQ-9 ≥ 5) (91). Estimated costs for the delivery of the TASK intervention, consisting of a notebook mailed to caregivers and 8 weekly calls from a nurse, were only $421 per caregiver (90). These encouraging findings led to further refinements of the TASK intervention, which is now being tested in a large randomized controlled clinical trial (TASK II; R01 NR010388; Clinicaltrials.gov NCT01275495).

Also evident in Visser-Meiley and colleagues' (85) review was the need for studies that document the effects of caregiver interventions on patient outcomes. A total of 17 out of 22 studies reviewed used combined patient and caregiver interventions, making it difficult to determine the effects of caregiver interventions by themselves on patient outcomes. Determining the effect of caregiver interventions on stroke survivor outcomes is recommended and would provide a stronger rationale for implementing caregiver programs in practice (85).

Forester et al. (83) concluded from their review of stroke caregiver intervention studies that the provision of information alone had no effect on mood, perceived health status, or quality of life for stroke patients or caregivers. Another review found similar results, concluding that although knowledge improved with information-only interventions, reduction in depression was small and probably clinically insignificant (88). Other studies that combined education with problem-solving strategies were much more effective than using education alone at improving caregiver knowledge, family functioning, problem-solving strategies, and even patient adjustment (32,92). For example, Grant and colleagues (93) found that theoretically based telephone problem-solving sessions with family caregivers of stroke survivors significantly enhanced caregiver problem-solving skills, improved preparedness, reduced depression, and improved several SF-36 Health Survey scores. These sessions consisted of an initial face-to-face visit, followed by 7 telephone calls over a 12-week period to teach and reinforce caregiver problem-solving skills (93,94). King and colleagues (95) tested a similar problem-solving intervention with 121 stroke caregivers, using a wait list control group design, and found significant improvements in caregiver depression and life changes. Threat appraisal and problem solving were significant mediators in the conceptual model used to evaluate the intervention (95). The advantage of these sessions was that they empowered family caregivers to identify, solve, and evaluate their own problems in providing care (93–95).

Dennis and colleagues (96) found that stroke caregivers randomized to a treatment group receiving home visits by a family care worker had very few significant differences in outcomes compared to a control group; however, training and measurement problems may have biased the findings (97). A similar study by Mant and colleagues (98) found that the use of a trained family support organizer who made one hospital visit, one home visit, and three telephone calls significantly improved several SF-36 Health Survey scores, suggesting the importance of adequate training and adherence to a treatment protocol for interveners. Follow-up data from this study showed that the effect of the family support intervention persisted for up to one year after the intervention (87). There have also been other stroke caregiver intervention programs that show promise within the veteran population that use telehealth or videophone technologies (99,100). The Transition Assistance Program (TAP) was found to reduce caregiver strain and there was a trend toward a reduction in caregiver depression ($P = .07$) (100).

Although most stroke caregiver interventions are delivered face to face or by telephone, there are a few stroke caregiver intervention studies that have reported using web-based interventions (101,102). Pierce and colleagues' (101) "Caring~Web" intervention provided education and online support to 103 users over 1 year. Although there were no significant differences in caregiver well-being, there were significant reductions in emergency room visits and hospital readmissions for stroke survivors (101). Smith and colleagues (102) tested a web-based conferencing and video education intervention in 38 dyads (spouse caregivers of male stroke survivors). Although there were no significant differences in survivor outcomes, caregivers in the intervention group showed significant reductions in depressive symptoms. They also found the intervention to be useful, and would recommend it to others (102). Although there may be current technological barriers for many of today's stroke family caregivers, these web-based interventions show promise for the future as more and more family caregivers develop computer skills over time.

Caregiver Clinical Trials in Other Contexts

Most caregiver intervention research has been conducted in the areas of dementia and older persons. The most widely known intervention program, the Resources for Enhancing Alzheimer's Caregiver Health (REACH), evaluated the effectiveness of multiple caregiver interventions implemented across six sites to provide a comprehensive evidence base for caregiver intervention research (103). Meta-analytic findings from these interventions with 1222 family caregivers showed active interventions to be superior to control interventions (104) and multicomponent interventions targeting multiple domains (knowledge, cognitive skills, behaviors, and affect) to be relatively more effective (105). Meta-analysis has also revealed that tailoring interventions to the individual needs of family caregivers is generally more effective than group interventions (106,107). Other comprehensive reviews of caregiver intervention studies in dementia (108,109) and old age (106,107,110,111) exist. Two reviews emphasized the need to look beyond outcomes to methodological design factors such as intervention integrity and theoretical rationale (109,110). *Treatment fidelity*, defined as strategies to improve the reliability and validity of behavioral interventions and address intervention integrity and theoretical rationale, is being increasingly emphasized in intervention research (109,110,112). Treatment fidelity consists of five components: treatment design, training, delivery of treatment, receipt of treatment, and enactment. Treatment design includes the theoretical model or clinical guidelines for the intervention, provider credentials, and information about the dosage (length, number, content, and duration of contacts) for both intervention and comparison conditions. Training includes detailed descriptions of how providers are trained, standardized, and maintained over time (for example, use of training manuals, role-playing, and audiotaping). Delivery of treatment involves ensuring that treatments are delivered as intended (for example, use of evaluation checklists to track adherence to protocol and need for retraining). Receipt of treatment refers to evidence that the study participants understood the intervention (for example, ability to verbalize what they have been taught, pretest/posttest, and ability to demonstrate skills). Enactment of treatment skills refers to evidence that study participants have incorporated treatment strategies into their everyday lives or that they use the strategies in a variety of settings (112). Although integration of these five components of treatment fidelity into clinical trials can be costly, time-consuming, and difficult to implement in clinical practice (113), rigorous attention to these components is likely to enhance scientific reporting, provide more plausible conclusions as to why interventions did or did not work, and improve treatment replication, making treatments more applicable to a wider variety of clinical practice settings (112).

RESEARCH FRONTIERS

The aging of the population, along with the current shortage of health care professionals to assist with the transition to home care, underscore the urgent need for public policies and programs to support family caregivers (114,115). This is especially true for family caregivers of stroke survivors, because the incidence of stroke is likely to increase as the population ages (5). As detailed earlier in this chapter, caregivers have a variety of needs and concerns about providing care, such as information, managing the survivor's emotions and behaviors, providing physical care, providing instrumental care, and personal responses to caregiving. Caregiver depression, deteriorating health, and other negative caregiver outcomes such as decreased social functioning and financial well-being are common. Family caregivers often feel neglected by health professionals in practice settings. Although there are a few stroke caregiver intervention studies with positive results, this body of research as a whole has not produced sufficient evidence for the effectiveness of stroke caregiver interventions. Clinically tested interventions for family caregivers of stroke survivors are prerequisite to the development of effective

public policies and programs that can be implemented into practice settings for family caregivers. Stroke also affects the entire family system (i.e., parents, minor children, spouses of adult child caregivers, siblings, and other relatives), although research is severely limited in this area. Interventions based on a family systems perspective have been recommended; however, further research is required to develop and clinically test interventions at the family systems level. The following sections summarize recommendations for future research and practice implications pertinent to stroke recovery and rehabilitation for families.

Recommendations for Future Research

1. More research that includes assessment tools to identify problem areas experienced by family caregivers is needed so that individualized caregiver interventions can be delivered (1,7,16–20). For example, further studies using the CNCC (7) to assess caregiver needs and concerns, the Oberst Caregiving Burden Scale (OCBS) (15) to assess difficulty with caregiver tasks, and the BCOS (8,9) to assess negative changes in caregiver lives as a result of providing care are needed (7–10,15,19). The use of the PHQ-9 (33) to screen for caregiver depressive symptoms also warrants further testing (10,19).
2. Quality outcome measures relevant to stroke caregivers that have documented evidence of reliability, validity, and sensitivity to change are needed to evaluate stroke caregiver intervention programs (85).
3. Caregiver intervention research should include interventions that are tailored or individualized to specific caregiver needs and concerns (7,10,12,15,19,20,45,46,85 ,107).
4. Stroke caregiver interventions that specifically address how to help caregivers manage the emotional and behavioral reactions displayed by stroke survivors are especially needed because managing survivor emotions and behaviors is among the most stressful aspects of providing care (5,10,15,16,19,25–30,45).
5. Multicomponent caregiver interventions covering multiple domains (knowledge, cognitive skills, behaviors, and affect) (105) and offering more than just information provision (83,88) should be the focus of future stroke caregiver intervention research.
6. Correct timing for interventions should receive attention when designing stroke caregiver intervention studies (85).
7. Studies that separate spouse data from adult child caregivers during analyses are needed to identify interventions appropriate for each group (85).
8. Studies that document the effects of caregiver interventions on stroke survivor outcomes are needed to provide a stronger rationale for caregiver interventions in practice (85).
9. Studies that look beyond outcomes to methodological design issues, including treatment fidelity, are recommended (109,110,112).
10. Studies that incorporate a theoretical rationale for interventions are recommended (45,46,109,110,112).
11. More research from a family systems perspective is needed to document the impact of stroke on entire families, as well as to develop and evaluate interventions at the family systems level (17,18,78).

Practice Implications

1. Because of the wide variety of needs, concerns, and negative outcomes experienced by family caregivers of stroke survivors, detailed assessment from the caregivers' perspective using tools such as the CNCC (7) is recommended so that individualized caregiver interventions or referrals can be provided (1,7,16–20,45,46,85).
2. Health professionals should assess and reinforce both patient and caregiver knowledge of stroke warning signs, lifestyle changes (i.e., diet, exercise, smoking, heavy alcohol consumption, and obesity), and risk factors for secondary stroke prevention (i.e., management of hypertension, diabetes, and cholesterol) throughout stroke recovery and rehabilitation (7,16–20,23,24,82).
3. Family caregivers should be asked about the stroke survivor's depressive symptoms and emotions, and how they are communicating with the survivor, to identify possible barriers to stroke recovery and rehabilitation that may be amenable to treatment, therapy, or psychological counseling (7,10,17–20,26,42,43,82).
4. Family caregivers should be encouraged to attend therapy sessions and ask questions about the survivor's medications, symptoms, and other stroke-related care issues (7,17–20,47,82).
5. Family caregivers should be referred to a social worker as needed to assist in dealing with financial problems and finding appropriate community resources (7,15,16,19,20,82).
6. Stroke organizations, such as the American Stroke Association (www.strokeassociation.org; 1-888-478-7653), the National Stroke Association (www.stroke.org; 1-800-787-6537), or the National Institute for Neurological Disorders and Stroke (http://www.ninds.nih.gov/disorders/stroke/stroke.htm; 1-800-352-9424), can be valuable resources for stroke survivors and their families (72).
7. Family caregivers should be asked how they are doing (7,10,16,19,82), particularly about their depressive symptoms and health. Refer them for treatment and/or psychological counseling as needed. Encourage them to seek regular checkups and to practice health promotion activities while providing care.
8. The entire family system should be considered during recovery and rehabilitation, not just the stroke survivor–caregiver dyad (17–19,78). Ask the stroke survivor and his or her family caregiver how other family members are dealing with the stroke, including any minor children, and refer them for treatment and/or counseling when appropriate.

CONCLUSION

Providing care for a family member with stroke can be difficult and can lead to negative consequences not only for the family caregiver, but also for the entire family. Researchers and clinicians are urged to explore ways to better support families in providing care for stroke survivors during stroke recovery and rehabilitation. Research regarding the needs and concerns, depressive symptoms, poor health, and other negative outcomes experienced by family caregivers has been reviewed, along with stroke caregiver intervention research and the need for a family systems perspective in helping families adjust after stroke. Perhaps with attention to the several recommendations for future research and practice outlined in this chapter, families may receive better care and support from health professionals in the future.

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48

Driving After Stroke

Hillel M. Finestone and Arthur M. Gershkoff

Cerebrovascular disease can cause physical, visuospatial and/or cognitive symptoms that can lead to unsafe driving. Careful assessment of cognition, insight, and judgment, as well as gathering a thorough history and performing a complete physical examination, are important in determining potential driving risks. However, clinicians know that returning to driving after stroke can be a very sensitive and emotional issue (1). Many stroke survivors relied on driving before their illness and consider it an essential component of independent living as well as a pleasure and a right of citizenship. Stroke survivors who are able to resume driving are better integrated into the community than nondrivers (2,3). But the fact that "driving is a privilege and not a right" must sometimes be compassionately conveyed to the patient with stroke.

Health care providers who draw attention to patients' physical, cognitive, and/or visuospatial deficits may thus threaten stroke survivors' image of themselves. However, attention to driving safely is a necessary part of the overall rehabilitation plan for virtually all stroke survivors. The issue must be addressed from several points of view:

- *Societal*: Although many stroke survivors safely return to driving, society must be protected from unsafe drivers, who expose themselves and others to the risk of bodily harm and property damage. Some stroke survivors may deny the severity of their deficits because of anosognosia (denial of illness) or severe impairment of judgment. The need to drive may be so strong that they purposely fail to report symptoms to their physicians, such as seizures or episodic loss of consciousness that would lead to mandatory loss of driving privileges (4). Society therefore has an obligation to create pathways to return to driving following stroke and administer careful and thorough driving evaluations that assess the safety of the stroke survivor. Safe and effective transportation is also needed for those who are no longer able to drive.
- *Ethical*: While the public must be protected from unsafe drivers, there is also an obligation to treat stroke patients fairly. It should *not* be assumed from the outset that residual neurologic deficits preclude safe driving (5,6). However, various jurisdictions have different regulations governing when and how a stroke survivor may return to driving.
- *Medicolegal*: The physician's potential liability for damages to others caused by an unsafe driver always lurks in the background. A few U.S. states and most Canadian provinces have clarified physicians' responsibility by legislating mandatory reporting of potentially unsafe drivers. The jurisdiction may then either revoke the license of someone judged unsafe to drive or require the patient to undergo standard or specialized driving assessments.

Though we are now more aware of driver safety following stroke, rehabilitation programs may not always address this issue. Of the approximately 78% of people who survive an acute stroke, 50% to 70% regain functional independence. A substantial proportion of these have the potential to return to safe driving but often must overcome or adapt to residual deficits. Some deficits, especially those that impair judgment or awareness of deficits, preclude safe driving, whereas others do not. A 1997 survey of 290 stroke survivors 3 months to 6 years after stroke showed that only 30% of subjects who drove before their illness resumed driving after the stroke. A total of 48% had not received advice about driving, and 87% had not received any type of evaluation of driver fitness before returning to driving (7). In another British study, published in 2008, very few patients recalled receiving any driving advice from their referring doctor while awaiting assessment for their transient ischemic attack (TIA) or minor stroke (8).

CONCEPTUAL DRIVING MODELS

Driving requires multiple skills, and models have been developed to conceptualize the types of skill interactions that occur. Michon described three levels of driving-related decision making: strategic, tactical, and operational (9). Strategic decision making, the highest level, refers to trip planning, such as the route that will be taken and determining whether the weather or time of day or night is appropriate. Tactical decision making refers to the driver's vehicle-handling decisions, such as how fast or slow to drive, whether to tailgate, and when to pass appropriately. Finally, operational decision making refers to basic driving actions, such as braking, steering, and reaction to a sudden possibly dangerous event. Galski et al. developed a more dynamic model that incorporated sensory

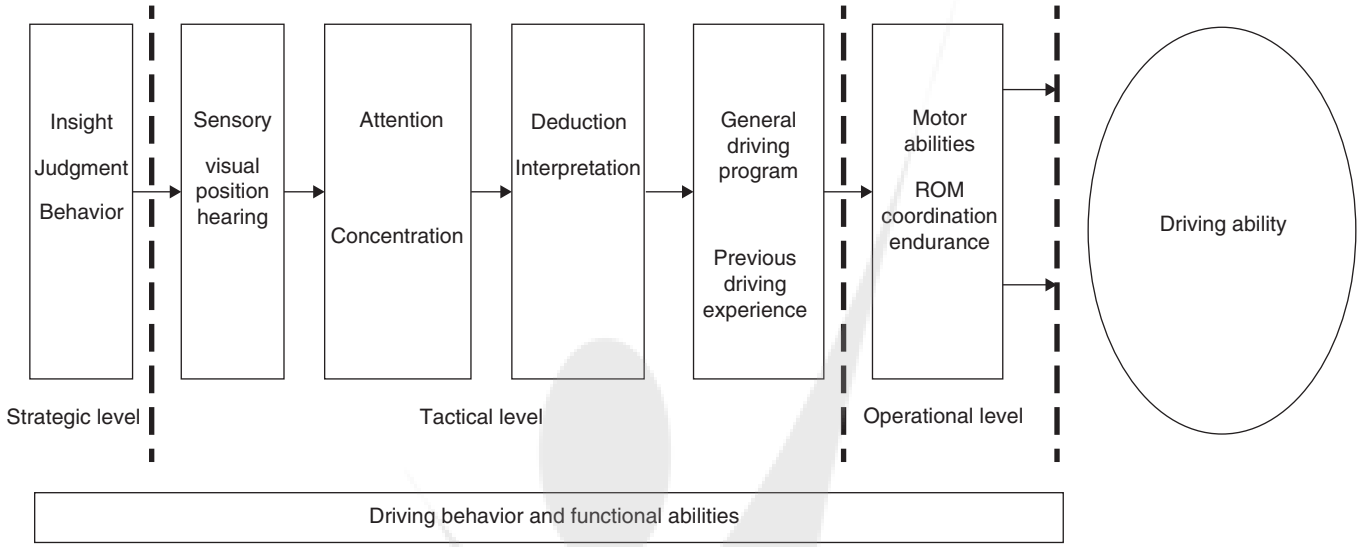

FIGURE 48.1 Model demonstrating the complexity of driving performance and how the physical, perceptual, and cognitive deficits that result from stroke may impede this performance at many levels.

Source: Reprinted with permission from Ref. (11). Marshall SC, Molnar F, Man-Son-Hing M, et al. Predictors of driving ability following stroke: a systematic review. *Top Stroke Rehabil.* 2007;14(1):98–114.

input, information processing, driving experience, and motor output skills (10). Marshall et al. combined the two models, as shown in Figure 48.1 (11). The figure amply demonstrates the complexity of driving performance and how the physical, perceptual, and cognitive deficits that result from stroke may impede this performance at many levels.

NEUROLOGIC DISORDERS AND CRASH RISK

In a review on the risk of vehicle crashes or traffic citations among patients with various diagnoses, it is of note that five of the seven studies show that drivers who have had a stroke have an increased risk of crashing compared to their counterparts without stroke (12). Diller et al. examined crash risk for Utah drivers based on medical conditions identified through a mandatory medical questionnaire at the time of licensure, followed by more extensive health screening (13). For each condition, the authors compared drivers having restricted licenses with drivers who were unrestricted. Neurologic conditions included a wide variety of diseases, but stroke was not separated out. Subjects with epilepsy in the absence of other neurologic disease were excluded. The data were linked to Utah Department of Transportation crash files. Among unrestricted drivers, those with neurologic conditions had 1.62 times the overall crash risk compared with a comparison group of 1773 unrestricted drivers without medical conditions matched for age, sex, and county of residence; the relative risk for at-fault crashes was 2.20. Subjects with neurologic conditions and restricted licenses had an increased relative risk of crashes, but this did not reach statistical significance. Separate analysis of drivers with epilepsy and episodic disorders of consciousness showed a significantly increased overall and at-fault crash risk for both restricted and unrestricted drivers (13). (It should be kept in mind that discrepancies in accident and infraction rates may exist between patient self-report and transportation authority records (14)).

However, a retrospective study of 1910 stroke patients indicated that the crash risk per person-year of driving for stroke survivors who return to driving is *not* higher than that for presumably healthy control subjects matched for age, sex, and zip code (15). The authors did not consider licensed drivers who voluntarily ceased driving or changed their driving exposure (16,17). Reduction of driving exposure has been noted with increasing age (18). The crash risk per mile driven rises substantially for drivers over age 65 (18); as the incidence of stroke increases substantially with aging, the crash risk per mile driven is therefore likely to be higher for stroke survivors as a group, regardless of neurologic deficits.

Nevertheless, specific neurologic deficits likely to be present following stroke play a role in driver performance and crash risk. In a study of visual impairments and their relationship to crash risk in 294 drivers aged 55 to 87 years, the most important deficit was restriction in useful field of view (UFOV), the visual field area within which a person can use rapidly presented visual information without moving the head or eyes (19). UFOV testing is different from visual field testing, which assesses visual sensitivity only. After adjustment for age, sex, race, chronic medical conditions, mental status, and number of days driven per week, impairment of UFOV of 40% or greater was associated with a 2.2-fold increased crash risk during 3 years of follow-up. Subcomponents of UFOV include processing speed, divided attention, and selective attention. Divided attention, which is frequently impaired following stroke, was associated with a 2.3-fold increased crash risk; the other subcomponents were not significantly associated with increased risk. Other vision parameters (visual acuity, contrast

sensitivity, stereo-acuity, visual field sensitivity [central and peripheral], and disability glare) were not significantly associated with increased crash risk (19). In another study, elderly drivers with substantial UFOV deficits had 15.6 times the crash rate at intersections compared with elderly drivers with normal UFOV (20). A meta-analysis by Clay et al. confirmed the significant relationship in older adults between UFOV and driving performance (21). In contrast to studies on UFOV, studies that examine the effect of visual field loss on driving have generally not shown a relationship between the loss and crash risk (16); however, stroke patients were not examined separately in these studies.

STROKE-RELATED DEFICITS AND DRIVING

Fisk et al. studied UFOV, visual acuity, peripheral vision, contrast sensitivity, and behavioral attention in 50 community-dwelling stroke survivors and a control group of 105 older adults without neurologic or visual impairment (17). They compared performance on these measures with a questionnaire of driving habits. Stroke survivors as a group demonstrated more impairment in UFOV, contrast sensitivity, and peripheral vision than controls, whereas stroke survivors who were drivers had less impairment of attention than those who were nondrivers. Stroke survivors who drove reported difficulty with challenging driving conditions and drove less than controls (17).

In general, the greater the severity of deficits, physical or cognitive, the lower the likelihood that the patient will return to driving. It has been estimated that every one-point increase in composite Functional Independence Measure score at discharge raises the likelihood that a stroke patient will return to driving by 5% (7). Smith-Arena et al. studied retrospectively the neurologic status at the time of admission to the rehabilitation hospital of 45 stroke patients referred to occupational therapy for driver prescreening (22). The 29 patients who passed the prescreening—23 of whom eventually passed an on-road assessment (ORA)—were significantly more likely than those who failed the prescreening to have intact visual fields and higher Mini Mental Status Examination (MMSE) and Motricity scores.

Aphasia presents a challenge to driving. In a 1980 study, 20 aphasic subjects (10 who had chosen to return to driving and 10 who had not) were evaluated as functional or nonfunctional to drive by a team including a physiatrist, driving instructor (off-road screening tests), occupational therapist, and speech therapist (23). The team's assessments of driving-related sensorimotor and cognitive domains were strongly predictive of the subject's decision whether or not to continue driving. Performance in spatial relationships was the most important variable that differentiated between those who chose to drive and those who did not, and between subjects who were judged as functional and those who were judged as nonfunctional to drive. The severity of aphasia had a significant effect on the subject's decision to drive but not on the team's rating. All aphasic patients who chose to drive were judged functional by the team (23).

Few studies have explored anatomic factors in driver performance following stroke. Using a driving simulator, Kotterba et al. studied 32 stroke survivors and found that patients with middle cerebral artery strokes performed more poorly than those with vertebral artery territory damage (24). This makes sense, given that middle cerebral artery strokes are likely to be larger in volume than vertebral artery strokes and are more likely to involve structures that affect cognition, vision, and perception. Patients with right-brain lesions are more likely than those with left-brain lesions to score poorly on visual and perceptual tests that are predictive of driving outcome (25). Akinwuntan et al. analyzed specific deficit areas in the ORA of 68 stroke survivors and found that subjects with attributes of visual neglect consistently drifted toward one side of the road and lacked adequate vision and perception during complex driving conditions (26).

Lastly, stroke patients may have a limited awareness of their disability (27) and thus tend to overestimate their driving ability (28). Losing the ability to drive has been documented to be unexpected, arousing strong feelings and reactions (29). It is no wonder that clinicians often consider the discussion of driving after a stroke such a difficult part of their practices.

DETERMINING FITNESS TO DRIVE

Numerous articles have attempted to outline the key factors that predict stroke survivors' ability to return to driving safely. Patient age and amount of disability (30,31), performance on cognitive tests (11,32), measures of strength and motor activity (33), normal visual fields (22), performance on a specialized driving track (34), and functions such as divided and/or selective attention and speed of processing (35) have been identified as important pieces of information for the clinician to consider. The majority of stroke survivors interested in return to driving will likely require an ORA, which remains the gold standard for determining driver safety. However, it must be emphasized that the physician's interview, examination, and assessment are vital components of the evaluation process. For the patient with apparent complete neurologic recovery, the physician may feel comfortable clearing the patient to return to driving, in which case the neuropsychological tests, closed-course driving tests, and driving simulator performance described in this chapter can provide helpful corroboration of the validity of this decision. If the patient has residual deficits, these screening tools can assist the clinician in determining if the ORA is necessary and when it should take place.

The On-Road Assessment

The ORA can take place in the patient's own vehicle, with a trained driving instructor sitting in the front passenger seat assessing performance. More often, and especially in cases in which safety is unknown or a true concern, the instructor will require a dual-control vehicle in which both driver and instructor have control over the brakes. Most dual-control vehicles have automatic transmissions. For standard-transmission

vehicles with a manual clutch, the instructor may have control over a second clutch; however, such vehicles are rarely, if ever, used or recommended for stroke patients.

Ideally, the instructor will be a driver rehabilitation specialist (DRS—see discussion following) or at least have experience with stroke patients. In the province of Ontario, Canada, provincial law mandates that, for a specialized ORA for a disabled individual, an occupational therapist must ride in the vehicle and evaluate performance as well. However, many areas of North America lack driving instructors with such expertise, and the physician may have to (or be required to) send the patient for an ORA by the state or provincial license certifying agency. The experience of the agency's instructors in working with stroke survivors and other disabled people may vary considerably.

The overall failure rate on the ORA by stroke survivors is 26% to 83% (16). Such a wide variability in failure rate attests to the wide variation in testing methods for the ORA. The method of assessing on-the-road driving performance may be highly structured but often differs between centers. In addition, different instructors may score a structured assessment differently. For example, the validity and reliability of a particular structured 10-mile ORA were evaluated in a Belgian study involving 39 stroke survivors (36). The results of this study demonstrated a significant variability in the pass rate between driving instructors. The state-registered evaluator failed seven of nine patients who had been passed by a driving instructor who had had more experience working with patients with strokes and other disabling conditions (36). The findings indicate a need for stroke survivors to work with instructors who are skilled in evaluating disabled people.

The ORA can be costly, and failure can lead to the serious consequences of loss or inability to re-obtain a license to drive. Regaining the license may entail overcoming considerable bureaucratic hurdles (even to obtain a training or learner's permit) and substantial expense in driving lessons. When the ORA is necessary, the physician can play a key role in determining when it should be scheduled to present the maximum likelihood that the patient will pass.

Predriving Cognitive and Neuropsychological Testing

A variety of studies have involved batteries of neuropsychological tests and correlated the results with ORAs (11,16,37). These studies show significant relationships between a number of psychometric tests and fitness to drive as measured by the ORA. They suffer from tremendous variability in the kinds of tests administered and the timing of testing following stroke. In most cases small numbers of patients were studied. The exact locations and extent of cerebral damage are generally not identified (16).

Engum et al. developed the Cognitive Behavioral Driver's Inventory (CBDI), which consists of brief neuropsychological tests with 27 individual scoring items. These tests evaluate the following domains of driver-related cognitive functioning: attention, concentration, rapid decision making, stimulus discrimination/response differentiation, visual scanning and acuity, and attention shifting (38). A summary score is average of the 27 items and is classified as pass, fail, or borderline. The CBDI has high internal consistency and validity based on correlations with the ORA. In a double-blind study of 81 patients, clearly passing the CBDI was 94% predictive of passing the ORA, and clearly failing the CBDI was 100% predictive of failing the ORA (39). The CBDI was further validated and shown to be sensitive in discriminating among 109 brain-injured subjects who passed the ORA, 54 brain-injured subjects who failed the ORA, and 41 nonbrain-injured control subjects (40). In a recent retrospective study of 172 patients, including 28 with left-brain stroke, 20 with right-brain stroke, and 58 with traumatic brain injury, the CBDI was found to be a significant predictor of pass or fail on the ORA for patients with right-brain stroke and traumatic brain injury but not for those with left-brain stroke (41).

Klavora et al. found the CBDI alone to be only 66% accurate in predicting success or failure on the ORA in 56 stroke survivors (42). These authors also evaluated the accuracy of the Dynavision Performance Assessment Battery, which uses a computerized apparatus to test and train visual scanning, peripheral visual awareness, visual attention, and visuomotor reaction time, and found the accuracy of the battery and subtests to be 66% to 77%. Some of the subtests of the Dynavision battery that take 5 to 10 minutes or less matched the predictive accuracy of the CBDI, which takes 60 to 90 minutes. Combining the CBDI and Dynavision battery yielded 100% accuracy (42).

In a study involving 23 subjects with stroke and 14 subjects with traumatic brain injury, Galski et al. compared 21 neuropsychological tests of attention, concentration, reaction time, memory, visual acuity, and visuospatial skills against a structured ORA consisting of 26 tasks (43). A driver evaluator converted the neuropsychological tests into a pass or fail score. Neither the pass/fail score nor any of the individual neuropsychological tests predicted the ORA outcome. The authors concluded that predriving evaluations should focus on screening out patients who are unsafe drivers rather than trying to predict reliably which patients are safe to drive (43). In a Swedish study, none of the neuropsychological tests offered was able to predict driving outcome (44).

In a study in Great Britain, 39 subjects who had had a stroke more than 6 weeks earlier were given a cognitive assessment by a psychologist and the ORA by the British School of Motoring (45). Significant relationships were noted for cube copy (spatial ability), dot cancellations time and misses (visual inattention, spatial ability, and memory), Rey figure recall (visual inattention), "What else is in the square?" (a children's game that tests reasoning ability), pursuit rotor (eye–hand coordination), road sign recognition (visual comprehension), and hazard recognition (visual recognition from videotape of an open-road drive). Using these, the authors developed a model for predicting driving

competency during the ORA; the model predicted pass or fail accurately for 95% of subjects. Complex reasoning skills seemed especially important (45).

A follow-up study, however, failed to validate the model in 40 stroke survivors (20 with left and 20 with right hemiparesis) (46), possibly because of a change in the ORA and the driving evaluator used. A new model was developed using dot cancellation, square matrices (based on "What else is in the square?"), and road sign recognition; this model predicted performance on the ORA with 79% to 82% accuracy and was eventually developed into the Stroke Drivers Screening Assessment. Two later studies involving a total of 66 patients showed this tool to be 80% to 81% accurate in predicting performance on the ORA (36,47). The instrument has shown excellent concurrent validity with more extensive neuropsychological measures of attention and executive functioning (48).

Other studies using multivariate statistical analysis have shown a significant correlation between various tests, including the Motor Free Visual Perception Test (MVPT) (25,49), single-letter cancellation test (25), Trail Making Test B (25), and figure of Rey complex drawing task (50), and subsequent performance on the ORA. In a multicenter trial of 269 patients, lower scores on the MVPT, increased age, and right-brain lesions were significantly associated with failure on the ORA, but the MVPT alone was insufficient to serve as the sole screening instrument for determining readiness for the ORA (49).

In a systematic review, Marshall et al. examined the predictors of driving ability following stroke (9). They noted useful screening tests, such as Trail Making Test A and B. Cognitive tests that assessed "multiple cognitive domains relevant to driving" were deemed to have the best reproducibility in predicting fitness to drive (11). A recent meta-analysis by Devos et al. of 27 studies encompassing 1728 stroke survivors confirmed the utility of the Compass Trail Making Test B, and road sign recognition tests; each test individually was 80% to 85% accurate in predicting potentially unsafe drivers, that is, those who failed the ORA (51).

Thus, cognitive testing in a variety of domains can be helpful in identifying potentially unsafe drivers. However, no single test or battery of tests predicts this absolutely. If the physician believes the patient to be unsafe, that too has some validity; there is a significant correlation between the objective driving score derived from standardized ORA and the global subjective evaluation of fitness to drive (52). In general, regardless of the predriving screening method used, the threshold for requesting (or insisting) that the patient undergo an ORA should, in the opinion of the authors, remain low.

Driving Simulators and Closed-Course Driving Tests

Traditionally, driving simulation involved watching films or videos of a car being driven through traffic and watching or tabulating the patient's reactions on mock driving controls, often adapted from an actual vehicle. Such simulation is noninteractive. Advances in computer simulation, video technology, and gaming have enabled development of highly realistic, interactive scenarios in which the video monitors wrap almost around the patient and the computer routine can change in response to the patient's actions. The computer can also monitor and record reaction time, errors, and appropriate or inappropriate use of steering and other controls (9).

Off-road, closed-course driving tests are recommended to evaluate vehicle operation skills and readiness for an in-traffic ORA (52). However, one small study showed no significant correlation between measures of driving on a closed course and performance on an ORA (53). A closed course thus may require a different set of skills than those required on an open-road ORA, and some stroke survivors may perform better in open-road driving—which may be an over-learned skill—than in a novel, off-road closed-circuit test.

Szlyk et al. found decreased performance on a driving simulator in patients with hemianopsia associated primarily with occipital lobe damage from stroke compared with a control group of similar age (54). In a Belgian study, 83 stroke survivors were assigned to simulator-based driver training (experimental group) or driving-related cognitive tasks (control group) (55). The subjects trained for one hour three times weekly for five weeks. The simulator consisted of the controls from an actual vehicle, with adaptive equipment as needed and with large-screen video and audio that simulated a 13.5-kilometer (8.4-mile) course under varied driving conditions. Visual and neuropsychological performance improved in both groups. The experimental group improved significantly more than the control group only in a road sign recognition test. Before training, only 27% of either group was judged fit to drive based on the ORA. After training, improvements in the classification of fitness to drive favored the experimental group. Ultimately, 73% of the experimental group and 42% of the control group were legally permitted to resume driving. Akinwuntan et al. noted in 2012 that driving simulators were improving and could potentially overcome "the problems currently faced in the evaluation and rehabilitation of driving after stroke" (56).

Galski et al. found that neuropsychological test results explained only 64% of the variance in ORA performance, while performance on the Doron simulator (a realistic but noninteractive driving simulator) predicted 63% (57). Together, the neuropsychological test and the simulator test explained 69% of the variance. The subjects' driving skills in a parking lot were also examined. The ability to follow directions, the presence of slow response, inattention and distractibility, and an index of overall observed behavior added 23% to the predictability, for a total of 92% of the variance. A factor analysis of the testing protocol identified five independent factors that predict performance on the Doron simulator: higher-order visuospatial abilities, basic visual recognition and ability to respond, anticipatory braking, defensive steering, and behavioral manifestations of complex attention (57).

In a study of 30 stroke survivors and 30 matched controls, a regression model was developed that included performance characteristics on a driving simulator and 3 psychological domains: attentional processing, executive capacity, and cognitive processing (58). A model based on performance variables on the simulator correctly predicted pass or fail on the ORA with 85% accuracy, whereas a model based on the psychological variables was 83% accurate.

A driving simulator has been noted to potentially improve stroke patients' "self-awareness" (59) and driving performance in "subacute stroke patients with mild deficits" (60) after six months but not five years later (61). A driving simulator may therefore serve as a driving trainer for the stroke patient. Similarly, the simulation of driving may also be used for educational purposes; that is, poor performance on the driving simulator may be more persuasive than paper-and-pencil neuropsychological test results to convince a patently unsafe patient to postpone the ORA and avoid driving. In this way, it may provide a safer alternative to the ORA for evaluating the driving potential of a stroke survivor who is likely unsafe but who insists on being tested. However, to prove or disprove driver safety, there is still no perfect substitute for the ORA administered by competent and experienced personnel.

Other Screening Instruments Not Specifically Tested in Stroke Survivors

Clock drawing, which evaluates memory, visuoconstructional ability, and executive functioning, can be a quick, useful, and simple screening tool. Failure on the clock-drawing test was found to be 90% accurate in predicting failure on an ORA in 100 adults aged 65 years or more (62). Clock drawing also correlated highly with performance on a driving simulator in 119 community-dwelling, active older Virginia drivers (63).

General screening tools for dementia, such as the Clinical Dementia Rating Scale and Folstein MMSE, have been studied in older adult drivers. Dubinsky et al. reviewed controlled studies of Alzheimer's disease and driving (64). Driving was found to be mildly impaired in drivers with probable Alzheimer's disease (Clinical Dementia Rating of 0.5, roughly equivalent to an MMSE score of 25, indicating only slight limitation in functional areas). The driving impairment was no different from that tolerated legally in other segments of the population (drivers aged 16–21 or drivers under the influence of alcohol with legal blood levels of less than 0.08%). Drivers with a Clinical Dementia Rating of 1 (roughly equivalent to an MMSE score of 19 to 24, indicating moderate limitation in memory and cognition that interferes with daily activities) had a significantly increased crash risk and performed more poorly on driving performance measurements. Stroke patients with cognitive deficits that correspond globally to these impairment levels probably share the respective levels of driving disability and crash risk.

The Assessment of Driving-Related Skills

The assessment of driving-related skills (ADReS) is the formal assessment tool developed by a consensus panel for the American Medical Association (AMA) (18). It was designed for assessing older drivers but is applicable to a wide variety of conditions, including stroke. For several of the subtests, there is evidence linking poor performance with increased risk of adverse driving events (18). The ADReS consists of the following subtests:

- Visual field testing by confrontation
- Visual acuity using a Snellen chart
- Rapid pace walk
- Manual test of range of motion, including neck rotation, finger curl, shoulder and elbow flexion, and ankle plantarflexion and dorsiflexion
- Motor strength (standard manual muscle test scored from 0 to 5) of shoulder abduction, adduction and flexion, wrist flexion and extension, hand grip, hip flexion and extension, and ankle dorsiflexion and plantarflexion
- Trail Making Test B
- Clock-drawing test (Freund method of scoring) (63)

If the patient fails any element of the ADReS, an ORA is recommended. Note that for stroke patients, significant hemiparesis will make it difficult for the patient to pass the motor strength screening (all muscles 4/5 or better in both upper extremities and the right lower extremity) and rapid pace walk test (10 feet and back in 9.0 seconds or less). Dominant upper-extremity involvement will affect handwriting and may affect performance on the trail-making and clock-drawing tests.

The ADReS has good inter-rater reliability among nursing, medical, and occupational therapy professionals (65). In a study of 50 licensed adults aged 65 or older, McCarthy and Mann found the instrument to be 100% sensitive in identifying subjects who subsequently failed an ORA (66). However, it was only 38% specific, meaning that many safe drivers (those who passed the ORA) failed the ADReS. A major reason for the high false prediction of failure on the ORA was failure of the clock-drawing test. To pass this test, the patient must draw the clock without error by the Freund scoring method. The authors noted that lowering the cut-off scores for passing the clock-drawing test from 8/8 to 6/8 would not reduce the sensitivity but would improve the specificity to 62% (66).

In McCarthy and Mann's sample, which did not include any stroke survivors, only 16% of patients failed the ORA. The high sensitivity and specificity of the ADReS may be different in a stroke population, in which the likelihood of failing the ORA is much higher (26%–83%) (16). However, the battery of tests is useful because it is a quick screening tool (15–20 minutes) that incorporates elements of the functional examination that the rehabilitation clinician will likely perform.

RETURN TO DRIVING (OR OTHER SAFE COMMUNITY TRANSPORTATION)

Adaptive Equipment to Aid in Safe Driving

For stroke survivors with significant weakness of the hemiparetic arm, a spinner knob attached to the steering wheel is required (Figure 48.2); this enables adequate control of the

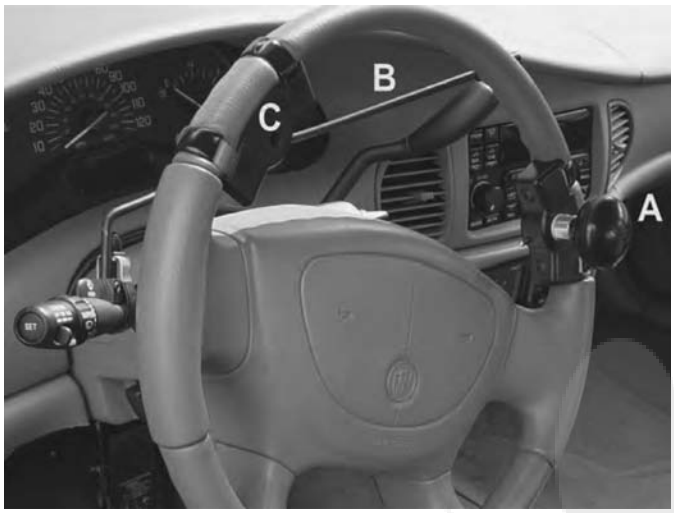

FIGURE 48.2 Adaptive equipment for hemiparetic drivers. (A) Spinner knob to be used at all times with the right hand for driver with left hemiparesis. (B) Left-to-right turn signal control. (C) Note that spinner knob can be placed on the left side for a driver with right hemiparesis.

Equipment available from Mobility Products & Design, PO Box 306, 144 South 100 West, Winamac, IN 46996.

steering wheel and must be used at all times during operation of the vehicle. Spinner knobs are now also available with switches to make it possible for the driver to control, without removing his or her hand from the knob, the turn signals, windshield wipers, horn, and high beams (Figure 48.3). If the person cannot control his or her right ankle, a right-to-left accelerator pedal converter may be needed (Figure 48.4) (67).

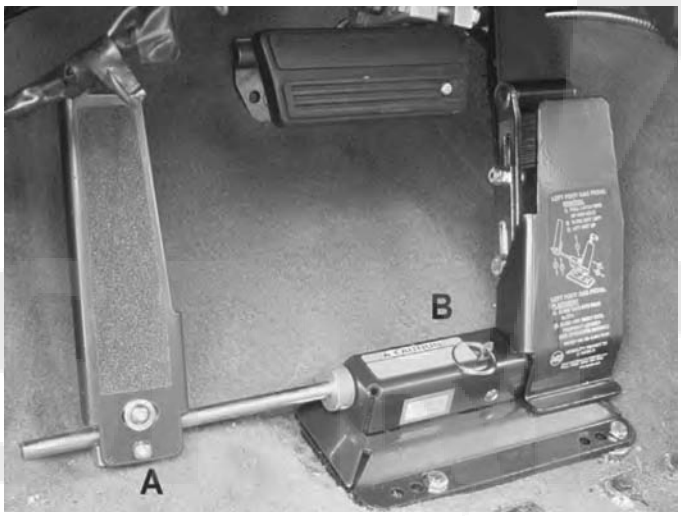

FIGURE 48.4 (A) Right-to-left foot control for accelerator pedal for a driver with right hemiparesis. (B) Note the pin for easy removal, so that the vehicle can also be used by an able-bodied driver.

Equipment available from Mobility Products & Design, PO Box 306, 144 South 100 West, Winamac, IN 46996.

FIGURE 48.3 Spinner knob with controls (switches) for turn signals, windshield wipers, horn, and high beam.

Image courtesy of Driving Systems Incorporated, Van Nuys, CA.

Similarly, for a stroke patient with left hemiparesis, controls on the left, such as a turn signal, will require left-to-right conversion (Figure 48.2). For all of these, the control is usually designed to be easily removed, so that the vehicle can be used by an able-bodied person as well (67).

The Driver Rehabilitation Specialist

A DRS is a driving instructor who "plans, develops, coordinates and implements driver rehabilitation services for individuals with disabilities" (68,69). A DRS generally undergoes a certification process through the Association for DRSs (formerly the Association for Driver Educators for the Disabled [ADED]). Certification requirements include education, work experience, and passing a written examination. However, in most states and provinces there is no absolute requirement for certification to work as a DRS in adaptive driving instruction or administration of ORAs for people with disabilities. A DRS usually has certification or training in another discipline, most often occupational therapy but also physical therapy, kinesiotherapy, speech therapy, or recreational therapy. A driving instructor without training in another discipline (e.g., a driving school instructor or state driver licensing bureau examiner) can qualify for the examination with three years of full-time work experience in the field of driver rehabilitation (68).

The Association for DRSs has several categories of membership in addition to individual members: mobility equipment dealers, businesses involved in manufacturing and distributing products used by a DRS and by individuals with disabilities, and facilities and businesses that implement or administrate driver rehabilitation services. The association organizes and administers the examination for certification, has developed best-practice standards for delivery of driver

rehabilitation services, and has established ethical standards of practice. Thus, it serves as a major resource for all professionals involved in driver rehabilitation (68).

Adaptive driving programs are available in a variety of settings. Many comprehensive rehabilitation hospitals and programs offer driving schools for the disabled. A few programs are located within universities and are often connected to research facilities that are federally funded. Some are sponsored by local affiliates of national nonprofit organizations that serve the disabled, such as United Cerebral Palsy. Some private commercial driving schools have developed the expertise to advise on adaptive equipment and provide evaluation and training of stroke survivors. A few state vocational rehabilitation programs also offer such training, but most provide funding for patients to participate in adaptive driving programs in other settings (67).

The DRS performs a clinical evaluation of the patient, including medical and driving history, vision examination, assessment of selected physical aspects, cognitive assessment, and ORA. The medical history includes determining current medical status and stability to undergo further testing, reviewing medications for their potential deleterious effect on driving, assessing the patient's current communication status, reviewing the driving history, determining the license status (to determine whether an ORA can be performed legally), and assessing the availability of a suitable vehicle for the ORA. The DRS must also establish that the patient is actually medically cleared for an ORA and that performance of the ORA, given the medical condition, does not violate state or provincial regulations (70).

If the stroke survivor has had a seizure within the state-mandated period during which driving is not permitted, the DRS cannot perform an ORA, even if requested by a physician. In several states the mandated period of driving abstention can be overruled by the medical board of the state licensing agency if appropriate medical documentation is provided.

If a patient lacks a legal license but is cleared medically for the ORA, the DRS can facilitate the patient's obtaining a temporary license from the state authorizing the evaluation in a dual-control vehicle. This is required of the patient whose license is revoked because of a stroke and its sequelae but who recovers sufficiently to be evaluated.

For driving prescreening, the DRS performs an extensive functional and driving-oriented vision examination using assessment tools and clinical observation. Physical capacities required to control a motor vehicle are evaluated: strength, range of motion, grip strength, sensation, proprioception, coordination, and muscle tone. The level of cognitive impairment and self-awareness is also scrutinized, often with neuropsychological tests. Reaction time is usually measured objectively, especially movement of the foot from the accelerator to the brake pedal; this can now be tested with portable equipment in the patient's own vehicle. The DRS also evaluates the patient's assistive devices and orthotics needed for ambulation and must determine whether these will interfere with driving (70). Spastic talipes equinovarus, foot drop, and the use of an ankle–foot orthotic to block right ankle motion will usually impair control of the accelerator or brake pedal; the DRS can establish whether modification of the vehicle with adaptive equipment is indicated.

In a 2003 survey of driving evaluation practices of DRSs, more than 70% used a brake reaction timer, 70% the trail-making test part A or B, and 65% the motor-free visual perceptual test. In addition, 30% used the MMSE, and about 25% the letter cancellation test. Other measures of vision, perception, and cognition were used by 15% or less (71).

At the start of the ORA, the DRS assesses the patient's ability to enter and exit the vehicle and determines whether specialized equipment is needed (70). Rarely, stroke patients require a specialized wheelchair lift to access the vehicle independently. The patient's sitting posture and position with respect to the steering wheel and controls are evaluated. A major component of the evaluation is the patient's ability to operate controls while the vehicle is stationary or moving. If the vehicle already has adaptive equipment, the DRS evaluates its condition and appropriateness for the patient (70).

Out on the road, the DRS assesses the patient's driving performance in increasingly complex traffic conditions. The purpose of the examination is to observe the patient in road settings, traffic density, and weather conditions that approximate as closely as possible those likely to be encountered normally (70). For patients with suspected deficits that might interfere with safe driving, the DRS should design the ORA to emphasize driver actions that stress those deficit areas, for example, frequent left turns and performance at intersections with moderate to high degrees of traffic flow for patients with suspected left hemineglect (67). Some patients may be cleared for limited licenses, for example, to drive only during daylight hours. For most patients it is necessary to demonstrate satisfactory performance of all usual driving maneuvers required of able-bodied drivers seeking licensure.

At the end of the evaluation the DRS indicates to the patient—and the referring clinician—whether the patient is safe or unsafe to drive. If the patient is deemed unsafe to drive, the DRS recommends whether further training would help achieve safe driving or whether the patient should retire from driving. If adaptive equipment is required, the DRS trains and tests the patient to assure competence in its use while driving. If further training is likely to benefit the patient, the DRS can develop a program of goal-oriented driving lessons, with the ultimate purpose of passing a second ORA (70).

Stroke survivors who possess a valid license, require no special adaptive equipment, and are judged safe to drive by the DRS can generally return to driving. If new adaptive equipment is required, usually the patient must also be retested and certified by the state using that equipment. In most cases drivers seeking commercial certification must also be retested by the state to resume commercial occupations legally.

Evaluation and training by a DRS is expensive, generally costing $80 to $120 or more per hour. Some insurance companies may pay for this, but most do not. Federal and

state vocational rehabilitation offices often pay for an ORA if it can be shown that return to driving will facilitate return to work.

The Physician's Approach to the Patient

Stroke patients vary considerably in their potential to be unsafe drivers, and physicians need to individualize their approach for each individual patient, depending on the severity of the stroke, the specific impairments involved, and associated comorbidities. Patients with moderate to severe deficits will be clearly unable to drive, either temporarily or permanently. Objective tests that characterize cerebral damage (computed tomography or magnetic resonance imaging) and quantify the impairments can help in developing a prognosis, but poststroke functional ability and driving performance will ultimately determine the potential to resume driving.

Patients with severe impairments and disabilities may need counseling to avoid driving and to seek alternative forms of transportation. Patients who deny or are unaware of their neurologic deficits (including many with right-brain infarcts and anosognosia) and those with cognitive deficits who may impulsively decide to drive present a particular problem. In many, but not all, states and provinces the physician is legally obligated to report all potentially unsafe drivers to driver licensing agencies. Family members may have to be counseled to take measures to prevent the unsafe driver from driving (e.g., lock the car, hide the keys). Family members may also have the right to report the likelihood of unsafe driving practices to the driver licensing agency, and the threat of this may add weight to the physician's insistence that the patient cease driving. Patients who insist on an ORA may need counseling to postpone the assessment until further recovery has taken place.

Those with milder deficits and those who have recovered should be assessed using the ADReS or another objective, quantifiable test. Cognitive testing with the MMSE or other instrument is also useful. Patients who recover full motor, sensory, perceptual, and visual function, who lack cognitive deficits by testing, and who pass the ADReS are probably safe to drive. However, reaction time may still be affected and should be measured if possible. If there is *any* question that residual (or premorbid) visual, sensorimotor, or cognitive deficits exist, the patient should be referred for an ORA. Patients with hemiparesis severe enough to prevent bimanual grip of a steering wheel or regular use of brake and gas pedals must be referred to a DRS for adaptive equipment or modification of the vehicle before the ORA.

Aphasic patients may recover in other neurologic domains to the point at which safe operation of a motor vehicle is feasible, but may have difficulty completing written or oral examinations and following the driving instructor's verbal instructions during an ORA. The physician or therapist should anticipate such problems during testing and urge the testing or licensing agency to make accommodations for the patient's needs. This may include waiving the written test. If a written test cannot be avoided, patients with aphasia may benefit from extra time and the use of multiple-choice questions rather than prose or essay responses. Those with alexia or anomia may require someone to read the questions and choices for answers. Multiple-choice tests designed using pictures instead of words will also help the aphasic patient. Some with severe deficits may fail because they are untestable or because the agency cannot provide the necessary accommodations.

Physicians often encounter patients who have recovered from stroke but who present with new weakness. Even if the patient seems to have recovered fully, as with a TIA, driving should be avoided until a full medical evaluation has been completed. Persistent (for more than 24 hours) new weakness warrants cessation of driving until completion of not only a medical reevaluation but also the ADReS, cognitive tests, and if appropriate, another ORA. A patient previously judged competent to use adaptive equipment—whether related to deficits from a prior stroke or from another disabling disease—may need reevaluation and training to use the equipment safely again. Repeated unpredictable TIAs, syncope, or seizures require definitive medical treatment before driving can be resumed. If the medical condition can be controlled perfectly or is always preceded by adequate warning symptoms, return to safe driving may be possible. The physician should adhere to state or provincial regulations for reporting such transient neurologic changes. Most jurisdictions support the decision that the patient stop driving and require a period of freedom from episodes of altered consciousness before a license can be restored. The Canadian Medical Association recommends that the stroke survivor wait at least one month after the stroke before resuming driving (72), but this is a guideline and not a law.

Patients who have undergone cerebrovascular or intracranial surgery should not drive until they are judged fully stable, free of postsurgical symptoms, and cleared by a neurosurgeon. Residual neurologic deficits should be addressed in the same way as persistent deficits following a stroke. Arteriovenous malformations and subarachnoid hemorrhage should be treated similarly; the risk of future bleeding/re-bleeding of arteriovenous malformations and aneurysms must be assessed. If the risk is low and residual neurologic deficits are stable and mild, return to driving can be considered. However, driving is contraindicated if the medical condition remains unstable or at high risk of recurrence (18).

Pre-existing comorbidities may influence driver safety in stroke patients who may previously have been safe drivers. The presence of arthritis, mild Parkinsonism, visual acuity problems, deafness, mild dementia, or other disorders of aging may not in themselves preclude safe driving, yet when combined with even mild neurologic deficits after stroke, they may adversely affect driver safety. Thus, driver rehabilitation may require the physician to evaluate and treat such secondary comorbidities.

Regardless of state or provincial reporting requirements, *it remains of paramount importance that the physician tell the patient, who is potentially unsafe, not to drive, until further*

TABLE 48.1 Tips to Reinforce Driving Cessation for Stroke Survivors Likely to Be Unsafe Drivers

1. Write on a prescription pad, "Do not drive." This emphasizes the strength of the message and can serve as a visual reminder to the patient.
2. Ask whether the patient wishes to risk an accident in which injury could occur. The patient, his or her family, or an innocent party could be injured. How would the patient feel if someone else were injured as a result of causing an accident?
3. Point out that an accident will very likely raise insurance premiums.
4. Owning, insuring, fueling, and maintaining an automobile can be very expensive. If the patient retires from driving and sells the vehicle, how much money could be saved?
5. Ask how much lower the cost would be to take taxis or public conveyances.
6. Develop a plan for alternative transportation with family members. Present that plan to the patient.
7. If the patient lacks a valid license or is not qualified to drive because of the medical condition, point out the legal risks of driving without a license.

Source: Adapted from Ref. (18). Carr DB, Schwartzberg JG, Manning L, Sempek J. *Physician's Guide to Assessing and Counseling Older Drivers*. 2nd ed. Washington, DC: National Highway Traffic Safety Administration; 2010.

recovery takes place or until the patient undergoes a definitive ORA. The physician may be found negligent if the patient is not counseled in this way and subsequently drives and has an accident. To protect the physician, it is important to document in the medical record that this counseling took place.

It is important to offer support and counseling to patients who are unsafe to drive or who resist giving up driving or being tested. A list of tips to reinforce driving cessation is given in Table 48.1 (18). Referral to social services will help the patient to identify, apply for, and ultimately qualify for alternative community-based or subsidized transportation. The stroke survivor may require door-to-door public van service, which may require medical justification; the physician should expect requests for documentation when patients apply for such services.

AMA Physician's Guide to Assessing and Counseling Older Drivers

A useful resource to assist physicians and other rehabilitation personnel in addressing driver safety is the *Physician's Guide to Assessing and Counseling Older Drivers* (18). This was a cooperative effort between the AMA and the U.S. National Highway Traffic Safety Administration. It was developed by consensus of an advisory panel of clinicians, researchers, and representatives of medical specialty societies and organizations that serve the elderly. The primary goal of the guide was to educate physicians and provide them with assessment and management tools to address driving in elderly populations, but overall it is also of value to physicians and therapists who work with stroke survivors of any legal driving age. The AMA guide is divided into chapters, many of which include specialized resources for evaluating and managing driver safety issues (Table 48.2).

The AMA guide lists a series of "red flags" for medically impaired driving that should alert the physician to potential driver safety issues. Those particularly applicable to stroke include concerns about the patient's driving expressed by family members, the presence of multiple chronic medical conditions, polypharmacy (especially use of medications with potential sedative effects), and a history of episodic or unpredictable events, such as hypoglycemia, cataplexy, angina, or syncope. Family members should be queried about recent crashes, near misses, traffic tickets, unexpected or unexplained episodes of becoming lost, and forgetfulness. The presence of any of these should trigger a formal evaluation of driver safety as outlined earlier.

COMMON PROBLEMS AND MEDICAL DECISION MAKING

Your patient has sustained a stroke. The following is a series of questions and answers concerning reporting, testing, and medical responsibility.

1. Do physicians have to report to "the authorities" that their patient sustained a stroke?

The answer to this varies according to the patient's residence, the type of stroke sustained, and the sequelae of the stroke itself. States and provinces have different responsibilities. Most provinces and a few states have mandatory reporting, which means that the physician must report the patient to the state or provincial motor vehicle licensing authority if the stroke has caused any type of physical, cognitive, psychological, or other abnormality that could affect the ability to drive. It does *not* mean that every patient with the diagnosis of stroke must be reported, as is the case in Belgium, where it is mandatory for physicians to report all acute stroke patients, who must then refrain from driving for six months.

There are stroke survivors without residual neurologic deficits who do not need to be reported; but it is the physician's responsibility to establish that fact with objective tests and examination. If the physician is uncertain about the apparent full recovery, reporting the patient may relieve the physician of potential liability for negligence or damages, if the patient is subsequently involved in an accident (see discussion following). Not reporting the patient in a state with mandatory

TABLE 48.2 Specialized Resources in the American Medical Association's *Physician's Guide to Assessing and Counseling Older Drivers*

CHAPTER	SPECIAL RESOURCE
1	Safety and the Older Driver: an Overview
2	Is the Patient at Increased Risk for Unsafe Driving? [Discusses red flags for further assessment]
3	Assessing Functional Ability [Description of all parts of the Assessment of Driving-Related Skills (ADReS), and the ADReS score sheet and test sheet for the trail-making test part B, which can be copied]
4	Physician Interventions
5	The Driver Rehabilitation Specialist
6	Counseling the Patient Who Is No Longer Safe to Drive
7	Ethical and Legal Responsibilities of the Physician
8	State Licensing and Reporting Laws [For each state: contact information, medical requirements for driver licensing, license renewal procedures, reporting procedures, and information about the medical advisory board]
9	Medical Conditions and Medications That May Impair Driving [Discusses a wide variety of medical conditions and diseases; separate sections are devoted to cerebrovascular diseases, seizures, and medications)
10	Moving Beyond This Guide: Future Plans to Meet the Transportation Needs of Older Adults
Appendix	Patient and caregiver educational materials: • Patient self-report questionnaire: "Am I a safe driver?" • Successful aging tips • Tips for safe driving • How to assist the older driver (for family members/friends) • Getting by without driving

Source: From Ref. (18). Carr DB, Schwartzberg JG, Manning L, Sempek J. *Physician's Guide to Assessing and Counseling Older Drivers*. 2nd ed. Washington, DC: National Highway Traffic Safety Administration; 2010.

reporting may leave the physician in violation of civil law and may make defending a lawsuit for damages more difficult.

In some states and provinces, reporting potentially unsafe drivers is encouraged but not required. In that case, before the physician sends any driving-related information to the state or provincial authority, he or she should obtain the patient's consent to do so. Liability for reporting confidential information without the patient's permission (technically a breach of confidentiality) and immunity from prosecution or lawsuits arising out of such reporting vary from state to state.

For example, the state of Illinois, which has no mandatory reporting for physicians, legally obligates *drivers* to declare at the time of license application or renewal whether they have "any mental or physical condition that might interfere with driving," among other topics. Drivers are also supposed to notify the motor vehicle department of any medical conditions that may cause a loss of consciousness or affect safe operation of a motor vehicle within 10 days of becoming aware of the condition. The driver is thereafter obligated to produce a "physician's statement, a medical agreement, and/or the appropriate court documentation." The physician, however, is neither legally obligated to submit information regarding the medical condition of a patient nor can be held liable for providing this information. A specific form that provides medical documentation related to the patient's ability to drive safely has a corresponding patient section that must be completed as well. The physician can request that any or all of the three components of a driving test (written, vision, and road) be performed. The state Medical Review Board may also compel the patient to take any or all of these tests (4).

In contrast, in Pennsylvania "all physicians and other persons authorized to diagnose or treat disorders and disabilities must report to The Pennsylvania Department of Transportation any patient 15 years of age or older, who has been diagnosed as having a condition that could impair his ability to safely operate a motor vehicle." Reporting is confidential. Physicians who report are granted immunity from breach of confidentiality, and are immune from civil or criminal liability related to a patient driving and becoming involved in an accident. Failure to report leaves the physician open to possible conviction of a summary criminal offense (for not reporting) and to possible liability in case the patient has a motor vehicle accident (73).

While the patient–physician relationship is usually built on trust, noncompliance with physician recommendations and treatment occurs frequently. The incidence of noncompliance with medical recommendations not to drive has not been studied in stroke survivors, but it has been studied in people with seizures. Salinsky et al. gave an anonymous questionnaire to 158 outpatients in an epilepsy clinic and found that if the patients were required by law to report seizures to the department of motor vehicles (but the physicians were not so required), 96% would tell their physicians if they had breakthrough seizures, but only 56% would report this to their department of motor vehicles (74). Under mandatory physician reporting, only 84% would inform their physician. A total of 17% endorsed that they would

inform the physician but continue to drive, despite advice from the physician not to drive and despite the automatic license suspension from the state after being reported (74). Extrapolating to stroke patients, it cannot be assumed that just because the physician tells the stroke survivor not to drive, the patient will automatically comply.

2. Does my patient with a stroke have to stop driving? To return to driving, is it necessary to undergo an ORA?

According to the Canadian Medical Association (72), patients who have had a stroke "should not drive for at least 1 month. During this time they require assessment by their regular physician. They may resume driving if functionally able, if a neurologic assessment discloses no obvious risk of sudden recurrences, and if all underlying causes have been addressed with appropriate treatment. When there is a residual loss of motor power, a road test may be required." While there is no absolute, evidence-based foundation for the one-month restriction, many provincial legislative bodies agree with this decision. Delaying return to driving to give the patient time to recover more fully, regain stability, or undergo testing makes sense medically.

3. What is the liability of the physician if a reported patient is involved in a motor vehicle accident?

Most, but not all, states and provinces protect the physician from at least some liability (damages or breach of confidentiality) if a patient has been reported for medical reasons to driving authorities. If a stroke patient who is not reported is personally involved in an accident (whether at fault or not), the physician could be sued for negligence and for damages resulting from the accident (18). The case against the physician would likely be strengthened if the plaintiffs can prove the physician was legally obligated to report the patient to state or provincial authorities or if the physician failed to counsel the patient not to drive. For example, if a poststroke seizure is not reported and the patient is not instructed to stop driving, the physician could be held liable if the patient is involved in an accident.

4. Do certain strokes require different types of reporting or attention by the physician?

In general, there is no specific type of stroke that absolutely requires a report to a driving authority. However, the Canadian Medical Association guide indicates that "untreated cerebral aneurysms" are an absolute barrier to driving any class of vehicle, and a waiting period of three months for a private driver and six months for a commercial driver is required (72). A recent "medical expert panel" reviewed guidelines for commercial motor vehicle drivers and recommended driving cessation for one year after a TIA or stroke (75). These recommendations have face validity but are based on somewhat limited scientific studies focusing on stroke and/or epilepsy risk following a TIA or stroke. They make medical sense but are quite empirically based and reflect how every case must be approached on an individual basis.

5. Can I restrict the type of driving that my patient performs?

A restricted driving license—meaning a license indicating that the person cannot drive at night, at certain speeds, or on certain roads—is available in only a few states and provinces in North America. In Utah, for example, the Utah Driver License Division indicates that a restricted license with speed and/or area restrictions may be issued if there are moderate impairments. The province of Saskatchewan has a restricted license as well. Marshall et al. studied whether people with restricted licenses were involved in more vehicle infractions or accidents than those without restricted licensing. The available data did not indicate a significant difference, but because of the use of provincial records, the driving patterns of the study subjects could not be ascertained (76). As a group, stroke patients appear to self-restrict when, where, and how much they drive (31). Older patients are known to self-restrict as well, for example, not driving as frequently in the dark or in inclement weather (31).

6. Can my patient with isolated homonymous hemianopsia return to safe driving?

Homonymous hemianopsia can affect safe operation of a motor vehicle, especially if the patient has associated perceptual deficits. In many, but not all, states, patients with homonymous hemianopsia fail to meet visual field licensing criteria (usually 110) (18). In Canada, however, hemianopsia alone is not an absolute contraindication to driving. A person with congenital homonymous hemianopsia took his case to the Supreme Court of Canada, where it was decided that if hemianopsia did not affect driving performance, it was not an absolute criterion preventing an individual from driving (77). Blindness of one eye also does not, by itself, make driving unsafe.

7. When should the physician inform the patient about the decision to report to driving authorities?

This issue should preferably be discussed as soon as the decision is made. In a state or province with mandatory reporting, the situation is made much easier. The physician emphasizes the legal obligations and necessity to report a person who may have impairments that could affect driving safety.

In jurisdictions without mandatory reporting laws, the physician reporting a patient without first obtaining consent risks liability for breach of confidentiality. However, even when reporting is mandatory and anonymous, it is ethically appropriate to share with the patient the physician's legal obligation to report. The physician should limit information in the report to the minimum needed for the state to process the report appropriately. Being open with the patient is important to maintaining the patient–physician relationship. It may also help the patient accept the reality that driving may not be safe. The physician should also obtain the patient's permission before speaking to family members and caregivers (18), unless the patient lacks the capacity.

8. What therapy is available to improve my patient's potential to drive safely?

In general, there are no specific therapies that have been shown to speed up the recovery process to enable earlier return to safe driving. The physician should address stroke-related disabilities with appropriate therapies, including strengthening, conditioning, and coordinating visuoperceptual training. The study by Akinwuntan et al. suggests that training with a computerized driving simulator may be helpful in preparing some patients to be safe drivers (55). Training in UFOV may also be of benefit for patients with right-brain lesions (78).

CONCLUSION

Driving after a stroke is possible, and clinicians are encouraged to work within the enacted legislations to enable their patients/clients to drive. However, evaluation of the patient who has sustained a stroke must take into account any possible residual physical, cognitive, and perceptual impairments that may impede safe driving. The authors have identified the imperfect but relevant research on driving after stroke, as well as the physician responsibilities and requirements to report unsafe drivers. In general, if there is uncertainty about the stroke survivor's ability to drive, a formal driving evaluation, including an on-road assessment, should be done. This may not always happen, but the authors believe that this is a principle that society should mandate. Future research should focus on the effects of specific neurologic deficits on driving, the consequences of driving cessation after stroke, better screening tools to identify unsafe drivers, and alternate systems of community transportation to support stroke survivors.

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49

Sports and Recreation

Amy X. Yin, Cheri A. Blauwet, and David M. Crandell

There is more to life than putting on your pants (1).
—Mary Vining Radomski

Sports and recreation can play an important role in stroke recovery and rehabilitation. The World Health Organization (WHO) defines *recreation* as engaging in programs of physical fitness, organized play, and sports (2). The WHO further defines *sports* as engaging in games or athletic events, performed individually or in a group. Sports need not be formal or competitive to be enjoyed. Participation in sports and recreation can be rooted in the context of specific rehabilitation goals of increased flexibility, strength, endurance, balance, and coordination. With the adoption of the Convention on the Rights of Persons with Disabilities, the United Nations has acknowledged sports, among other areas, as a human right for persons with disabilities (3). This includes the encouragement and promotion of participation, to the fullest extent possible, of persons with disabilities in sporting and recreational activities.

> Participation in disability sports rebuilds lives. When your life has been turned upside down by a disability, you need successes and you need accomplishments and you need them immediately. Participating in sports rebuilds. It's both a rehab tool and a lifestyle tool available to everyone (4).
>
> —Kirk Bauer, Executive Director, Disabled Sports USA (DSUSA)

Every individual, with or without a disability, requires access to opportunities in sports and recreation to ensure full participation in the community as well as functional independence. Sports and recreation can be powerful tools to enhance the abilities of stroke survivors, rather than focusing on the impairments or functional loss incurred at the time of injury.

The origin of sports and recreation for individuals with disabilities in the United States can be traced to informal games at veterans' hospitals in the 1940s. Many veterans from World War II returned home with newly acquired physical disabilities and emotional trauma from their experiences. By playing wheelchair basketball, veterans with disabilities rediscovered the joy of participating in sports. The first documented game of wheelchair basketball took place in California in 1946 (5). By the late 1940s, intrahospital games had led to state and national competitions in the United States.

Around this time, Dr. Ludwig Guttman, a neurosurgeon working on the spinal injuries unit at Stoke Mandeville Hospital in England, introduced sports and recreation as part of the standard rehabilitation program for his patients. In 1948, Dr. Guttmann organized an archery competition for 16 servicemen and women with disabilities called the Stoke Mandeville Games. These games were held to coincide with the opening ceremony of the 1948 London Summer Olympics. Today, the Stoke Mandeville Games are considered to be the precursor to the modern Paralympic Games (6).

> By restoring activity of mind and body, by instilling self-respect, self-discipline, a competitive spirit and comradeship, sport develops mental attitudes that are essential for social reintegration (7).
>
> —Dr. Ludwig Guttman

In 1960, the first official Paralympic Games took place in Rome, Italy, featuring 400 athletes from 23 countries. By 1976, sport categories for amputee and blind athletes had been added to the Summer Paralympic Games in Toronto. In 1980, athletes with cerebral palsy were also added to the roster (6). As of 2012, there are 10 impairment types eligible for participation in competitions. Athletes with impairments such as reduced muscle power or range of motion, hypertonia, ataxia, athetosis, visual impairment, and intellectual impairment may qualify to compete in the Paralympic Games. Individuals who have sustained a stroke may certainly experience any number of these impairments (8).

As the Paralympic movement evolved, it became clear that a focus on grassroots programs was necessary to create equal access to disability sports opportunities in the United States. At the 1996 Summer Paralympic Games, the Atlanta Paralympic Organizing Committee developed a legacy program to nurture community-based adaptive sports. BlazeSports Georgia was founded and named after the Atlanta Paralympic Games' mascot, "Blaze." Initially a local

program, this evolved into a national organization in 2002. By that time, BlazeSports America was in partnership with programs and teams in at least 60 communities and 29 states in the country. In 2006, the organization became international, expanding programming into low-resource settings such as Egypt, South Africa, Iran, and Haiti. Today, BlazeSports is recognized by the United States Olympic Committee as the national coordinating body for competitive youth sports for individuals with disabilities, including cerebral palsy, traumatic brain injury, and survivors of stroke (9).

The 2012 London Paralympic Games reached new heights of sports competition participation and coverage. A total of 4250 athletes from 164 countries competed in 20 sports and 503 medal events. 251 world records were broken. Media coverage expanded to include more than 100 countries and territories. The London Games were also the first to emphasize social and online media, with 1.9 million visitors to the official website of the Paralympic Movement (www.paralympics.org) and more than 9 million views of sporting action on the International Paralympic Committee (IPC) YouTube channel (10,11). While this was a breakthrough Games in terms of global expansion, it was exceeded by the recent 2014 Sochi Paralympic Games. The Sochi Games was record-breaking in terms of athletic performances, ticket sales, and media coverage. In fact, it attracted a record cumulative global TV audience of nearly 2.1 billion people (12).

THE ROLE OF SPORT IN STROKE REHABILITATION

Cardiovascular Fitness and Secondary Stroke Prevention

Therapeutic exercise is a mainstay of stroke rehabilitation. It may lead to improvements in physical function as well as flexibility, range of motion, muscle tone, strength, and coordination. Regular exercise has been shown to have a broad impact in individuals with disabilities. Some of these effects include improvements in restorative sleep, maintenance of bone density, improvement in weight control, and impact on preventing secondary disabling conditions (13). Specific to the stroke population, there is growing evidence that exercise may play a role in secondary stroke prevention and mitigation of cardiovascular complications (14). A decline in aerobic fitness resulting from physical inactivity may increase the risk of cardiovascular disease and subsequent strokes or myocardial infarctions (15). In a study of 33 stroke survivors, Baert and colleagues noted that those most at risk for aerobic deconditioning after stroke were individuals who were premorbidly diabetic, premorbidly less active in work or sport activities, and/or initially more severely impaired by the stroke (16). These patients would likely most benefit from aerobic conditioning. However, the cardiovascular effect of a contemporary stroke rehabilitation program is often too low to induce a positive aerobic training effect (17). In this setting, it is useful to consider the role of vigorous or intensive adaptive sports participation as a tool for improved cardiovascular fitness and with it, secondary stoke prevention.

Studies also implicate cardiovascular exercises in improving cerebral blood flow after stroke. In a study by Ivey et al., 38 participants, all more than 6 months after stroke, were randomized into a treadmill training group versus a nonaerobic stretching group. Transcranial Doppler studies were performed both before and after the intervention. Findings revealed a statistically significant improvement in ipsilesional and contralesional cerebral vasomotor reactivity in the treadmill training group. Additionally, the treadmill training group displayed a 19% increase in peak oxygen update (VO_2 max) as compared to the nonaerobic stretching group (18).

Furthermore, recent evidence reveals that physical activity can impact both cardiovascular health and several functional parameters after stroke. Michael et al. conducted a pilot intervention study using adaptive physical activity in stroke survivors (19). The intervention produced improvements in balance, six-minute walk time, and peak exercise capacity. Exercising in group sessions also promoted self-worth and reinforced behavioral change for improved daily function. Stoller et al. performed a meta-analysis of prospective controlled studies utilizing cardiovascular or aerobically based training strategies within six weeks of stroke. Across these studies (n = 11), improvements were found in peak oxygen uptake (VO_2 max) and walking distance (20). These findings were supported by a 2009 Cochrane Review on physical fitness training for individuals with stroke. In this systematic review of 24 randomized controlled trials with a total of 1147 subjects, cardiorespiratory training involving walking-based activities (e.g., treadmill training) was found to improve both walking endurance and walking speed. Although this supported the use of cardiorespiratory interventions in stroke rehabilitation for functional gains, the authors could not determine the effects of these training programs on death, overall level of dependence, and degree of disability (21).

Prior to engaging in vigorous physical activity, stroke survivors must be aware of the inherent risks and benefits of participation. To date, evidence supports the overall safety of exercise as an intervention in this population (22–24). Duncan et al. reported no major adverse outcomes such as cardiac events or death during a series of aerobic exercise sessions for stroke survivors. Although subjects involved in the study did experience a total of three recurrent strokes, no strokes occurred during an exercise treatment session or at a time clearly correlated with bouts of exercise (24). A subsequent meta-analysis of aerobic exercise training in individuals with stroke found very few adverse events, and investigators concluded that it would be unlikely for exercise training to contribute to stroke recurrence (15). In sum, evidence supports the use of vigorous physical activity as safe and effective in improving both aerobic fitness and functional parameters after stroke.

Neurorecovery and the Use of Gaming Technology

Another key aspect of stroke rehabilitation is the facilitation of neurorecovery. Earlier and more aggressive rehabilitation takes advantage of neural plasticity and brain remodeling to regain function (25). Starting therapy with higher-level activities soon after stroke can improve functional outcomes even in individuals with severe cognitive and motor impairments (26,27). A study by Horn and colleagues (28) indicated a strong and consistent association between improvement in outcomes and activities that challenge individuals beyond their current functional level. In this cohort of 830 people, participants practiced upper-extremity functional activities as rehabilitation exercises rather than focusing on trunk strengthening alone. Results revealed a relative increase in trunk strength as a secondary outcome of the upper-extremity activities. The authors concluded that there may be many benefits to attempting high-level activities that otherwise would seem excessively challenging according to common clinical practice. Thus, sports and recreation for stroke survivors may be an important component of a comprehensive stroke rehabilitation program (29) and can encourage patients to push themselves beyond their own expectations.

Specifically, gaming has become an increasingly utilized recreational activity to help stroke recovery. Studies on stroke rehabilitation point to task repetition as a way to enhance brain remodeling and maintain long-term function (30). Effective therapy for motor learning after stroke includes progressively challenging, high-repetition, goal-oriented, skilled movement tasks (31). These interventions target neural plasticity for lasting change, but it is difficult to achieve the high frequency and intensity of movement needed in any given therapy session. Patients are also often unable or unwilling to adhere to the prescribed home exercises. Novel recreational activities using robotics and virtual reality (VR) gaming technology may assist individuals in achieving the specific task-related training needed to capitalize on early neuroplasticity.

Several small studies have demonstrated that interactive gaming and VR technology combined with conventional therapy may yield increased functional gains. A meta-analysis by Saposnik et al. evaluated the use of computer-based VR technology for upper-extremity motor recovery after stroke in 195 individuals (32). The authors analyzed data amassed from both randomized controlled trials and observational studies. The pooled data from 5 randomized controlled trials indicated that the VR group was 4.89 times more likely to achieve motor improvement compared to the control group. The 7 observational studies showed a 20.1% improvement in motor function in the VR group as measured by the Wolf Motor Function Test, Box and Block Test, and Jebson-Taylor Hand Function Test. This study was supported by a Cochrane review of 19 studies with 565 total patients in which VR and interactive gaming were shown to be more effective than conventional therapy in improving both upper-limb function and activities of daily living (33). Other studies also suggest that interactive gaming and VR may have a role in cognition as well as lower-extremity function and dynamic balance (34,35).

Gaming and VR systems may vary from intricate robotics or complete immersion systems to low-cost commercial gaming products that are readily available. Regardless of the complexity of the system, these recreational technologies have the potential to keep people on track in their rehabilitation and recovery. Gaming strategies may reinforce sensorimotor components of neural plasticity through the use of sensory input for repetitive and demanding goal-oriented movements and postures (36). It is clear that recreational gaming may be an underutilized tool in furthering the functional recovery of individuals with stroke.

Performing Arts and Sports Alternatives as Novel Rehabilitation Strategies

Recreational activities such as listening to or performing music, dancing, and participating in tai chi or yoga should also be considered as potential strategies in the rehabilitation of stroke survivors. Clinicians need to remember that individuals with stroke have diverse interests. For those who are not sports inclined, there are many alternative forms of recreation or leisure that can keep anyone engaged.

Tai chi is an ancient exercise that is beneficial and exceptionally suitable for today's stroke survivor. Taylor-Pillae and Coull enrolled 28 individuals who were at least 3 months after stroke in a 12-week pilot study (37). Participants in this study performed 150 minutes or more per week of tai chi, which aligns well with national physical activity recommendations for individuals with disabilities. The study demonstrated that tai chi exercises are safe and lead to improvements in balance in stroke survivors. It was also well tolerated by study participants and resulted in high patient satisfaction. Additionally, modified and/or adapted yoga can lead to significant changes in poststroke balance as well. In a pilot study by Schmid et al., clinically meaningful improvements in balance and balance self-efficacy were found among yoga-based rehabilitation participants (38). In postintervention interviews, study participants reported improved confidence in maintaining their balance and were more willing to attempt new activities in different and challenging environments. Even as further randomized studies are needed to determine the full spectrum of functional benefits of tai chi and yoga, the evidence remains promising.

Music and performing arts may optimize rehabilitation learning by creating a multisensory environment (39). A study by Sarkamo et al. suggested that individuals with stroke who listen to music on a daily basis may experience structural gray-matter changes as well as improved auditory and verbal memory, focused attention, and mood early after stroke (40). Although the mechanism for this was unclear, the authors put forth several theories. Cognitive arousal and emotions from music may biochemically modulate the dopaminergic mesolimbic system or enhance glutamatergic

neurotransmission. Other possible mechanisms involve neural plasticity. Music may provide environmental enrichment that increases brain remodeling, or it may decrease poststroke stress and cortisol levels, which are maladaptive. Although the mechanism by which multisensory stimulation from music and performing arts may not be well understood, there appears to be little harm and potentially much to gain with its use.

Beyond the potential for music to affect cognition and neuroplasticity, it may also have a direct impact on functional skills. Several studies have used music-movement therapy or music-supported therapy with musical instruments for rehabilitation (41,42). Rodriguez-Fornells et al. described the use of musical instruments such as the piano or drums for stroke rehabilitation (42). There are many possible reasons why music-supported therapy can be advantageous. The use of musical instruments may once again promote neuroplasticity because of the high number of repetitions that are required to play or practice with an instrument. Furthermore, music-supported therapy can shape the complexity of the movements based on function and progress. Another advantage is the immediate audio-motor coupling, whereby each movement is reinforced by auditory feedback from the instrument. Lastly, music-supported therapy may feed into emotional–motivational effects. Music can improve general mood as well as decrease anxiety and depression (42,43).

Though dance therapy is a commonly used strategy within other fields of rehabilitation, little has been published regarding its use in the stroke population. One case report did use adaptive dance, specifically the tango, as therapeutic treatment in a stroke survivor who reported great interest and enjoyment (44). More study is needed to evaluate the potential functional and rehabilitative benefits of dance therapy in stroke survivors.

Stroke survivors may choose from a wide assortment of recreational and leisure activities in order to stay active. Whether it is performing tai chi or yoga, listening to or playing music, or dancing, all these activities are fun and may aid individuals with stroke in their recovery.

Social Integration and Quality of Life

For those who wish to pursue active lifestyles after a stroke, the potential for sport and recreation to improve mental health outcomes and quality of life (QOL) is profound (45,46). A preponderance of evidence has demonstrated the positive impact of community sports participation on confidence, self-efficacy, community integration, and socialization in stroke survivors. Several recent studies illustrate this concept well. Stuart et al. randomized 78 adults who were at least 8 months after stroke into either a progressive, community-based exercise regimen at a local gym or "usual care" in an outpatient physical therapy setting within a rehabilitation facility (47). Participants engaged in a community-based exercise regimen had significant improvement in social participation domains of the Stroke Impairment Scale (SIS). This improvement was greater than that of participants who engaged in usual care. Another study by Rand et al. evaluated the association between physical activity and health-related QOL (48). Those with a higher level of daily physical activity (as measured by accelerometers) scored higher on the Medical Outcomes Study Short-Form 36 (SF-36) physical component section.

In and of itself, social participation is positively associated with a high QOL after stroke (49–51). Leisure satisfaction has been found to correlate highly with overall life satisfaction (52), and the failure of stroke survivors to resume prestroke leisure activities can interfere with poststroke functioning (49). Bhogal et al. found that a reduction in social and leisure activities both in and outside the home led to increased rates of depression, ineffective coping, and difficulties in social integration in stroke survivors. These findings were more common in those who were young at the time of their stroke (49). Even if stroke survivors regained their physical independence, they frequently did not return to the typical social activities that they had enjoyed prior to acquiring a disability (51). Kwok et al. found that the presence of depression had greater adverse effects on QOL than deficits in basic functional disabilities. Additionally, it was noted that group exercises promoted socialization and community reintegration, thus lessening the negative effects of depressive symptoms (53).

Given this positive association between physical activity, sports participation, and QOL after stroke, it is important that opportunities be available for individuals to engage in community programs within various settings. Here we offer two examples: sports participation in a clinical rehabilitation setting and sports participation within a university-based educational system.

The Spaulding Adaptive Sports Center (SASC), an initiative of Spaulding Rehabilitation Hospital, focuses on creating an innovative and exciting adaptive sports and recreation program. Taking advantage of Spaulding's unique location on the banks of the Charles River in Boston, SASC's flagship program offers a variety of water- and land-based activities. Participants represent a wide spectrum of rehabilitation diagnoses and include both inpatient and outpatient stroke survivors. SASC program staff represent the multidisciplinary construct of rehabilitation. The team consists of professionals trained in therapeutic recreation, physical therapy, and occupational therapy as well as volunteers from the nursing and medical staff. Recruitment is achieved from our inpatient rehabilitation programs, outpatient therapies within the Spaulding network, and the community. Seasonal sporting activities currently include downhill skiing, cycling, windsurfing, outrigger canoeing, kayaking, rowing, paddle boating, and wall climbing, among others. One component of the program specifically designed for stroke survivors is the use of modified hand cycle and windsurf equipment for participants with hemiparesis (Figures 49.1 and 49.2).

The emergence of organized sports programs within collegiate sports departments has also offered the opportunity for individuals with disabilities, including stroke

FIGURE 49.1 Adapted windsurfing.

or cerebral palsy, to engage in sports while also attending university. In one study, college students with disabilities were offered the opportunity to engage in sports such as swimming, horseback riding, racquetball, fitness, bowling, tennis, tai chi, walking, and/or weightlifting. Students who engaged in the activity for 5 to 24 weeks reported that their perceptions of social self were expanded by the experience, and that they initiated more social activities (46). Participants indicated that the program got them out of the house, gave them opportunities to meet new people, and offered opportunities for increased interaction with persons both with and without disabilities (46).

Participation in adaptive sport and recreation represents the desire of stroke survivors to have typical athletic experiences and to reach their optimum level of physical fitness, skill, enjoyment, and life satisfaction. The goal of comprehensive rehabilitation for stroke survivors is the attainment of an optimal level of independent living and QOL. Combining the two components into a "game plan" can promote healthy lifestyles and reduce the effects of impairment and disability. For many, adaptive sports and recreation is an integral part of stroke recovery and serves to increase enjoyment in leisure activities, enhance the sense of self-confidence and achievement, and ensure community access and social integration.

CASE HISTORIES: EXAMPLES OF THE "DIDS" AND "DID-NOTS"

To understand sports and recreation as a rehabilitation tool for stroke survivors, it is important to appreciate the individual's own concept of these topics before and after stroke. We characterize two major prestroke categories as the "dids" and the "did-nots." The "dids" are those individuals who participated actively in either recreational or competitive sports prior to their stroke. The "did nots" are those individuals who, like many sedentary adults, did not participate actively in any sports or recreation program. It is useful to examine the stroke survivor's self-concept of sports participation to best understand what strategies may be the most appropriate for him or her.

"Dids"

Case One

A 37-year-old engineer experienced a cardioembolic stroke as a consequence of aortic valve replacement surgery. Sequelae included a mild left-sided hemiparesis and mild left visuospatial neglect. Prior to his stroke, he was physically active, working in construction and playing regularly in an

FIGURE 49.2 Adapted cycling.

adult hockey league. He had also played college hockey at a competitive Division I program and was the coach of his young son's hockey team.

Two of his rehabilitation goals were to return to skating and to continue to coach his son's team. He did well in acute rehabilitation, went home, and continued to attend outpatient therapy. During his initial follow-up appointment, he reported that he was happy to be back at the hockey rink, coaching his young son. During his next follow-up, he reported that he was now also skating with his son.

After several months, he was back to playing hockey himself. His comment was that although he had "lost a step" and had some difficulty up against the boards, he was still able to play competitively and safely. Most importantly, he was still having fun. He joked that he had always been better than his younger brother at hockey, but the situation was reversed after his stroke. Despite this, he was not deterred and was determined to improve and get back to beating his brother. His participation in sports offered a healthy outlet for his drive to compete, an inherent part of his personality that was not affected by experiencing a stroke. This drive motivated him to push his rehabilitation efforts even further, and make substantial progress in only a brief period of time.

Case Two

A 34-year-old psychologist experienced a brainstem hemorrhagic stroke caused by an arteriovenous malformation at 38 weeks of her first pregnancy. She remained hospitalized and delivered her child via a cesarean section. She and her new son did quite well; her residual deficits included mild left hemiplegia, intermittent double vision, and right facial hemisensory deficit.

Six months after her stroke, she expressed frustration with her ongoing standard outpatient physical and occupational therapy program, especially with the rate and level of her functional recovery. Prior to her stroke, she was an accomplished athlete, competing in singles tennis at a Division I university. She was also the age-group winner in several local triathlons. Even well into her pregnancy, she was running and biking up to 30 miles per week. During her rehabilitation program, she had developed left patellar tendonitis and had also exacerbated back and shoulder problems from prior sports injuries.

At the time of outpatient follow-up, her rehabilitation program was refocused on her goals of wanting to walk at typical speeds without asymmetry, and also to run again. She was referred to a local sports therapy program that was experienced in working with elite athletes and utilized aquatic therapy. For her, it was an excellent fit because the treatment approach matched her identification as an athlete, not as a stroke survivor. She was used to pushing herself, and her therapist was able to raise the effort to a level and intensity that she could relate to. She was not willing to settle for any goals that did not include running again and, with time, was able to achieve this goal.

These two examples of "dids" show the importance of sports in these individuals' lives, which intuitively did not change in the setting of having experienced a stroke. In these cases, setting sport-specific goals was no different from establishing other short-term rehabilitation goals. Returning to sports helped each individual reach the highest functional level possible and continued to be a positive driving force in their rehabilitation.

"Did-Nots"

Case Three

A 54-year-old bus driver experienced a pontine stroke thought to be related to poor adherence to his prescribed antihypertensive medications. His impairments included a mild dysphagia, right-sided weakness, and poor sitting and standing balance. His family related that, prior to his stroke, he was not physically active. They described his daily activity level as "sitting behind the wheel . . . followed by sitting on the couch."

Immediately after his stroke, he was admitted to an inpatient rehabilitation facility where he made only very slow progress during his initial weeks of hospitalization. His interdisciplinary care team attributed this limited improvement in part to low motivation and discussed strategies to move him forward in his recovery. Recreational therapy and adaptive sports were recommended.

When the therapist discussed with him the different activities that were available, he couldn't believe what he was hearing. He incredulously replied, "You want me to go *windsurfing*?"

Despite his initial reluctance, he acquiesced. He was escorted to the dock by the adaptive sports staff and went for his first sail with a tandem windsurfer designed for individuals with hemiplegia. After his session, his family immediately noticed his improved vigor and spirit when he returned to the patient floor. He couldn't stop relating his positive experience to the other patients. His performance in therapy also gained some momentum. Feedback at subsequent interdisciplinary meetings was very positive, and the team consensus on his prognosis changed to believing he would likely meet his inpatient rehabilitation goals. Both the patient and his family also came to realize that if he could windsurf after his stroke, then many of the hurdles they had envisioned could be overcome with time and a proactive attitude.

Case Four

A 58-year-old senior accountant experienced an intracerebral hemorrhage as a complication of anticoagulation therapy for a deep vein thrombosis. This required an emergent right-sided craniotomy and resulted in a seizure disorder, which was managed during a series of acute and rehabilitation hospitalizations over the course of a year. The patient had a significant left-sided hemiparesis and impairments in attention, memory, and motivation. He was also clinically depressed. Despite his employer's promise that "you'll have your job when you return," he found himself unemployed with little prospect for a new job during a severe economic recession. This contributed to his ongoing frustration with his recovery.

His wife described her husband as a "nonadventurous type" who was quite sedentary in his work before the stroke, though he did sing in a choir. As his efforts in sending out resumes remained unfruitful, he related that he was not sure how he could perform in an interview, even if he did get a call back. Shortly thereafter, he was referred to an Adaptive Sports Program. He had always admired the many rowers he had seen over the years on the Charles River not far from his former office, so he selected rowing as his first activity. With a minor adjustment to secure his oar, he was out enjoying his new view of Boston. He was thrilled, as was his wife, and he continued to attend adaptive sessions with improved performance and a buoyed outlook on his abilities. He joined Boston's Community Rowing Program and now rows independently in a modified shell. He has also returned to his choir, which continues to give him a spiritual lift.

He is still working on his ultimate goal of returning to work as an accountant. Despite his inability to find compensated work, he has been quite satisfied in volunteering part-time for a community housing agency. With this, he has learned new skills and has improved his communication while handing out books from a loaner cart and relating his story to medical and physician assistant students throughout the year.

These two cases of the "did-nots" illustrate the need for stroke survivors and their families to understand the benefits of sports and recreational participation for recovery. For both the "dids" and "did nots," being an "I do" is an important part of stroke rehabilitation, increasing the use of leisure time, sense of enjoyment and achievement, self-confidence, and community access. Not only can sports and recreation aid physical strengthening and conditioning, they can help reshape the view stroke survivors have of themselves and their abilities.

FUTURE IMPLICATIONS

Advocacy for Exercise Prescription and Community Access

As outlined in this chapter, physical activity, sports, and recreation may greatly affect outcomes related to enhancing secondary stroke prevention, neurorecovery, and QOL. Strong consideration must be given to the routine use of an exercise prescription when recommending rehabilitative tools for stroke survivors. Whether at the time of hospital discharge, in the outpatient clinic setting, or as a component of community reintegration strategies, the concept of "Exercise is Medicine" (54) is aptly suited to this population.

Currently, at the time of discharge from inpatient stroke rehabilitation, patients are connected with either home-based or outpatient-based physical, occupational, and speech therapy services. Given that these services are typically offered through a well-established structured rehabilitation program, this transition is quite fluid. Patients are ensured continuity in establishing a schedule, finding location for therapies, and recruiting appropriate professionals for the provision of rehabilitation services. It is important to reinforce the importance of exercise and physical activity throughout this process. Furthermore, as stroke survivors undergo the stepwise transition from home or outpatient-based services to greater independence, sports and recreation are even more vital in helping patients attain long-term maintenance of an active lifestyle. Indeed, this is where many stroke survivors fail to engage in programs, such as adaptive sports or community-based exercise (e.g., local gyms), that may ensure ongoing cardiovascular fitness, previously achieved level of mobility, and health-related QOL. Physicians and rehabilitation professionals can play a critical role in supporting the success of this more complex transition from structured rehabilitation to a program based on community independence.

The achievement of this goal requires a multifaceted strategy aimed at decreasing barriers related to public access of fitness facilities and sports programs. Additionally, negative attitudes that propagate misconceptions about the willingness of individuals with physical and/or cognitive disabilities to engage in sports and exercise must be changed. In a 2008 survey of 83 adults with unilateral

stroke, the 5 most commonly perceived barriers to exercise were: (a) cost of the program (61%), (b) lack of awareness of an accessible fitness center in the area (57%), (c) no means of transportation to a fitness center (57%), (d) no knowledge of how to exercise (46%), and (e) no knowledge of where to exercise (44%). Conversely, the least common barriers from the perspective of stroke survivors were (a) lack of interest (16%), (b) lack of time (11%), and (c) concern that exercise would worsen their condition (1%) (55). From the standpoint of structural barriers, needs analyses are required to establish the gaps in community resources. Areas for investigation include accessible fitness facilities, fitness programs appropriate for individuals with mobility impairments, and adaptive sports programs serving the needs of both developmental and elite athletes (56). Regarding attitudinal barriers, there is an overwhelming need to provide further educational programs to professionals outside the scope of traditional rehabilitation (e.g., athletic trainers, fitness class instructors, coaches) to ensure that these individuals have the appropriate skill set to work with the unique population of stroke survivors. Finally, the creation of direct referral services from rehabilitation-based settings to community-based settings can serve to transition stroke survivors at the completion of structured therapies.

Rehabilitation professionals, including physiatrists, therapists, nurses, case managers, and social workers, are uniquely suited to be the drivers of change on this critical topic. Through a multidisciplinary approach, ongoing advocacy initiatives will push our communities, as well as stroke survivors themselves, to a more comprehensive understanding of the need for engagement in physical activity, sports, and recreation.

Final Quips: "The Bruschi Effect"

On February 18, 2005, public health officials in Boston, Massachusetts, reported a significant increase in neurologic and stroke-like complaints in emergency departments around the city. An unusually large number of young men came in complaining of headache, blurred vision, and unilateral weakness. The greatest increase (25%) in these visits was found among young men ages 20 to 49. There was no geographical clustering and no known toxic exposure or unusual illness reported (57). This phenomenon was termed the "Bruschi Effect" (Figure 49.3) and occurred after the media broke the story that New England Patriots professional football player Tedy Bruschi had suffered a mild stroke and was hospitalized at the Massachusetts General Hospital. Even though there had been a significant increase in stroke-related complaints, public health officials did not detect any corresponding increase in the actual diagnosis of stroke. A compensatory decrease in the number of stroke-related visits was observed the following week.

> When there is heightened media coverage of a particular illness—in this case, stroke—it is not unusual for the public to react. (57)
>
> —Dr. John Rich, Medical Director of the Boston Public Health Department

In 2005, Tedy Bruschi was a 31-year-old defensive linebacker and 9-year NFL veteran at the top of his game. He was a pivotal player in the Patriots' 2005 Super Bowl victory with a key fourth-quarter interception. It was just 10 days later that he was taken urgently via ambulance to the hospital after complaining of left arm and leg numbness,

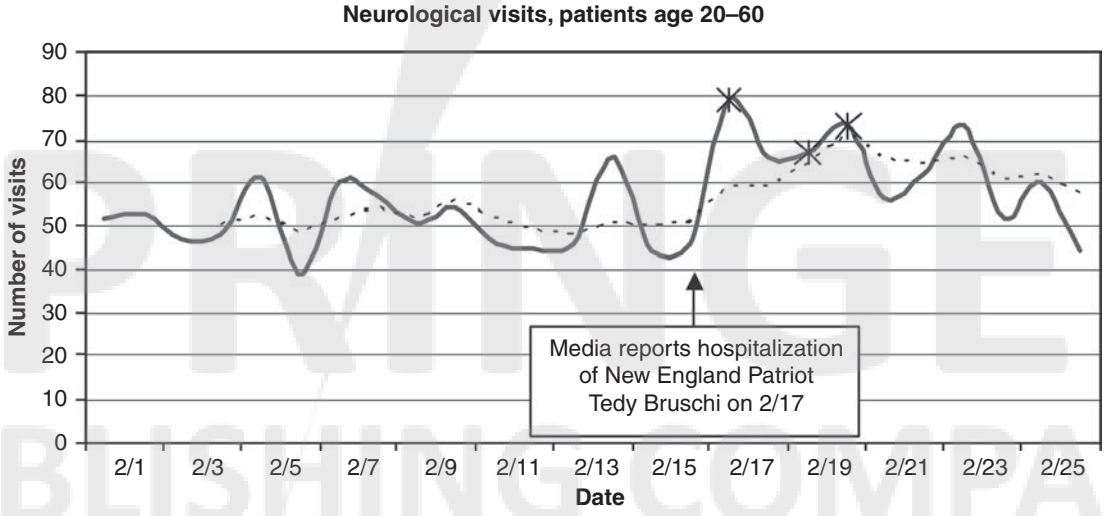

FIGURE 49.3 "Bruschi Effect."

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blurred vision, and headache. He had experienced a small right-sided stroke, and an echocardiogram revealed a patent foramen ovale (PFO). He did well with his rehabilitation and the PFO was subsequently closed. After only eight months, Bruschi returned to playing football professionally.

His stroke and return to play resulted in a secondary and more lasting "Bruschi Effect," in which there continues to be an overwhelming emotional response to his unprecedented comeback. Bruschi has received thousands of letters from stroke survivors, noting that his personal story of stroke recovery has been inspirational, offering hope and an optimistic perspective to individuals around the country who have also experienced stroke.

> I don't think America knows very much about strokes, that you can get back to your life after you have a stroke. There can be a full recovery. If your normal life after a stroke is just getting back to work, maybe your normal life is playing professional football. That was my normal life. That's what I wanted to get back to. I was fortunate enough that I was able to rehabilitate myself 100% and get back to playing football again. (*USA Today*)
>
> —Tedy Bruschi

For Bruschi, returning to playing football was living his life his way. He has used his experience to raise awareness about stroke through the American Heart Association. He has been a popular and successful spokesman both on and off the field and has inspired many stroke survivors to return to sports and recreation.

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50

Sexuality After Stroke

Monika V. Shah and Marni G. Hillinger

The importance of sexuality in the scope of human experience is profound. Sexuality is more than sexual intercourse alone. It is a complex, multidimensional phenomenon that incorporates biologic, psychological, interpersonal, and behavioral dimensions. The ability to form and sustain an intimate relationship is a fundamental aspect of human life. The impact of sexuality on quality of life after stroke and other neurologic diseases is even more powerful. Unfortunately, studies on quality of life in general and on sexual life specifically after stroke are relatively few. Although stroke is the leading cause of long-term disability worldwide, few epidemiological data are available on sexual functioning and sexual satisfaction after stroke.

The goal of this chapter is to highlight the potential challenges related to sexuality, sexual function, and intimacy that arise after stroke from a rehabilitation perspective. Because there is a higher incidence of stroke in the elderly population, the effects of aging and medical comorbidities are also reviewed. For the purpose of clinical practice, there is also a discussion of the general evaluation and management of sexuality in the poststroke population.

PHYSIOLOGY OF SEXUAL FUNCTION

Our understanding of sexuality has its foundation in the work of Masters and Johnson published in 1966 (1). It is from their work that the sexual response cycle was categorized into four phases: excitement, plateau, orgasm, and resolution (Figure 50.1). This classification provided a means by which health care professionals could more clearly identify and treat sexual dysfunction. Later, in 1974, Kaplan simplified this into three phases: desire, excitement, and orgasm (2). Regardless of the model used, it was clearly understood that sexual function relies on a complex network of both central and peripheral neural pathways.

Sexuality involves the integration of sexual interest, physiological functioning, and sexual satisfaction (Figure 50.2). The cerebral cortex represents only one level of sexual functioning at which the brain influences human sexual arousal and response. Subcortical structures, including the limbic system and parts of the hypothalamus, also play an important role in the integration and control of reproductive and sexual functions. Sexual interest may arise from thoughts, emotions, and memories, which are all mediated through complex cerebral mechanisms. Thus, sexual arousal can occur without any sensory stimulation. Sexual satisfaction is achieved not just by processes of physical arousal, but is also influenced by the feeling of intimacy as well as the health of one's own self-image. These additional aspects of psychological health can operate on both a conscious and subconscious level. By understanding the physiological, cognitive, and emotional aspects of sexuality, clinicians can better understand the impact of stroke-related disability on human sexuality.

Prevalence of Sexual Dysfunction

In the General Population

Sexual dysfunction is defined as any of a group of sexual disorders characterized by disturbance either of sexual desire or of the psychophysiological changes that usually characterize sexual response. Accurate estimates of prevalence are important in understanding the true burden of male and female sexual dysfunction as well as identifying risk factors for prevention efforts. Most studies of prevalence figures are quite variable, as they depend on case definition, characteristics of the study population, and time frame of the prevalence estimates. The paucity of information led to a gathering of 200 multidisciplinary experts from 60 countries, including members of major urology and sexual medicine associations, who attempted to provide accurate estimates of prevalence, epidemiology, and risk factors. This international consortium described a prevalence of about 40% to 45% of adult women and 20% to 30% of adult men having at least one manifest sexual dysfunction. There was a consensus that the incidence increases as men and women age. Common risk factor categories associated with sexual dysfunction include individual general health status, psychiatric and psychological disorders, and sociodemographic conditions (3). Most studies also confirm these rates of prevalence and find that, although many men and women experience sexual dysfunctions, few seek medical care to address them (4). Recent evidence also suggests that patients are more likely to seek medical care related to sexual dysfunction if their physician inquires about sexual concerns on a routine visit (5).

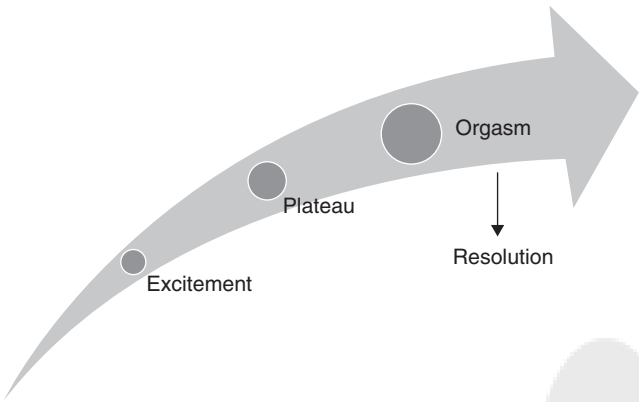

FIGURE 50.1 Classification of sexual functioning.

Source: From Ref. (1). Masters WH, Johnson VE. *Human Sexual Response.* Boston, MA: Little, Brown; 1996.

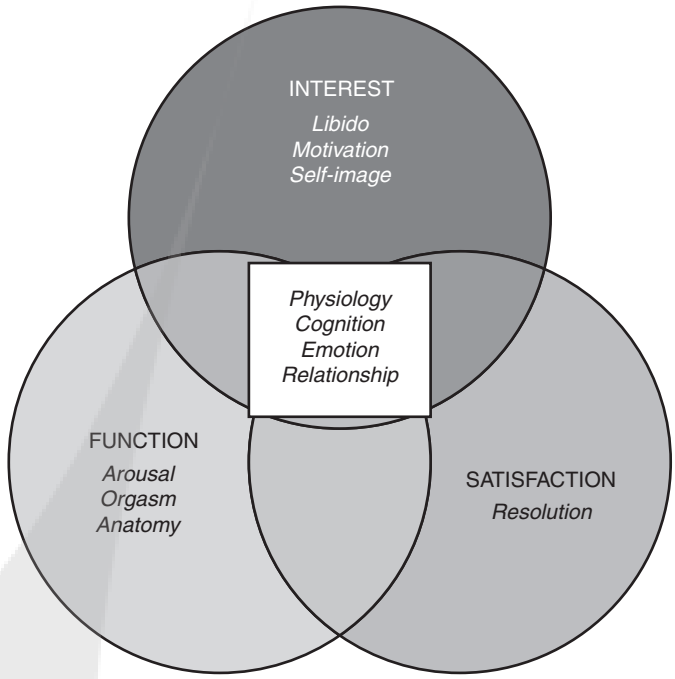

FIGURE 50.2 Concepts in sexuality and sexual functioning.

In the Stroke Population

Studies on the prevalence of sexual dysfunction after stroke are sparse compared with studies of the general population. Most poststroke studies include a small sample size of subjects with a median age of 50 years. In general, the prevalence of sexual problems after stroke or any other neurologic disability is consistently higher than in the general population, with a range of 57% to 75% (6). As the incidence of stroke itself includes a much wider age group, it becomes even more important to include both extremes of age in studying prevalence, risk factors, and treatment of problems related to sexuality.

Some studies on sexuality after stroke emphasize the importance of psychological factors in poststroke sexual functioning (7). Korpelainen and Monga suggested in separate reviews that sexual problems following stroke are never a consequence of stroke alone; rather, they may be caused by a variety of associated medical conditions and psychosocial factors (8,9). Most studies focus on sexual interest and physiological aspects of sexual ability following stroke, and there still remain few studies that address the psychosocial or intimacy issues among stroke patients and their partners.

Classification of Sexual Dysfunction

As described earlier, Masters and Johnson classified their findings into a linear sexual response cycle of excitement, plateau, orgasm, and resolution (Figure 50.1). Men and women were described as having similar physiologic characteristics. More recent research suggests that women do not always fit into this model and that their sexual experience follows a more complex pattern that extends beyond achieving adequate vaginal lubrication and having an orgasm. Thus, it is a challenge to formulate a single model that can adequately represent a single population or group. Indeed, the sexual experience in stroke survivors encompasses the impact of changes in self-esteem, body image, relationship and intimacy, pleasure, and satisfaction, in addition to the severity of disability, pain, weakness, spasticity, and many other physical variables.

Therefore, many approaches to the classification of sexual dysfunction have emerged since the time of Masters and Johnson. One modification of the Masters and Johnson model, described by Helen Kaplan Singer, adds desire as an initial response; Kaplan includes the role of subjective feeling, which involves interpersonal and psychological as well as biologic factors.

The most common classification system used by clinicians for the diagnosis and treatment of sexual dysfunction is the *DSM-5* criteria, which is also adapted from older models previously described. Table 50.1 lists the classification system for both males and females. Because of the complexity of female sexual dysfunction, the American Foundation for Urologic Disease developed another system, a consensus-based classification (Table 50.2). Although these classification systems have been revised over time to include psychological causes in addition to the organic causes of sexual dysfunction, with a particular emphasis on problems in women, there remain other important limitations. For example, disease-specific issues that can affect sexuality and sexual functioning should be assessed during comprehensive evaluation, but they are not well addressed by these classification systems.

Psychosocial Factors in Sexual Dysfunction

Korpelainen reported that psychosocial factors play a large role in determining sexual drive, activity, and satisfaction

TABLE 50.1 *DSM-5* Classification of Sexual Dysfunction

Male

- Delayed ejaculation
- Erectile disorder
- Male hypoactive sexual desire disorder
- Premature (early) ejaculation

Female

- Female orgasmic disorder
- Female sexual interest/arousal disorder
- Genito-pelvic pain/penetration disorder

Affecting both males and females

- Substance/medication-induced sexual dysfunction
- Other specified sexual dysfunction
- Unspecified sexual dysfunction

Source: Adapted from *Diagnostic and Statistical Manual of Mental Disorders (DSM-5)*. 5th ed. Washington, DC: American Psychiatric Association; 2013.

following stroke (8). Bodrini and colleagues also highlighted the crucial role that psychological and interpersonal factors play in sexuality following stroke (10). Along with common psychiatric problems seen after stroke, such as depression, anxiety, or posttraumatic stress disorder, impairment of social dimensions, such as lack of a partner or loss of job, may also play a significant role in sexuality issues after stroke.

Dependency in ADLs

It has been suggested that the degree of dependence in ADLs is a strong predictor of a decrease in sex frequency (11,12). This dependency can cause feelings of embarrassment and vulnerability as one's privacy is compromised. This may be particularly problematic when the sexual partner also provides personal care, and this is consistent with the finding that sexual dysfunction is also common in sexual partners of stroke survivors (8). This shift in role from caregiver to partner or patient to partner can have a negative effect on sexual identity. One solution is to have some aspects of care, such as toileting, carried out by a nonfamily caregiver whenever possible.

Role Shift Within the Family

The profound role shift within a family after stroke may present as anger and frustration on the part of the patient and spouse. Loss of previous roles results in a serious change in the quality and style of the interpersonal relationship, and it takes time and patience to rediscover a loving partnership. Recognizing and anticipating such changes early after stroke and providing opportunities for counseling can allow better adjustment to role changes in a partnership. Thompson and Ryan (2009) found that poststroke spousal relationships were significantly different in the realms of sexuality, sexual desire, and sexual functioning (13).

TABLE 50.2 American Foundation for Urologic Disease Classification for Female Sexual Dysfunction

1. Hypoactive sexual desire disorder
   a. Hypoactive sexual desire
   b. Sexual aversion disorder
2. Sexual arousal disorder
3. Sexual orgasmic disorder
4. Sexual pain disorders
   a. Dyspareunia
   b. Vaginismus
   c. Other sexual pain disorders

Source: Basson R, Berman J, Burnett A, et al. Report of the international consensus development conference on female sexual dysfunction: definitions and classifications. *J Urol*. 2000;163(3):888–893.

Altered Body Image and Self-Esteem

Across the spectrum of medical diseases and disability, changes in self-image can have a profound impact on quality of life and satisfaction (14). Specifically, neuromuscular changes that affect movement, the use of assistive devices or adaptive equipment, and changes in bodily function can result in feelings of decreased attractiveness and self-esteem, followed by shame, frustration, and even depressed mood. There may be real or perceived fear of rejection, betrayal, and/or abandonment by the partner, resulting in loneliness or isolation and avoidance of social or sexual situations.

Lack of Sexual Partner

Because stroke survivors are often of advanced age, many have survived their sexual partner. For those who are not in a relationship, it is often assumed that sexuality is not an issue. But lack of a sexual partner does not erase a person's concern about attractiveness, sexual functioning, and potentially finding a partner in the future. Unfortunately, social opportunities for meeting others and finding potential sexual partners are often limited after stroke, which reduces the likelihood of engaging in sexual activity. It is important to provide reassurance that sexual functioning and intimacy are still possible and to assist patients in full reintegration to the community through comprehensive rehabilitation.

Fears, Myths, and Unrealistic Expectations

There are certain fears and myths around sexuality and sexual performance that are common among stroke survivors. Most commonly, the fear of a recurrent stroke can result in reduced sexual activity, decreased libido, and sexual dissatisfaction (15). Monga and others interviewed patients with stroke and their spouses about sexuality. The most common factor identified as causing a decline in sexual activity was the fear by both partners that having sex might adversely affect blood pressure and cause another stroke (9); similar fears have been described in patients with coronary artery disease (CAD) (16). In reality, the cardiac response associated with sexual activity is equivalent to climbing two flights of stairs at a brisk rate (17). The

energy expenditure is equivalent to 2 to 3 metabolic equivalents of task (METS) during the preorgasmic phase and 3 to 4 METS in the orgasmic phase (18). This level of exertion, though significant for some patients with stroke, is unlikely to overly stress cardiac function or result in a dangerous rise in blood pressure. Therefore, education, reassurance, and a focus on general physical fitness may be appropriate in certain stroke patients.

Unrealistic expectations of what constitutes a normal sex life may lay a foundation for failure. Normal sexuality is unique to each couple, as is their unique relationship. A healthy couple's perception of normalcy should align more with their personal life expectations than that of society or the media. It may be useful to discuss these misconceptions early with both patients and their partners. The recognition of unrealistic expectations, fear, and myths can serve as an educational opportunity.

Physiological Factors

Neuromuscular changes, including fatigue, weakness, and spasticity, can play a role in sexual function after stroke. Neuroendocrine factors also play a role in normal sexual function.

Neuroendocrine Abnormalities

Any brain lesion, as occurs during stroke onset, can affect the neuroendocrine system and produce an imbalance of hormone production and release, leading to erectile dysfunction, decreased arousal, and/or infertility. From a strictly physiological standpoint, normal sexual functioning involves the interaction of libido and potency. In males, erectile dysfunction (ED) is the most commonly cited complaint in able-bodied patients as well as those with disability. It is well known that testosterone levels steadily decrease with advanced age; however, hormonal replacement has shown limited success in resolving erectile dysfunction. In females, low sexual desire and reduced coital frequency are most often reported. These symptoms tend to correlate with reduced estrogen levels. The female reproductive system and menstrual cycle are controlled by the interplay of hormones and endocrine organs. In general, other physiological changes may include decreased vaginal lubrication, anorgasmia or delayed orgasm, priapism, retarded or premature ejaculation, retrograde ejaculation, breast hyperplasia, gynecomastia, and others.

Location of Stroke

It is likely that the location of the stroke-related brain injury is related to sexual dysfunction. A lesion located in deeper structures of the brain that regulate sexual function, such as the pituitary gland or hypothalamus, may result in disrupted neuroendocrine and hormonal functioning. Specifically, subarachnoid hemorrhage is commonly associated with neuroendocrine dysfunction (19). Disturbance of sexual functioning is related to severity of neurologic impairment, but no specific pattern has been detected. Early reports suggested that frontal strokes and strokes in the left hemisphere are more strongly associated with depression, which can impair sexuality, but other studies have disagreed. A systematic review by Carson and others in 2000 concluded that there is no evidence for an association of left hemisphere or frontal lobe stroke with depression (20,21). Jung et al. (2008) noted that lesions in the right cerebellum were associated with disorders of ejaculation, whereas patients with left basal ganglia lesions demonstrated decreased sexual desire (22).

TABLE 50.3 Non-PDE5i Options for the Management of Erectile Dysfunction

1. Intracavernous injection therapy—alprostadil, papaverine, phentolamine
2. Vacuum tumescence
3. Hormonal therapy
4. Penile prosthesis

Erectile Dysfunction

ED is the inability to achieve or maintain sufficient erection for satisfactory sexual functioning. ED is the most common cause of sexual dysfunction in the general male population (23). It is estimated that 50% of men over the age of 40 have experienced some degree of ED. It is likely that the incidence in male stroke survivors is even higher given the multifactorial nature of this problem. Atherosclerosis, an important risk factor for stroke, may cause reduction of blood flow that affects end organs, including genitalia. In males, this may reduce the success and effectiveness of erection. In females, there may similarly be a reduction in vulvar lubrication and engorgement. In addition, medications used to manage stroke risk factors and prevent secondary stroke may contribute further to ED. With the advent of phosphodiesterase 5 inhibitors (PDE5i), a group that includes sildenafil, tadalafil, vardenafil, and the newer udenafil and avanafil, there is medical treatment for ED; however, these medications are not a panacea. It is important to identify any underlying psychological factors that may significantly contribute to ED. Table 50.3 includes alternative forms of treatment for ED.

Decreased Libido

Low sexual desire is the most prominent sexual finding in females with or without a disability. Disorders of tactile sensation and disturbed lubrication are found to have some relation to a decline in desire. Moreover, disability-related physical limitations as well as altered body image appear to be the most cited reasons for low sexual desire and reduced sexual activity. Coexistent medical issues and medication side effects will also contribute to physiological changes similar to ED in men. Other reasons for low sexual drive include underlying psychological factors such as fear of rejection by a partner, anger in the relationship, or other interpersonal conflicts. Treatment will depend on the underlying cause.

Fatigue

Fatigue is a common sequela of stroke, impacting daily activities as well as psychological well-being. Fatigue can limit sexual activity and cause a reduction in libido in both men and women. As many as two-thirds of patients experience some level of poststroke fatigue (24). The cause of fatigue after stroke is unclear and may be a result of multiple factors; Choi-Kwon et al. (2005) demonstrated that prestroke fatigue, a high score on the modified Rankin scale, and poststroke depression may be possible risk factors (25). The increase in energy output that patients with stroke require to complete usual daily activities such as transfers, walking, bathing, toileting, and dressing may cause fatigue. Fatigue may also be a consequence of altered sleep–wake cycles. Various medications that are used for secondary stroke prevention or to treat stroke-related symptoms might have sedative effects. Treatment of fatigue may include management of insomnia and the sleep–wake cycle, use of neurostimulant medications, change in medications, or change in timing of medication administration. Counseling on timing and flexibility with sexual activity is also an important strategy for managing the effects of fatigue.

Weakness

Of the various neurological impairments following stroke, weakness is perhaps the most common (26). The pattern and severity of weakness after stroke need not prevent sexual activity if there is effective communication with the partner. Alteration in usual sexual positioning will often compensate for weakness quite effectively and increase sexual satisfaction. In patients who do not have severe paralysis, there may still be some evidence of weakness in relation to poststroke fatigue that can impact sexual performance and vary from day to day. It is important to include resistive training for both upper and lower limbs in a comprehensive rehabilitation program, as it can produce significant strength gains for patients even after six months after stroke. Training patients and their partners with illustrations of sex positions appropriate for patients with weakness and hemiplegia can be helpful.

Spasticity

Besides the challenges of mobility and positioning during sex, spasticity may prevent a couple from returning to sexual activity because of the unpredictability of dystonic movements and muscle spasm during sexual intercourse. Significant spasticity may preclude certain usual sexual positions when the patient assumes dystonic postures, so communication with the sexual partner is important. Discussion of sexual functioning should be included in comprehensive spasticity evaluation. In females, the presence of adductor spasms may require targeted treatment. Focal chemodenervation or motor point blocks of the hip adductors may be effective. The use of intrathecal baclofen has been studied in patients with spinal cord lesions from multiple sclerosis and spinal cord injury. Although intrathecal baclofen can reduce severe adductor spasticity, it may compromise both erection and ejaculation (27). This may be reversible, but patients should be informed of this side effect. Adjustment of the intrathecal baclofen dose may also help resolve these problems.

TABLE 50.4 Tips for Poststroke Patients With Neurogenic Bladder

1. Empty bladder shortly before sexual activity.
2. Indwelling catheter may be temporarily removed and replaced under the direction of the physician.
3. In females, catheter may be taped to one side.
4. Reduce fluid intake 4 hours prior to sexual activity.
5. Plastic covering may be used on the bed to protect covering.
6. Cleaning supplies should be kept close to bedroom or bed.
7. Avoid positions that may put pressure on the bladder.

Poststroke Pain

Although stroke sequelae may often produce decreased sensation, there may be other areas of the body with heightened or even painful sensation. In the case of dysesthesia, proper diagnosis is necessary to differentiate central poststroke pain, complex regional pain syndrome type 1, diabetic peripheral neuropathy, or other causes of tactile pain. Appropriate treatment can be provided if the correct diagnosis is made. Although rare after stroke, vaginismus and vulvodynia of muscular or noninflammatory origin can occur. Some studies suggest that botulinum toxin can be effective in treating these conditions by effectively blocking nociception (28,29).

Neurogenic Bladder

Neurogenic bladder after stroke can include detrusor hyperreflexia, or, simply, incontinence from uninhibited bladder. This may be a source of fear or embarrassment in patients who wish to resume sexual activity. Avoidance of sexual activity is commonly reported in patients with urinary incontinence. Education on timed voiding and voiding before sex can minimize frequency of incontinence. For patients using a chronic indwelling catheter, it is important to provide information on catheter management during sexual intercourse (Table 50.4).

Chronic Medical Conditions and Medications

Chronic medical conditions that coexist with stroke can cause sexual difficulties either directly or indirectly. Specifically, mood disorders such as depression are commonly observed after a stroke, and frequently affect sexual relationships. Also, common risk factors for stroke, such as hypertension and diabetes, are important contributors to sexual dysfunction. For example, vascular disease associated with diabetes can impact arousal, and cardiovascular disease may

inhibit intercourse because of dyspnea or fatigue. Secondary effects of stroke such as urinary incontinence may also cause sexual dysfunction or decreased sexual activity because of embarrassment and fear of having an accident. Medications used to treat many medical conditions are often associated with changes in sexual functioning. Unfortunately, the sexual side effects of chronic medical conditions and the medications used to treat them are often underreported and underdiagnosed. Therefore, it is important for the clinician to recognize and inquire about these effects and address any issues around sexuality for patients with stroke.

Poststroke Depression

The prevalence of major depression after stroke is reported to range from 16% to 40% within the first year (30–32). Although underreported, it is well known that sexual dysfunction is common among individuals with major depressive disorder (MDD) (33–35). In a study by Kennedy and colleagues, 40% of men and 50% of women with major depression reported decreased sexual interest and reduced arousal (36). Mood and sexual function have an interactive association such that anxiety or depression may adversely affect sexual function and sexual dysfunction may lead to depression.

The changes in mood may be related to the severity of neurologic deficit (9,10); it has also been reported that younger age, greater stroke-related disability, and inability to work at three months might relate to persistent depression (32). Together, these lead to a general loss of self-esteem. Although sexual dysfunction is not considered a direct symptom of MDD, it may represent depression-related anhedonia. However, in contrast to patients with mild stroke, those with more severe physical impairments are at risk for developing emotional disorders and a consequent decrease of sexual intercourse and perceived sexual dysfunction. The treatment of poststroke depression has been examined in several placebo-controlled, randomized clinical trials that show efficacy with drugs such as nortriptyline and citalopram (37–39). Studies also support early treatment with antidepressants, which can significantly increase the survival of both depressed and nondepressed patients (40). It is important to recognize that treatment of depression may improve sexual functioning, but use of antidepressant medication may also cause sexual dysfunction (41,42). As an alternative, enhanced social support when possible may have a positive influence on poststroke depression, improving the patient's esteem and sexual identity. With appropriate treatment, the progression of recovery following stroke can be altered, including improved recovery in ADLs and cognitive impairment.

Antidepressants

Selective serotonin reuptake inhibitors (SSRIs) are typically considered the medication of choice for the treatment of poststroke depression. They are popular in part because of their good safety profile and relatively benign adverse effects, especially compared with the older tricyclic antidepressants and monoamine oxidase inhibitors (MAOIs). However, many of the antidepressant classes are not free of treatment-emergent adverse events. Specifically, one of the most prominent adverse effects seen with antidepressants is sexual dysfunction.

In particular, the SSRIs have been shown to cause sexual dysfunction in 30% to 70% of patients treated for depression (43). The clinical implication is that compliance rates of antidepressant therapy may decrease with the recognition of sexual side effects. Therefore, it is important for clinicians to monitor and recognize sexual side effects when starting empiric antidepressant therapy.

Several strategies can be employed to manage antidepressant-induced sexual dysfunction (Table 50.5). Although some patients develop a tolerance to antidepressant side effects over time, it is usually only a small number of patients. If tolerance does not occur, other strategies include reduction of dose, addition of agents that may counteract sexual side effects, direct treatment of sexual side effect using drug holidays, or other techniques. Although antidotes such as yohimbine, amantadine, and buspirone have been suggested, they have not been shown to be effective in clinical trials. Some practitioners continue to support the use of these agents as an option in their patients. There are significant data showing that some classes of antidepressants and certain specific agents have had success in treating depression without a severe impact on sexuality. Bupropion, mirtazapine, and nefazadone have been well studied and have shown the least risk of inducing sexual dysfunction (44–46). Studies have also shown lower rates of sexual dysfunction with venlafaxine, a serotonin–norepinephrine reuptake inhibitor (SNRI), compared with SSRIs (42).

TABLE 50.5 Antidepressant Therapy: Recommendations to Reduce Sexual Dysfunction

1. Reduce dose: It may be possible to reduce dose to minimize sexual side effects while still maintaining therapeutic efficacy.
2. Schedule dose after sexual activity: The drug concentration may be at its lowest if the dose is scheduled after usual time for engaging in sexual activity.
3. Treat sexual dysfunction: There are pharmacological and nonpharmacological methods that may be useful in the case of erectile dysfunction.
4. Augment with a drug that may reduce dysfunction: Some studies suggest that there are medications that may counteract sexual dysfunction, such as dextroamphetamine, amantadine, buspirone, and so forth. These may be taken prior to sexual activity.
5. Change to another antidepressant: Certain antidepressants, such as nefazadone and bupropion, have been shown to have less effect on sexual functioning.
6. Take a drug holiday: It may be appropriate to provide a weaning schedule depending on the agent and length of treatment.

Diabetes

Diabetes is a multisystem disorder that includes a high prevalence of sexual dysfunction in both men and women. Studies by Kolodny in the 1970s and McCullogh in the 1980s describe the natural history and prevalence rates of sexual dysfunction as it relates to diabetes (47,48). Reports of dysfunction in diabetic men range from 27% to 75% (49–51) ED; ejaculatory dysfunction, and sometimes decreased libido, are commonly cited in men with history of diabetes. It is typically the combination of neuropathy and vasculopathy rather than hormonal changes that cause ED in diabetic men. In addition to diabetes, there is also mounting evidence that truncal obesity may be an independent risk factor for the development of ED (52).

Treatment of diabetes-related sexual dysfunction is similar to treatment of ED in general. Most studies suggest that PDE5i drugs are 70% to 80% efficacious in this population (53,54). Currently, there are no prophylactic measures available to prevent diabetic ED. Tight control of blood sugar should be the initial treatment, followed by treatment of malnutrition and general physical condition. Hormonal therapy can be considered in addition to the use of medication for ED. A referral to a urologist can be made to consider intracavernous injection therapy, vacuum therapy, or penile prosthesis.

Studies of sexual dysfunction in diabetic women are limited, but have consistently reported decreased orgasmic response (55,56). Other symptoms reported include decreased libido, reduced vaginal lubrication, dyspareunia, and vaginal infections. The pathogenesis of diabetic sexual dysfunction in women is complex and multifactorial, as are its evaluation and treatment. The cornerstone of treatment begins with education of the woman and her partner that decreased sexual desire and responsiveness may be caused by diabetes and challenges in the partner's relationship. As in men, nutritional and medical status should be optimized, including a thorough review of medication use. Counseling may be appropriate if no other reversible cause is found.

Coronary Artery Disease

It is now well documented that several of the risk factors for CAD are risk factors for ED. These may include hypertension, diabetes, dyslipidemia, and smoking. The incidence of ED has been reported to be as high as two-thirds of patients with myocardial infarction. Recent studies suggest that ED is an early symptom of cardiovascular disease and may precede CAD by two to three years in a majority of patients. Both of these conditions, ED and CAD, have shared risk factors that contribute to endothelial dysfunction and impede the ability of the arteries to dilate appropriately in response to stimuli (57).

The Princeton Consensus Conference developed guidelines for the safe management of cardiac patients with varying degrees of coronary risk regarding sexual activity and the treatment of ED. It reports that the PDE5i drugs are effective in treating ED in patients with CAD. Low-risk patients can usually receive PDE5i drugs without additional cardiac workup. In high-risk, unstable cardiac patients, the workup for sexual dysfunction should be deferred until the cardiac problem has been corrected or stabilized. Generally, this class of medication is considered safe in patients with stable CAD and does not pose any additional risk for ischemia. In contrast, the use of nitrate medications or alpha-blockers in combination with PDE5i is contraindicated. The American College of Cardiology/American Heart Association consensus position on medications such as sildenafil is that it is safe for patients with stable CAD who are not taking nitrates (58).

Antihypertensives

Hypertension is the major independent risk factor for stroke, so it should be treated aggressively to provide adequate blood pressure control. Unfortunately, sexual dysfunction has been associated with many of the antihypertensive medications (Table 50.6) (59,60). It is important to understand the sexual side-effect profile of various classes of antihypertensives, as this will affect not only compliance, but also a patient's quality of life.

TABLE 50.6 Sexual Side Effects Associated With Antihypertensive Classes

ANTIHYPERTENSIVE CLASS	ERECTILE DYSFUNCTION	DECREASED LIBIDO	IMPAIRED EJACULATION	PRIAPISM	GYNECOMASTIA
Beta-blockers	+	–	–	–	+
Diuretics					
Spironolactone	+	+	–	–	+
Thiazides	+	+	+	–	–
Antiadrenergics					
Central	+	+	+	–	–
Peripheral	+	–	+	+	+
Calcium channel blockers	–	–	+	–	+
ACE inhibitors	–	–	–	–	–
Angiotensin II blockers	–	–	–	–	–
Vasodilators	+	–	–	+	–

Many studies have reported ED in male subjects related to treatment with antihypertensive medications. Certain medication classes tend to show a higher prevalence of sexual dysfunction than others. In general, diuretics and beta-blockers have the most negative effects on sexual performance. Beta-blockers, such as propanolol, with high lipophilicity and nonselective beta blockade, are associated with ED. Thiazide diuretics are essentially devoid of central or autonomic nervous system activity, yet they are associated with ED, possibly because of fluid and zinc depletion (61), even though the definitive pathogenetic role of zinc in ED remains unclear. Spironolactone can cause ED as well as gynecomastia and a decrease in libido. As an alternative to these medications, ACE inhibitors and angiotensin II antagonists have minimal sexual side effects and are often better tolerated by patients. In fact, some studies report a positive impact on sexuality and quality of life with the use of medications such as losartan, an angiotensin II antagonist. There are several reports suggesting that drugs that inhibit the renin-angiotensin system exert favorable actions on erectile function (62–66). It is important for practitioners to communicate openly with patients and work with them closely to minimize the sexual side effects of antihypertensive agents while maintaining antihypertensive efficacy. In addition, PDE5i drugs may be used effectively in this population, even when they are taking concomitant antihypertensive medications (67,68).

Seizures

Seizures are a common complication after stroke, with a reported incidence up to 10% (69–71). Some patients who experience a first seizure go on to develop epilepsy, especially those with late-onset seizures that occur beyond two weeks following stroke onset. In general, patients with epilepsy have hyposexuality. In males, there may be decreased sexual desire or ED. Men with epilepsy have a 57% increased risk of ED versus 3% to 9% in the general population (72–74). In females, epilepsy is associated with menstrual irregularities or reproductive dysfunction. Estrogens lower seizure threshold, so seizure frequency may increase during menses or pregnancy.

Sexual disorders are distinguished by a temporal relationship with seizure activity. There are two categories:

- Those directly related to the epileptic discharge period (ictal)
- Those unrelated in time to seizure occurrence (interictal)

Hyposexuality has been linked to interictal seizure activity, whereas hypersexuality has been reported in the setting of ictal seizure activity (75–77). Monga et al. described three case reports of patients who demonstrated a hypersexuality and deviant sexual behavior after stroke (78). In all three cases, temporal lobe lesions were noted on cranial computed tomography, and all had a history of poststroke seizure activity.

The association between diminished sexuality and chronic anticonvulsant use is well established. Antiseizure medications, such as phenytoin and carbamazepine, are commonly associated with sexual dysfunction. In males, they can decrease the testosterone level, which, in turn, reduces sexual desire. Antiepileptic drugs alter the serum concentrations of sex hormones and the regulatory feedback loop of the hypothalamic–pituitary–gonadal axis. Rattya et al. examined the effects of carbamazepine, oxcarbemazepine, and valproate in epileptic men and suggested that oxcarbemazepine may be the best choice of anticonvulsant in epileptic patients suffering from hyposexuality (79).

Cognitive Impairments

Cognitive changes after stroke can cause memory problems and difficulty expressing emotions, which may influence intimacy and sexual activity. Cognitive deterioration relating to dementing disorders can include disinhibition, agitation, or depressed mood, which can cause interpersonal difficulties and negatively impact a couple's sexual relationship (80,81). These behaviors may be seen in basotemporal and orbitofrontal lesions (78,82). For example, a patient may make socially inappropriate verbal comments of a sexual nature in public whereas prestroke the person would have suppressed this verbal output. Disinhibited syndromes in brain injury as a whole have been a frequently described phenomenon and can involve disinhibited behavior in multiple realms, such as motor disinhibitions (e.g., aggressive outbursts) and emotional disinhibition (e.g., emotional lability) in addition to sexual disinhibition (82). Infrequently, hypersexuality can be seen following a stroke. It has been described in lacunar strokes, which affect the frontolimbic system, and in thalamic infarctions; some literature has compared this symptomatology to Kluver–Bucy syndrome (83,84). It has been proposed that hypersexuality following stroke may relate to dysfunction in the fronto-subcortical circuits secondary to thalamic infarctions (83). Coping with disinhibited behaviors and hypersexuality following a stroke can be challenging. Reducing external distractions during intimacy and using verbal and nonverbal communication for sexual expression may aid in managing these symptoms. In addition, optimizing sleep–wake cycles may minimize the cognitive impairments experienced by some patients after stroke.

Aging and Sexual Dysfunction

There is a notable and sharp decline in sexual activity with age. Pfeiffer et al. studied sexual interest and activity as people age; in their study, 50% of individuals aged 60 to 65 were still sexually active in comparison to 20% in the 78 to 83 age group (85). For those who care for patients with stroke, it is important to understand the normal age-related changes that impact sexual functioning in the elderly. Proper understanding of sexuality and aging can also minimize the myths and misconceptions that many clinicians have about sexuality in the elderly. This section discusses the physiological and psychological changes commonly seen in the older adult and older stroke survivors.

Physiological Changes in Elderly

In the aging male, the most common changes in sexual physiology occur in both erectile function and ejaculation (80,87). Stein et al. reported that 40% of men aged 70 to 79 and 60% of men over 80 experience ED (86). For example, men tend to show increased time required to produce a full erection, an increase in the time that erections can be maintained prior to ejaculation, a decrease in the force of ejaculation, and an increase in the duration of the refractory phase (80). The high prevalence of diabetes, CAD, hypertension, depression, and the use of various medications also contribute to these changes in sexual functioning.

In older women, the physiological effects of aging on sexual function are primarily caused by decreased amounts of circulating estrogen after menopause. Lower estrogen levels not only contribute to a decline in sexual interest and coital frequency, but also reduce vaginal lubrication, resulting in painful intercourse and less pleasurable sex. However, other studies have suggested that many women experience an intensification of sexual desire during menopause. In these cases, the negative effects of menopause are more than offset by the freedom to explore and enjoy sexual activity without the worry of becoming pregnant (87).

Psychological Attitudes in the Elderly

In our modern culture, there is often still an expectation that older people are, or ought to be, asexual (87). Although sex roles have changed and there has been more freedom of sexual expression since the 1960s, the stereotypes that older people are physically unattractive, uninterested in sex, and incapable of achieving sexual arousal are still widely held (88).

Modern Western society has generally viewed sexuality in older adults in a very restrictive manner. Studies of nursing staff in extended care facilities have identified significant staff discomfort about sexual expression among the elderly residents. Older residents who display any form of sexual expression are often regarded by staff as having a behavioral problem and may even be tranquilized (89). Staff attitudes toward masturbation or sexual activity between unmarried residents are often disapproving and repressive, and adult children may complain of permissive institutional attitudes toward their parents' sexual expression (90,91).

It is still quite common for society to consider sexual expression or activity to be unnatural or unacceptable in the aging population. Clearly, educational intervention is needed to dispel negative myths, stereotypes, and self-fulfilling attitudes in older people and to promote the perception that full sexual expression is part of the entire extent of adulthood.

Opportunity for Elderly

Opportunities for sexual contact are greatly reduced in those with advanced age. Gender differences in life expectancy may impact the sexual experiences in older adults. For example, demographic data indicate that there are many more women than men over the age of 65. If marital status or living with a partner is a measure of increased opportunity structures for sex, elderly heterosexual women have a limited opportunity for sexual expression. In contrast, decline in sexual activity for men is less likely to be due to the lack of a partner (87). A physiological change, such as ED, is likely the reason for reduced sexual activity in men. The lack of privacy in nursing homes is a major obstacle to sexual expression. Not surprisingly, older residents report that, because of a lack of privacy and inhibiting staff attitudes, they have little opportunity to experience intimacy.

Because many types of professionals are involved in the provision of health services to older people, staff-wide education about the importance of sexuality in the promotion of mental and physical health for older adults is important and should lead to more positive attitudes. Greater knowledge and acceptance of older adult sexuality and sexual functioning are important goals for all sex educators, counselors, and therapists trying to meet the needs of older adults (92).

Management of Sexual Dysfunction

Comprehensive medical evaluation should precede any treatment intervention for sexuality dysfunction after stroke. Early referral to the appropriate health care professional is a key strategy. Physician specialists involved in evaluation and management of sexual dysfunction include physiatrists, urologists, gynecologists, primary care practitioners, or neurologists. A thorough evaluation includes review of sexual, medical, and psychosocial history followed by medical and neurologic examination and laboratory testing. Medical risk factors for sexual dysfunction include hypertension, diabetes mellitus, depression, and cardiovascular disease. Medications should be reviewed to identify those that cause sexual side effects. Lab studies should include hormonal evaluation to exclude a diagnosis of hypogonadism (testosterone and prolactin levels) and testing to screen for diabetes. Social history should be elicited to discuss other risk factors, including obesity, tobacco, alcohol, and illicit drug use. It is also important to distinguish disease processes from the normal physiologic aging process. Other specialists vital to the management of sexual dysfunction after stroke include rehabilitation nursing, physical, occupational, and speech therapists, as well as social workers and psychologists. Referral to physical or occupational therapists may be appropriate in situations where positioning or energy conservation techniques would be warranted. A rehabilitation physician can provide spasticity management, including oral medications, focal chemodenervation, and other methods to reduce spastic dystonia or painful spasms that interfere with sexual functioning. Sexuality counseling is the responsibility of all involved in the care of adults with neurologic disability.

Sexuality Counseling

In 1976, Annon described the PLISSIT model for approaching sexual dysfunction and intimacy problems. PLISSIT stands for

TABLE 50.7 PLISSIT Model

P = Permission
LI = Limited information
SS = Specific suggestions
IT = Intensive therapy

permission, limited information, specific suggestions, and intensive therapy (Table 50.7) (93). Though this is not stroke specific, it does provide some valuable guidance. Permission involves offering both the patient and the partner, who often assumes a caregiver role, a chance to discuss issues related to sexuality. It may also validate the patient or partner to include healthy sexual functioning as part of the overall goals of rehabilitation.

Premorbid sexual knowledge may be variable depending on familial, religious, or cultural backgrounds; therefore, it is helpful to provide basic information regarding sexual issues. Some patients may require more specific suggestions to ameliorate problems related to their sexuality, such as methods of communicating with a partner to allow for intimacy or an explanation of a medication's effect on sexual functioning. There will certainly be areas that fall out of the realm of the clinician's expertise; therefore, in specific cases a referral for intensive therapy may be beneficial. It is also important to reassure patients that it is safe to participate in sexual activities. The timing of receipt of information regarding sexual function is also important. Receiving this information prior to discharge from acute rehabilitation is generally preferred by patients (94).

Here is one potential introductory dialogue a physician might use:

> As you prepare to return home, I wanted to briefly discuss some issues that haven't been addressed during your rehabilitation stay, such as resuming sexual activity. Some people are concerned about the safety of having sex after stroke, and I wanted to reassure you that it is perfectly safe to do so, and that this does not increase your risk of having another stroke. Many people are able to resume their sex lives without difficulty after stroke, but others experience some challenges because of the stroke itself, or sometimes due to the medicines prescribed for other problems, such as depression. Please let me know if you have any questions or concerns about sexuality now that I can address. We will also have a chance to review any issues that might arise once you are back at home when I see you in the office in several weeks.

CONCLUSION

Sexual dysfunction after stroke is common and can have a significant impact on the quality of life of the affected patients and partners. Altered sexual activity after stroke may have a medical cause that is often directly or indirectly a result of neurologic changes in libido, sexual behavior, and sexual performance. Comorbidity and general health status, together with psychological factors, are also important determinants of poststroke sexual functioning.

Treating sexual dysfunction is part of the holistic approach to rehabilitation. Counseling should include dispelling stereotypes, myths, and misperceptions, not only for the stroke survivor, but also for the partners and rehabilitation staff members. Counseling stroke survivors on sexual problems is a challenging experience, but it is necessary for improving their quality of life. Education in the field of sexuality and aging is also essential for all health professionals who are in contact with older people, both in institutions and the wider community.

Studies demonstrate that disorders of sexual functions are most significantly associated with various psychosocial factors, such as patients' general attitude toward sexuality, fear of impotence, and ability to discuss sexuality, as well as with the degree of poststroke functional disability. Therefore, providing this opportunity for evaluation and management is paramount. With emerging awareness of the primary importance of quality of life as the critical indicator of good patient management and the advent of more effective treatment of sexual dysfunction, it is no longer acceptable to ignore this very important dimension of life.

RESOURCES

1. http://www.ncbi.nlm.nih.gov/pubmed/17514993
2. http://www.heartandstroke.com/site/c.ikIQLcMWJtE/b.5487841/k.7481/Stroke__Relationships.htm
3. http://www.stroke.org/site/PageServer?pagename=HOPE

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51

Vocational Rehabilitation After Stroke

Mark A. Young, Steven A. Stiens, and Alessandra Hirsch

According to Sigmund Freud, "Love and work are the cornerstones of an individual's humanness." A stroke can threaten to strip a person of that core humanness and of the treasured roles shared with others. In no domain can that issue be more poignant and the financial impact more devastating than in the vocational and work environment. Viewed from within the traditional "impairment-disability-handicap classification" paradigm,[1] an individual who experiences a stroke faces an *impairment*, generally defined as "any loss or abnormality of anatomic structure, physiologic, or psychological function of an organ or system" (1). Examples of impairments resulting from stroke include weakness, sensory deficits, and cognitive and communication deficits. A *disability* is the term used to describe the inability of an individual to complete a routine task as a result of the *impairment*. A *handicap* refers to a disadvantage stemming from an impairment or disability in performing a role in society. An example of a stroke-related "impairment-disability-handicap" adversely impacting work might be a left internal capsular ischemic stroke with right hemiplegia (impairment) that prevents a computer programmer from typing on a computer (disability) and returning to work (handicap). The use of appropriate assistive technology, such as speech recognition software in this case, might allow this individual to return to work, thus overcoming the handicap, while still having an impairment and disability.

[1]The "impairment-disability-handicap" classification system, although somewhat dated, remains a classic and instructive model for conceptualizing the disability spectrum. While its application has more recently been supplanted by the World Health Organization International Classification of Functioning, Disability and Health (see http://www.who.int/classifications/icf/en), the authors of this chapter have elected to utilize the classic system because of its historic significance and relevance to vocational rehabilitation.

The decision to return to work after a stroke can be affected by a number of factors, both physical and mental. The psychological effects of stroke (especially poststroke depression) may have as large an impact as the physical consequences of stroke (2,3). About 40% of stroke survivors experience significant poststroke depression (4). Poststroke depression may be associated with not returning to work, but the cause-and-effect aspects of this association are complex. The causes of poststroke depression are not fully understood, with damage to the brain suspected of precipitating this condition in many cases and the psychosocial stressors of sudden disability also playing an important role in many cases. In any given case, it may be hard to determine whether a patient hesitates to return to work because he or she is depressed or is depressed because of the loss of work in his or her life. It is important to recognize also that, although there are approximately 5.4 million stroke survivors in the United States, there has been only sparse research on the subject of return to work after stroke. Fewer still are studies that examine strategies to improve those rates.

Kirk Douglas (Figure 51.1), the famous actor of *The Bad and the Beautiful* and *Spartacus* suffered a stroke at the age of 80 and wrote a book about his struggles with depression and recovery. In it he describes the depth of his depression, which centered around his own perceived inability to go back to work as an actor: "I was tired of being a big, strong, tough guy. I began to cry. The room seemed to get darker and a big black cloud engulfed me. I cried and cried until my pillow became wet with tears […] I didn't want to see anybody. What good is an actor who can't talk? […] I felt so helpless—so useless. I will never make another movie—I will never write another book. Will I ever talk again?" (5)

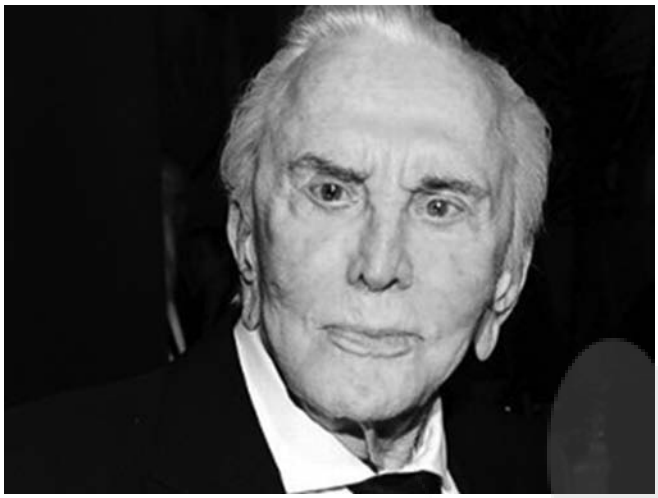

FIGURE 51.1 Kirk Douglas after his stroke.

The preceding excerpt is from Kirk Douglas's book, *A Stroke of Luck.* In it, he describes his own vocational battle with stroke, and emphasizes not only the feelings of helplessness but also the importance of speech and language. Although his story is perhaps unique because of the high-profile nature of his job, his experience is not. Aphasia from stroke can have a profound impact on vocational opportunities and return-to-work (RTW) potential.

Risk Factors: Barriers to Overcome

Depression is only one of many factors affecting stroke survivors and their decisions regarding return to work. The reported range of RTW rate for stroke survivors ranges from 4% to 77% of patients (3). This large variation is due to varying definitions of "RTW" used in different studies. Some studies recognize only paid work, whereas others include persons who do not work outside of the home at baseline and who resume managing their own homes. This also illustrates how individualized a decision to return to work can be for each stroke survivor. In spite of the challenges of defining *work,* there are some factors that consistently appear important in determining RTW rates. They include age; stroke severity; psychological social and societal factors; and cultural and geographical factors.

Age: The Younger the Better

Younger patients are more likely to return to work after stroke. Generally, patients over the age of 65 tend to have a low rate of returning to work, for a number of reasons. Patients who are near retirement age are inclined to see a stroke as a sign to retire (6). Although much of the time this is a reasonable response to circumstances (recognizing both the difficulty in returning to work and, typically, less financial need to do so), a premature and undesired retirement can have a negative impact on a patient's mental health after stroke. As Freud reminds us, many rely on work as a source of purpose as well as joy. Patients who see themselves as forced into early retirement may become depressed despite the fact that they reached an appropriate age to retire by conventional criteria.

Conversely, the very young stroke survivor may also have greater difficulty vocationally. A severe stroke in very young patients who have not yet entered the workforce can often prevent those patients from ever entering the work force in the first place.

Stroke Severity: The Major Predictor of Return to Work

It comes as no surprise that more severe strokes tend to result in lower RTW rates. In fact, stroke severity is the best predictive factor for returning to work (6). Stroke severity tends to be correlated with how long the patient is hospitalized. A more severe stroke typically necessitates a longer hospital stay and also tends to result in more severe long-term neurological and functional impairments impacting ability to work. Irrespective of cognitive or physical limitations, an extended period of absence from work may reduce patient motivation to return and increase the likelihood that the original job will no longer be available. Finally, recurrence of stroke is also a barrier to RTW. A recurrent stroke may lead to additional neurological impairments; it also may discourage the patient from trying to return to work. The fear that another stroke may occur, resulting in another leave from work and additional impairments, is a disincentive for returning to work for both stroke survivor and employer (7). It should be noted, however, that stroke severity can be measured from a variety of perspectives, including motor, cognitive, and behavioral effects. Many studies have revealed that the hemisphere of the brain where the stroke occurs does *not* predict a patient's likelihood of returning to work (8). The behavioral outcomes of these lesions are what really determine perceptions and job options. A stroke that impairs a patient's language abilities, memory, vision, intelligence, and/or socializing skills affects his or her ability to re-enter daily life (9). Like other types of brain injury, stroke survivors can benefit from compensatory techniques and neurobehavioral therapy to optimize vocational and behavioral outcomes.

Psychological Social and Societal Factors: Positive Mood, Family, and Education Can Help

When measuring qualitative factors, there is less of a consensus in the literature. Alcohol use, for example, was identified in some studies as an important barrier to RTW and in others had no effect at all (6). As mentioned earlier, depression is an important factor in returning to work, and is one that both may deter patients from returning to work as well as potentially result from premature retirement. In either case, if a patient is suffering from depression before attempting RTW, the chances of that patient actually doing so are small (2). Marital status has no effect, whereas both a high education level and cohabitatation with someone else increased

RTW rates (6). The type of job previously held by the patient also has an effect on RTW rates. In fact, patients who held white-collar jobs were 37% more likely to return to work than those holding blue-collar jobs (6).

Cultural and Geographical Factors: Traditions, Policies, and Economy

There are variations in RTW rates among different countries. Japanese people are more likely to return to work, perhaps because of a strong cultural emphasis on work, often in spite of the severity of the stroke and its outcomes. The United States has among the lowest RTW rates, with 19% as a low estimate. Germany also has a low RTW rate, with only 14% of its stroke patients returning to work. France, Portugal, and Israel hold some of the highest rates, with 73%, 73%, and 67%, respectively (6). The causes of this variation are not well understood; theories suggest that it is a function of the health care practices and facilities in these countries, or perhaps the cultural role that work occupies in the local culture.

An overall breakdown of RTW among stroke survivors is shown in Figure 51.2. This graph can be interpreted in several ways. With such low RTW rates, there is considerable opportunity for improvement. Vocational rehabilitation is a relatively new field, and longitudinal studies of its effectiveness will require more data. It seems clear that we should work vigorously to help individuals who are of an age when RTW is a priority (generally below age 65 or even younger), who have residual impairments that do not preclude return to the workforce, and whose job environment is conducive to returning to work. For the majority of stroke patients, however, RTW is unlikely as a result of a combination of these factors, and therefore, realistic expectations should be set, and exploration of alternatives to return to full-time employment should be encouraged.

Fluctuations in the economy also affect efforts to return to work. During an economic recession, it is often difficult even for the able-bodied to find jobs and certainly even more difficult for a patient with a visible disability. A cold economic reality may manifest itself in the high association of unemployment and stroke. The limited number of available positions are often filled by younger, able-bodied individuals who may also possess more formal qualifications (albeit possessing less experience). Of course, this should not discourage patients living with stroke from seeking a RTW. Rather, it should remind the stroke survivors and their families as well as their vocational rehabilitation counselors (VRCs), that returning to work or finding a new job may be more difficult today than in the past. A longer period devoted to a job search is now to be expected, but returning to work is by no means impossible in this economy.

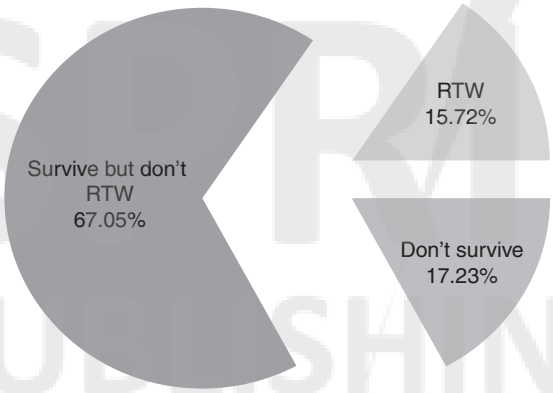

FIGURE 51.2 Stroke patient outcomes.

Defining Employment: Labor to Achieve an End, Livelihood

Perhaps the biggest problem with existing studies on RTW rates is the variable definitions of *work* used by the authors. Some investigators only include patients who return to a paying job in their definition of *work*. Others include students and housewives who return to their studies and housework; some include volunteering. The lack of standardization on this topic accounts for the wide range in reported RTW rates. According to the *Oxford English Dictionary*, *work* is an "action involving effort or exertion directed to a definite end, especially as a means of gaining one's livelihood; labour, toil; [one's] regular occupation or employment" (10). This seems to be an appropriate definition, and one that the authors of this chapter will use. It focuses on a human's livelihood first, which is the essential reason *why* RTW is so important to stroke survivors. One of the earliest mentions of the word *work* comes from Milton's *Paradise Lost*: "Man hath his daily work of body or mind appointed, which declares his dignity" (10). This usage captures the psychosocial impact of work, and explains why many stroke survivors pursue this goal despite the challenges they encounter.

Factors Impacting the Feasibility of Stroke Survivors Returning to Work

Capability and Motivation: Making the Decision to Return to Work

The first step in returning to work is, of course, making the decision to pursue this goal. Although the typical duration of recovery varies widely among stroke patients, many stroke survivors achieve a relative plateau in their recovery within three to six months (6). Although the majority of recovery takes place in that time period, some degree of continued gradual improvement is common, and there is no absolute time limit on functional gains after stroke. Despite the best rehabilitation efforts, many patients remain with significant disability. Initially, it is the treating physician's responsibility to direct and coordinate care to minimize stroke severity, prevent recurrent stroke, and initiate rehabilitation while the patient is in the hospital so that ultimately a decision can be made about the feasibility of a RTW. Physicians are often tempted to provide the patient with a premature recommendation regarding RTW. It may be better to keep

the option of RTW open (when realistic) and give the recovery process more time, leaving options open as community reintegration begins. Ultimately, it is the patient's choice to return to work or not; but a doctor can often make the best estimate regarding a stroke survivor's physical abilities and how they might fit into the workplace. Patients and doctors should both stay open-minded about the possibility of returning to work. The process of stroke rehabilitation includes mastering many daily activities that are a prerequisite for RTW. It is generally accepted that early intervention gives the patient the best chance for RTW (11). Early intervention primes the stroke patient to get into the mindset of returning to work, both mentally and physically. Individuals who sustain a stroke are often in the prime of their careers and are accustomed to performing at a high level in the workplace. After a stroke, patients may question what kinds of contributions they can make in the workplace. Early intervention is important in encouraging patients to meet their full potential. If the physician can introduce a vocational rehabilitation specialist or counselor to the patient before he or she is discharged, the idea of returning to work can be planted for further nurturing as recovery takes place. Some hospitals have VRCs on staff, and these specialists should be utilized when available. The possibilities that they present to stroke patients should encourage patients in their hopes for the future. However, a survey study by Culler et al. suggested that some stroke survivors felt that they were compelled to return to work earlier in the recovery process than they felt ready. They felt that this undue pressure caused them anxiety and was a deterrent that prolonged the process of returning to work. In spite of this one report, most doctors and specialists agree that early intervention still produces the best results in terms of the patient successfully returning to work; the most successful RTW patients are those who begin evaluating their vocational situations before leaving the hospital.

These early evaluations should include a number of parameters, including the key issue of whether the patient *wants* to return to work. In either case, the reasons for such a decision should be thoroughly assessed. Many patients have "Freudian" (which are, in this case, good) reasons for wanting to resume employment: their jobs give them joy and purpose in their lives. They like to be busy, and working helps them feel productive and important. In addition, the social element that the workplace provides can be therapeutic for a recovering stroke patient from a psychosocial perspective. Socializing with coworkers not only provides them with a community, but also can help these survivors overcome solitude and dysphoria. These nonfinancial psychosocial considerations are valid, and perhaps even the most cogent reasons to return to work. Financial considerations are paramount for some patients, of course, and certainly a valid justification for RTW. Sometimes, in the face of formidable hospital bills and/or family reliance on the patient, a stroke survivor will feel that resuming employment is not a choice but a necessity to regain income and retain health care benefits. Although many factors outside of the control of the health care team are involved, ideally work should be a tool that stroke patients can incorporate into their ongoing rehabilitation rather than an unavoidable need. Patients and their families should understand their options (including formal designation as disabled in order to qualify for Social Security Disability Insurance payments) and may benefit from engaging a lawyer. From a rehabilitation provider's perspective, ideally patients would be free to make their own decisions without feeling undue pressure or any shame in either choice. Patient must not be made to feel guilty, especially if they decide not to return to work because they feel they are not ready or because they see stroke as an opportunity to retire.

Twenty percent of the societal costs of stroke are estimated to be the result of loss of employment. Each individual's decision or ability to return to work is unique and specific to that person and situation. These decisions should be approached on a patient-by-patient basis. However, guideline advice and models exist to help predict whether or not a patient is likely to return to work. In a comprehensive study done by Satoru Saeki, a set of criteria were assessed in stroke patients looking to return to work. Saeki's study focused on workplace accommodations for and functional abilities of stroke survivors. The project was designed to streamline the process of managing the poststroke existence and, in so doing, outlined four guidelines for returning to work, listed in the following box.

Saeki et al.'s General Criteria for Return to Work (12)

1. Good performance at activities of daily living (ADL), which include eating, climbing stairs, shopping, driving, housework, dressing oneself, etc.
2. Walking a distance of 300 meters or more without needing a break
3. 15 seconds of mental activity with high performance and sustained concentration
4. Emotional acceptance of the disability

Of these four, Saeki suggested that the first three will not be sufficient to propel a patient back to a work environment without the fourth. Indeed, returning to work is as dependent on a patient's mental state as his or her physical status. Even patients with more minor impairments will not perform well after RTW if they do not feel ready or are unable to cope with their disability.

Anticipatory Rehabilitation: Processes That Enhance Vocational Success

The immediate and acute management of patients after stroke includes rapid diagnosis, imaging, and, in selected cases, thrombolysis, followed by treatment to prevent recurrence. Rehabilitation begins with the assessment of functional deficits and development of a plan for remediation and compensation. In reporting a diagnosis and a preliminary prognosis, outcomes and RTW should be included when appropriate, keeping in mind the uncertainty of the ultimate outcome of

RTW plans at this early phase of care. Expressing hope keeps the patient, family, and coworkers engaged in expecting and supporting functional improvement. As patients are admitted to the hospital, their sense of personhood and station in life is often compromised. A patient's sense of self-identity can be preserved by including a picture of the family at the bedside and the vocation of the patient in the introductory and social history portion. For example, the patient is a 64-year-old trial lawyer with a new right middle cerebral artery ischemic stroke. A prior professional picture of the patient showing him or her in his office standing in front of his legal books can help to bolster professional self-worth. If there are communication, perceptual, and/or mental status deficits, a patient's life role can be expressed in photographs.

Addressing the patient's occupation is very reinforcing because work, for many, is a core element of their identity. Reviewing the tasks performed by the patient in his or her job during each day provides background on the patient's premorbid capabilities. Such detailed knowledge enhances the design of the rehabilitation program in physical therapy, occupational therapy, and speech–language therapy. Photographs or videos of the worksite provide specific evidence of the challenges of accessibility. Use of these at the bedside helps patients picture themselves back at home and at work soon. With the cooperation of family and willing coworkers, a video can be made that illustrates the worksite and includes encouraging testimonials from coworkers about support they would offer the patient upon his or her return.

As rehabilitation is initiated, clothing that the patient might wear in the work setting may be an option for the patient to wear each day in rehabilitation. As basic mobility is achieved, the tasks of transfer and wheelchair propulsion and gait can be designed to approximate activities at home and work. Initially, visitation with the patient should be limited to immediate family and close friends. Preliminary misjudgments about the patient's capabilities for RTW should be avoided. The vocational counselor should be consulted early to make preliminary contact with the employer; if unavailable, then a family member or friend may make this contact to keep the employer informed. As patient improvement ensues, planned visits from coworkers can be arranged as the patient's improving function can be showcased. Later in the process, assessments such as work capacity examinations can be utilized to assess perception, strength, and endurance. As is feasible depending on employment type, work samples can be brought to the therapist to assess more subtle aspects of cognition and problem solving. When community reintegration has been partially achieved, visits to worksites that approximate the preferred work setting allow assessment of the patient's performance without impromptu and premature pre-interviewing from those at the target worksite. In the latter stages of placement, mock-up worksite environments can be designed for practice in therapy. Successful accommodations can be designed for the actual worksite based on these therapy simulations. Finally, the patients can be transitioned back into the worksite with increasing hours and frequency as endurance increases.

Following is a case study of a patient with a stroke. Readers are encouraged to assess whether a physician should recommend that this patient return to work.

Case Study 1

A 70-year-old male physician sustains a right internal capsular ischemic stroke. After three months, he has regained most of his abilities with the exception of hemiplegia in his left arm and hand and slightly slurred speech. Before he had his stroke, he was working as a general internist at a local teaching hospital. His mental capabilities appear mildly affected; for example, he now takes 15 instead of 10 minutes to complete a crossword puzzle, and he has mild difficulty remembering list items. He is articulate, has intact language abilities, and retains strong verbal abilities. When asked about his job, he reports that his favorite part was teaching medical students and residents. He states that work as a physician, and teaching in particular, gives him a strong sense of purpose in life; he does not wish to consider retiring at this time despite adequate financial resources to do so.

Vocational Rehabilitation Process: Early Consultation, Evaluation, and Planning

While this patient is in the hospital, an inpatient rehabilitation assessment should start and a plan should be designed. (13,14). Then, once released from the acute hospital, he should continue care at an inpatient rehabilitation facility, where he should be assigned a vocational rehab counselor if available. There, the vocational counselor will recommend assessment and therapy with the interdisciplinary team. Because he has no use of his left hand, the likelihood of him being able to carry out the entire range of clinical procedures previously performed is low. If he returns to clinical practice, he may need to hire a physician's assistant or equivalent to conduct procedures ranging from injection administration to suturing wounds. The rehabilitation center should administer a neuropsychological assessment. It is hoped that this will confirm his apparently well-preserved cognitive abilities, and determine if any more subtle deficits might be present. If his performance on this assessment is impaired, a follow-up assessment when he is more fully recovered may be appropriate.

Given this physician's pre-existing interest in teaching, it may be helpful to encourage him to focus his subsequent career on teaching. This may reduce his need for workplace accommodations or assistants. A part-time status might allow him to retain the status and self-worth he derives from work without the same productivity expectations from his employers. This patient has a fairly high likelihood of returning to work because of the type of job he held prior to the stroke, because of his relatively strong mental capacities, and because his physical disability is limited to one arm. His age is a factor that may influence this decision; he may choose retirement if he is personally dissatisfied with his work abilities after completing rehabilitation.

The Particular Job Focus: Previous or New

When patients decide that they wish to return to work, the first step in this process is determining whether they can resume their prior jobs. Often, patients have a long work history and a devoted staff of coworkers at their jobs. A vocational counselor can be a valuable intermediary between patients and their employers, keeping the employers informed of the patients' progress and RTW plans and preventing undue pressure on the patients to return to work before being fully rehabilitated. Many, and perhaps most, stroke survivors have some residual impairments that may affect job performance and that should be addressed in developing a RTW plan. These residual physical, cognitive, and psychological factors may require specific rehabilitation efforts as well as specific workplace accommodations such as modified duties or adaptive equipment. Some patients will express a desire to wait until they are "fully recovered" before they return to their jobs, fearing social pressure and judgment by their workplace peers and employers (15). However, in many cases the likelihood of regaining all function is low. In fact, the actual work setting can be psychologically and physically therapeutic in itself. As Brendan Conroy observed in a prior edition of this text, "it is helpful for the survivor to return to work *in order* to feel normal" (15).

If capable, one is more likely to be successful at the job previously held than at a new one entirely. Of course, returning to the same job depends on a plethora of factors, first and foremost of which is whether the patient possesses the physical and mental *capacity* to do so. Because many stroke survivors emerge from rehabilitation with some residual impairment, the decision to resume the same job requires careful assessment and planning, in a process that often includes trial completion of work duties. In the case of mild impairments where few accommodations are needed, the stroke survivors will often return to work part-time at first, working daily for several hours per day, perhaps three days per week. This allows patients to gauge their abilities and endurance in a real-work environment, and fine-tune any accommodations that have been established. From the employer's perspective, having an employee return on a part-time basis initially allows the supervisor to assess the quality of that person's work and determine realistic productivity goals. In cases where an employee has special or unique skills, a graded RTW provides the employer with at least partial access to the employee's skills.

A common scenario for successful RTW involves a patient returning to work at the same company as before, but in a new capacity. This approach leverages existing relationships between the employee and employer, but addresses the changes in abilities that may have resulted from the stroke and may make return to prior duties impractical. Focusing on the stroke survivor's specific interests and preferences for job tasks can help assure that there is good congruence between the assigned duties after stroke and the person's abilities.

Statistically, it is more likely that a stroke survivor who was employed prior to the stroke will return to his or her prior employer than work in an entirely new job. In a study by Culler et al. on ten stroke patients, eight returned to their prestroke employer. Three out of eight returned to the same position, one had a temporarily modified work schedule, and two had permanent modifications. Of the remaining two, one returned to work in an entirely different position as an assistant to her former boss, and one did not RTW at all (7) (see Figure 51.3).

Another larger study utilizing a retrospective cohort design followed 183 individuals below the age of 65 who were actively employed prior to their strokes, and assessed RTW after a stroke (16). This study focused on the association between stroke patient characteristics and RTW. Factors positively associated with successful RTW after first stroke included normal muscle strength and absence of apraxia. Employment in a white-collar occupation also

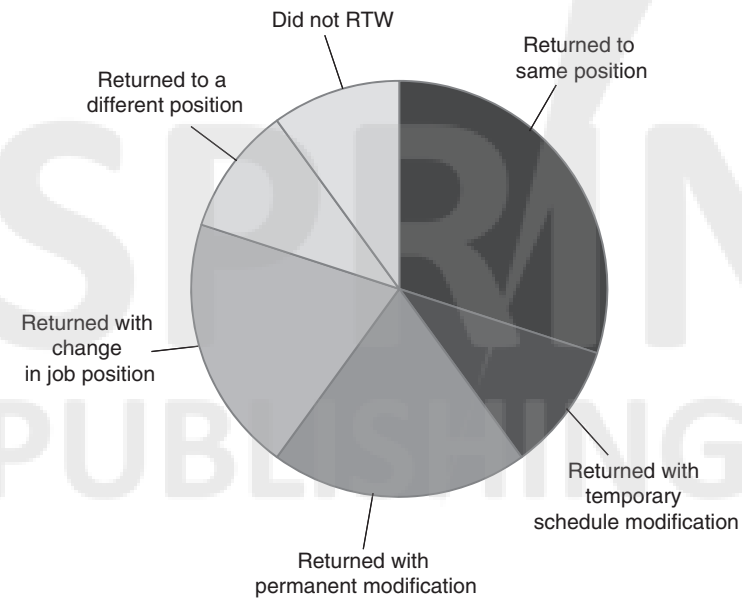

FIGURE 51.3 Return to work breakdown for 10 stroke victims.

Source: From Ref. (7). Culler KH, Wang YC, Byers K, Trierweiler R. Barriers and facilitators of return to work for individuals with strokes: perspectives of the stroke survivor, vocational specialist, and employer. *Top Stroke Rehabil*. 2011;18(4):325–340.

positively predicted RTW. The availability of governmental resources such as a social security system also impacted likelihood of RTW (16).

In the study by Culler et al., none of the stroke survivors found a job with an entirely new employer or company. The reasons for this are several, and include the existing trust between employer and employee and sense of mutual responsibility to each other. Finding a new job is often very difficult for stroke survivors, particular if they are visibly disabled. Despite the legal protections afforded by the Americans with Disabilities Act, subtle discrimination against disabled individuals in the employment market is widespread. New positions also typically entail a steeper learner curve than a familiar position (or even a new position within the same company), and are thus more demanding for the employee. Despite the fact that stroke survivors may have an easier time with their prestroke employers, a number of factors can limit returning to work even in this circumstance. For a person with disabilities, the workplace must be accessible; equally importantly, the employee with a stroke must be willing to use these accommodations (7).

Many employees also cite the employer's attitude as being essential to their own ability to RTW. Clearly, a strong support system is essential in creating a successful environment for RTW. But other factors come into play as well: how long the patient has been absent from work can influence the likelihood of returning to work. If there is an extended delay before attempting to RTW, the stroke survivor's position may have already been filled or work permanently redistributed. Another consideration is the employee's work performance prior to the stroke. Many employees do not consider whether the employer was satisfied with their performance prior to the stroke, and find lack of employer motivation for RTW an unexpected barrier. VRCs often cite this as an oversight on the part of the patient (7).

Culler et al. categorize the changes that a poststroke employee undergoes into two categories: internal and external. Internal changes involve a change in the person's attitude and self-perception. A common example (and perhaps the most important one) is learning to *accept* one's disability and work with it, in spite of the impairments that remain. External changes involve a change in job tasks and accommodations, such as switching from full time to part time or taking a bus to work instead of walking. Both internal and external changes are typical for stroke survivors, and awareness and acceptance of these changes are important factors in successful RTW.

Case Study 2

A 60-year-old left-handed woman with hypertension recently sustained a left hemisphere embolic stroke. Her problems include mild nonfluent (expressive) aphasia with anomia (word finding difficulty), moderate right-arm weakness, mild lower-extremity weakness, and some difficulty walking. She worked as a receptionist at a talent agency prior to her stroke and would like to return. Over a three-month period, she has recovered fairly good motor control and strength of her right arm and leg, but still has difficulty using her right hand for fine motor tasks. She is adept at using a computer keyboard one-handed with her left hand and has no difficulty writing with her left hand. She walks with a straight cane in the left hand and an ankle–foot orthosis (AFO) brace on the right lower extremity. Her children are grown and her husband is deceased. She lives alone in an apartment building. Her hobbies include swim aerobics at the gym and a women's book club.

Recommendation

This patient is still within standard working age, and because working seems to be an important factor in her life, she should pursue RTW. However, because of her nonfluent aphasia, a job as a receptionist is probably not the best option for her. With the help of her vocational counselor, she should contact her prestroke employer and inquire about disability accommodations, but should also look into transferring her position, perhaps to another department. Or, she could work assisting another receptionist, and might focus on memo writing, agenda organization, stocking and purchasing, and so on, as opposed to answering the phones. In the modern digital age, many companies focus on e-mail rather than voice-based correspondence, and she might play a role in customer service for nonvoice methods (e.g., an online customer service chat system).

Vocational Rehabilitation Services (VRS): Vocational Counselor and the Interdisciplinary Team

The vocational rehabilitation process enhances capabilities that enable employment in the patient's preferred job. Anyone with a disability who is seeking employment can benefit from VR services; in the case of stroke specifically, it is recommended that VR counseling begin early, during inpatient rehabilitation if feasible (Figure 51.4). VRS is paramount to a stroke survivor, especially in the current economic climate. As mentioned earlier, even many able-bodied individuals struggle to obtain employment in today's economy. Prospective employees with disabilities, particularly disabilities that impede cognitive function, are at an even greater disadvantage. VRS strive to close that gap and enable many disabled persons to RTW successfully.

VRS are offered not only by a rehabilitation institution, but also by a group of professionals trained and experienced in vocational rehabilitation. VRCs are often the most active in guiding assessment and seeking specific treatment for clients. Almost all VRCs must undergo accreditation and become licensed counselors in the field of vocational rehabilitation, which requires a master's degree (11). These professionals understand all aspects of the rehabilitation process and can collaborate with the interdisciplinary team to seek specific assessments, develop specific motor skills, and provide ergonomic modification to the worksite. Therefore, while the counselors play a leading role, the patient must keep in

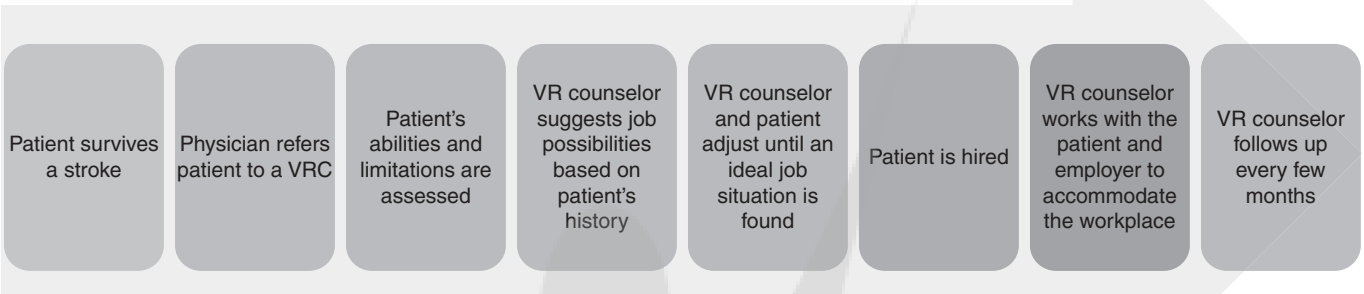

FIGURE 51.4 Schematic timeline of vocational rehabilitation after stroke.

mind the adage "it takes a village." Similarly, it takes a team of individuals to help a stroke survivor RTW. Other members of the team may include physical, occupational and speech therapists; a psychologist; physicians; family members; and technological service providers, as well as the employers themselves.

The core goal of a VRC is to assess and rehabilitate a stroke client to meet work requirement needs.

Vocational Counselor: Contributions to Vocational Rehabilitation (11)

Collect educational, vocational, medical, and psychological information to best understand the person's recent vocational skills, and current condition after stroke.

Provide and coordinate appropriate analyses (e.g., physical demands, reasonable accommodations, work capacity evaluation) so the person can make an informed choice about his or her career options.

Help design a plan for independent living and career pursuits.

Identify skills, knowledge, and further training necessary to pursue a career consistent with the person's interest and abilities.

Develop an individualized plan for achieving employment that lists the steps needed to reach the person's job goal.

Provide labor market information and other resources to obtain job leads.

Follow the person's progress at work to help in maintaining the job.

The preceding text box lists the major interventions provided by the vocational counselor to the interdisciplinary rehabilitation process for a patient with stroke.

ACHIEVEMENTS IN SELF-CARE, PSYCHOLOGICAL ADAPTATIONS, COMMUNITY MOBILITY, AND SELF CARE

The preceding section described the general duties of a VRC, but vocational counselors individualize their services to meet each client's needs. A study by Culler et al. discussed the experience of vocational rehabilitation from the perspective of the stroke survivor, the VRC, and the employer. Though all three agreed on most of the commonly experienced barriers to a successful RTW, the vocational specialists pointed out some unique impediments to the process. These included a lack of awareness of the extent of the patient's disability, and the need for continued medical care; however, the most important barrier was a lack of motivation to RTW (7). A lack of motivation on the part of the stroke survivor can result in his or her failure to contact the VRC or other professionals. A connection between counselor and patient cannot form properly if there is unwillingness on either part.

In addition to requiring communication between parties, a good relationship is dependent on frequent communication between every member of the stroke patient's interdisciplinary team. An important factor, according to a survey of 21 vocational specialists, was the patient's motivation surrounding return to work. For example, if a patient is unwilling to fill out the necessary paperwork, he will have difficulty returning to work. In fact, it was apparent to these specialists that emotional factors often have a larger impact than physical ones (7).

The journey between having a stroke and returning to work is a process that involves a number of individuals and a significant amount of time. Several months may elapse before employment is regained, and even more follow-up time is required, often on the scale of years (7). Every state in the United States has a vocational rehabilitation program. A list of them can be found at https://askjan.org/cgi-win/TypeQuery.exe?902. Although the quality and capacity of these services vary, these are key resources for anyone with a disability who is seeking to obtain aid in returning to work.

Case Study 3

A 33-year-old disabled male construction contractor with a history of atrial fibrillation had a left frontal lobe ischemic stroke. His problem is not physical weakness, but rather what seems to his family to be a shift in his personality. He has very unpredictable mood changes and is often irritable and unwilling to cooperate. Before the stroke, he was congenial, helpful, and even-tempered. He previously worked as a contractor leading teams to frame houses for a home building company. What would be the process for such an individual with a VRC?

Recommendation

The biggest vocational focus for such a patient is his own interests and affinities. Perhaps certain aspects of his prior job remain appealing to him: for example, planning and organizing the materials needed to frame rooms and support floors. The VRC should work with the patient to determine what these affinities are. His behavioral issues require further evaluation and treatment. It is unclear if he might have poststroke depression, or perhaps some component of pseudobulbar affect. Treatment of his behavioral issues should be undertaken before attempting RTW.

The VRC can also work on social skills training and effective communication skills with the patient. Only when the patient is ready to RTW should he do so; this should be determined in consultation among the VRC, the patient, and the psychologist or psychiatrist. In addition to determining the right duties and timing of RTW, consideration should be given to any necessary job accommodations. The patient should be educated on how to explain his condition to fellow workers to minimize conflict in the workplace. Frequent breaks might help such a patient with his mood swings, and the personnel at the company should be aware of his condition so that other workers can make an effort to both recognize and accommodate his behavioral difficulties.

EMPLOYER ACCOMMODATIONS

There are various steps that an employer can take to accommodate a stroke client upon RTW. The accommodations themselves are generally split into two categories: physical and interpersonal. Obviously, stroke clients with physical disabilities might find it difficult both to get to work and, once there, to meet the physical demands of that work. Because of this, there is a set of "reasonable accommodations" that an employer is expected to make for the employee. For each job, there is a set of essential job duties that any employee is expected to meet, regardless of disability. For example, a copyeditor at a publishing house must have good grammar; a receptionist at a medical office must be able to greet and interact with patients. However, beyond those essential functions, employers are legally prohibited from discriminating based on the Americans with Disabilities Act.

Once a person of with a disability is hired, he or she must work with the employer to determine which accommodations are necessary and reasonable. The patient's activity limitations should be communicated to the employer as restrictions outlined by the rehabilitation physician. Restrictions might include weight lifting limits, no use of ladders or stairs, and the like. Under Title I of the Americans with Disabilities Act, employees must provide accommodations to persons with disabilities under their hire unless doing so causes unnecessary hardship (17). The U.S. Equal Employment Opportunity Commission provides a list of some common accommodations (18):

- Making existing facilities accessible
- Job restructuring
- Part-time or modified work schedules
- Acquiring or modifying equipment
- Changing tests, training materials, or policies
- Providing qualified readers or interpreters
- Reassignment to a vacant position

For a stroke patient, these accommodations are essential in creating a productive and comfortable work environment. However, many employers are unfamiliar with this process, and may have concerns about the feasibility and cost of these accommodations, as well as their legal liability regarding accommodations. An ongoing dialogue between employer and employee is necessary for these accommodations to take place. Specific modifications can often be requested in writing and explained by an occupational therapist. If a stroke survivor needs a change in the work environment, he or she must ask for it. However, if unable to do so, the stroke patient may have a family member or even (and especially) the VRC or rehabilitation physician ask the employer on the patient's behalf.

Interviewing for a new job can be especially challenging for someone with a visible disability. A potential employee is not required to disclose a disability during an interview, by phone, or otherwise. An employee may decide to tell a potential employer about the disability, but, so long as it does not impede the employee's ability to perform essential job functions, he or she is not obligated to do so. In Culler et al.'s 2011 article, an employer stated "[T]hroughout the hiring process, we just really don't look at any disability as a reason to hire or not hire that individual. We always try to get the best candidate based on the skills and experience." Regrettably, this attitude remains far from universal.

Assistive Technologies

Assistive technology is any piece of equipment, computerized or not, that improves the functional capabilities of someone with a disability (11). These items can be home-made or store-bought, and span a very wide range of disabilities and severities.

Visual Deficits

Visual deficits are common comorbidities of stroke. Often, stroke patients may also be challenged by macular degeneration, glaucoma, or retinopathy. Visual deficits themselves are varied: refractive visual field loss, ocular motility disorders, and visual perceptual disorders. Many of these are easy to accommodate. Beyond eyeglasses, there are many computerized technologies that make it easier for a visually impaired employee to work with computers. Screen enlargers and magnifiers are built into most computer operating systems; if these are not sufficient, there are external magnifying devices are easily mountable onto a computer screen itself. This is useful for low-vision stroke survivors.

For patients who become blind after stroke, there are still more visual aids, such as screen readers, which read the text on a computer screen out loud to a user. Newer devices, such as the iPhone, may have built-in screen readers and visual magnifier tools. Siri, Apple's speech recognition system, can assist with placing phone calls, performing web searches, and other functions for the visually impaired. Windows is a leader in screen-enlargement technology, and continues to accommodate its users. Thunder, a company that works with Microsoft for Windows devices, even has an application that reads out the names of approaching bus stops while one is riding the bus.

Fine Motor Deficits

Many stroke survivors experience loss of motor control or coordination. Assistive technology exists for these patients as well. Something as slight as a tremor can seriously affect someone's work productivity. However, many keyboards come equipped with sensitivity compensations. For example, a person with a tremor might lightly hit a key many times without meaning to. A keyboard can compensate for this by being less sensitive to touch. Phones and tablets now guess at which word is being typed, which can help compensate for spelling errors. Computers can increase their response time to give someone the chance to catch up with what they are typing. A keyguard can reduce accidental key strokes by sitting over the keyboard itself, and other jackets that color-code the keys can make it easier for someone with both visual and motor deficits to type effectively.

Some patients have trouble with wrist movement; a trackball or joystick can help them work around the difficulty of having to use a conventional mouse. With a trackball, only a finger is required to move the cursor. Patients with distal but not proximal motion might opt for a joystick, which gives somewhat greater control but still reduces reliance on use of the wrist. Touchpads are still more useful, reducing much hand movement entirely. The recent popularity of touch-sensitive tablets such as the iPad makes them very good mobile computer options.

Gross Motor Deficits

Some patients are left with major impairments in motor abilities after stroke. For someone with a brainstem stroke, there may be impaired motor abilities in all four limbs. In spite of these challenges, a motivated individual may be capable of returning to work. A "sip and puff" control system allows someone to move the cursor with only head movements, and to click the mouse using sip-and-puff motions. A head-tracker, which attaches to the computer being used, can track a reflective dot on the user's forehead and determine movement of a cursor. In this case, clicking commands can be achieved through voice, or sip and puff. More specific is an eye-tracker, which uses a similar technology but tracks eye movement. This is particularly useful for patients without any upper body movement.

If a patient has use of the lower extremities, a foot mouse can be very useful. In this case, one pedal is used to move the cursor, and another to click, somewhat like driving a car. Of course, for patients with preserved language and speech abilities, hands-free speech recognition technology is becoming better and better, as it becomes a mainstream way of communicating and working.

Hearing Impairment

Although hearing loss is infrequently a direct consequence of stroke, it can sometimes coincide in older stroke patients with age-related hearing loss. Hearing aids may be useful for some patients. For those who use computers in their work, headphones may be useful. Deaf patients can use visual cues on the screen in lieu of sounds in many cases.

Social Media

Recently, with the explosion of social media (including in the workplace), stroke survivor support groups are very easy to find and join. On the "Stroke Survivor" Facebook group, many of the 898 members post their stories of experiencing a stroke and returning to work. Others thank them for their contributions. That group is one of dozens on Facebook just like it, with this number growing steadily. Some are regional, like the Stroke Survivors of Ottawa Association; and some are age-based, as is the Young Stroke Survivors Action Group. The Stroke Association even has a Twitter account, where other members hashtag phrases like "#stroke" and "#strokesurvivor" in their tweets.

Having a community can be an essential means of overcoming a recent stroke, and of finding a way to RTW, and it has never been easier to become a part of one than now. The face of rehabilitation is changing with the new world

of communication. Stroke survivors no longer have to feel so alone—in fact, a whole social network is right at their fingertips.

CONCLUSION

William Arthur Ward (1921–1997), acclaimed writer and inspirational philosopher, once remarked: *"A true friend knows your weaknesses but shows you your strengths, feels your fears but fortifies your faith; sees your anxiety but frees your spirit; recognizes your disabilities but emphasizes your possibilities."*

Inspired by this doctrine, physiatrists working closely with the rehabilitation team are uniquely suited to helping stroke survivors in their quest for vocational recovery. This chapter has attempted to provide a broad overview of this essential process, based on the collective experience of the authors. The process of applying fundamental rehabilitation principles toward this noble goal is truly its own reward.

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52

Stroke From the Survivor's Perspective

Deborah Mack

When I had my stroke, I was working as a freelance writer and writing fiction. I'd recently signed a contract for a three-book publishing deal under which my first novel would be released the following summer. Fortunately, I received treatment quickly, and my recovery seemed miraculous. I remember walking around the CCU, feeling blessed. But then I looked at all the bed-ridden patients around me and felt horrible. After I had my stroke, I suffered a period where I couldn't sleep at all, along with a great deal of emotional lability, which I was told was normal for stroke victims. So, when I'd go to the hospital for rehab for the minor deficits at that time, I'd actually cry if I heard an announcement of a Code Blue or need for CPR. The only physical problems I had right after the stroke were slight weaknesses in my left hand and left leg. My mouth was also slightly affected, although not enough to make my speech slurred. Although my mouth would go lopsided when I smiled during the first few days after my stroke, I recovered enough within a week without rehabilitation so that no one who wasn't a trained observer could tell I suffered any deficit at all.

I underwent a few weeks of outpatient physical, occupational, and speech therapy to compensate for the minor physical deficits the stroke had caused. I remember tiring easily, which I was also told was normal. So, I made a point of taking breaks when I needed to. There were times I'd get so tired, I had to lie down.

However, after a couple of months of rehab, I seemed to be fine. I was released from further care with a clean bill of health, after having an outpatient surgical procedure to close the ASD in my heart. This hole between the atria had allowed a blood clot to reach my brain, thus causing the stroke. Once I'd had the procedure and finished rehab, I figured that was that.

Mind you, I wasn't exactly wet behind the ears when this happened. I was a practicing attorney for nine years. And I knew from experience that horrible things happen when people make the wrong choices. I also knew that life wasn't fair, from growing up poor. My family didn't live in a nice middle-class neighborhood with a white picket fence around the house. And my father was a writer, who wasn't always there for us. But he always encouraged me to be a writer. So, that was my therapy. I found solace in my work.

Because my first novel was due to come out soon, I'd arranged to speak at a local women's business club. While I was in the hospital, my husband had to cancel that speaking engagement. However, I also had a monthly deadline coming up to submit an article. After I was released from the hospital, I seemed to have fully recovered. So I got in touch with my editor and asked for an extension because I'd had a stroke. She asked me if I'd rather have someone else write it instead, but I refused. I told her I could do it if I could just get a little more time to turn it in.

I could have easily accepted her offer, but to be honest, I was afraid of being replaced. When you're a freelancer, you need to be dependable. I didn't want my editor to think my health had been compromised. As I said, I thought I was fine. Needless to say, that didn't turn out to be the case. I had the rug pulled out from under me five or six months later when I developed symptoms of dystonia in my left hand and foot (the side affected by the stroke). My first response was to seek treatment from the neurologist who'd evaluated me after I left the hospital. She diagnosed my condition, and she referred me to a movement disorder specialist and a group of physical therapists. I continued to work as if nothing had changed. In fact, I poured myself into my work because I was getting so little relief from medical treatments. And it's hard to simply relax and enjoy life when your body is constantly moving against your will.

Although my movement disorder physician was a most empathetic person and I felt lucky to have her as a doctor, my physical therapists seemed relatively clueless about my condition and state of mind. One even took this weird tone with me when I asked, "Will this *ever* get better?" Her response was, "You've had nerve damage." And she said it so matter-of-factly that I felt like an idiot for asking. Then, I wanted to slap her silly because no one should talk to a suffering person like that, least of all a person who's treating suffering people.

To make matters worse, my first novel went out-of-print nine months after it was published when the small press that released it went under. Talk about having the rug pulled out from under you.

At first, my treatment consisted of Botox injections, some medications, and physical therapy until the physical therapists basically threw up their hands and said they

couldn't do any more for me—as if they'd done anything for me in the first place. The Botox injections were a less-than-ideal treatment for my problem. The toxin weakened the muscles in my hands and arms, so my fingers ended up even less controllable. After the shots, instead of fully clenching, some of my fingers hung limp and useless from my hand, while other parts of my hand kept clenching. My grip was a joke. Dystonia is weird that way. After any given treatment, I might get some relief in one part of my hand while other parts remain clenched. This made typing a tedious chore.

Many well-meaning people suggest I use speech recognition software. This advice is actually contrary to my best interests in the long run. Because my dystonia was caused by a stroke, it makes more sense for me to keep typing. In this way, I hope to retrain my brain, like other stroke patients. This concept has been supported not only by my doctors, but also by a book I read called *Train Your Mind, Change Your Brain* by Sharon Begley. This book led me to seek alternative solutions to Western medicine.

One of the most frustrating aspects of trying to get good information about my condition has been the lack of communication between researchers. I'm assuming this failure to share knowledge is probably because of the competitive nature of research done to win prizes, grants, or other professional or financial compensation.

For me, the most interesting part of Sharon Begley's book was learning that the Dalai Lama held an annual neuroscience conference. Along with discussing how stroke patients can retrain their brains due to brain plasticity, the book explored the potential for Eastern medicine, meditation, and Buddhist techniques to aid in stroke recovery. Although dystonia wasn't mentioned in the book, I wondered if anyone at the Dalai Lama's Institute had even heard of my condition.

I looked up the Dalai Lama's Institute online and sent them an email asking if they knew about dystonia. To my surprise, they responded. However, they knew nothing about dystonia. This disheartened me and not only because dystonia is the third most common movement disorder. It just seemed to stand to reason that the institute would be seeking solutions for a neurological problem that Western medicine was incapable of treating adequately.

I even went so far as to try to contact Sharon Begley, but my email to her didn't go through. So often when I read news about brain research that didn't solve what I thought was a genuine problem, I'd wonder why they did it when people with dystonia were desperately seeking solutions. After a while, I had to stop asking that question. I could go mad, continuing to wonder why the medical and research community didn't have its act together.

I'd try to talk to people about my situation, and they'd come up with scenarios of their own. My question was always, "Why me?" One person explained to me that she had a difficult child, who seemed like he would never amount to anything. This was her and her husband's cross to bear for all the years they raised him. Eventually, he grew up and turned out fine. The ending of the story was the part where it all fell apart for me. I wanted to say, "Where's my happy ending? Don't I deserve a break from the torture?"

Naturally, people suggested finding support groups. My first attempt at finding such support was by reaching out to the dystonia community through the Dystonia Medical Research Foundation, because their name came up in a Google search right at the top. I got to know various people in my area through this organization and others online through Twitter. The problem with this approach was that dystonia manifests itself in myriad ways. Every type is different, so it was hard to find anyone with whom I could truly find totally common ground. In fact, if anything, getting involved with the dystonia community made me all the more aware of how fortunate I was compared to some. I still needed to find support, and this seemed inadequate.

The one time I spoke to a psychologist about my condition, he said, "Well, it won't kill you, right?" Right, doc, it'll only make you wish you were dead. Every damn day. For the rest of your life. And I was young. And it wasn't fair.

As a result, I had to simply go on with the capabilities I still possessed and a whole lot of unanswered questions. This meant that the best I could do was try things and hope that they made a difference. I tried all sorts of alternative therapies, ranging from acupuncture to acupressure to neurofeedback to nutritional supplements. I also tried a variety of pharmaceuticals. Everything I tried involved time and/or money. Each time I tried something, I'd hope for even the slightest improvement, only to have my hopes dashed.

There were days when I would get so frustrated, I'd simply howl at the top of my lungs. I'd curse god even though I didn't believe in a deity. I wasn't about to start believing in one that would do this to me. But then I'd feel bad because I knew that there were others who had it worse than I did. In fact, I was lucky I could do what I could. I was still able to write. I could walk. I could still think clearly. These were things I realized I should appreciate from a larger perspective. I realized that I was nobody special. I knew rationally that god wouldn't care more about my problems than anyone else's. This led me to question why a just god would create so many problems for all of us to begin with.

As a result, any suggestion that I look for support from god or religion seemed ridiculous. Even seeking support from other people seemed hopeless. When I tried to explain how I felt to others, they always told me to hang in there and not to lose hope. Often they suffered from chronic illnesses of their own, and they suggested possible solutions with the best of intentions, not knowing that their situation was completely different from mine.

Ultimately, coping with my condition involved a combination of finding joy in my life, family, and work and reaching out to others for support, although it took time for me to achieve a better work–life balance and to realize the source of that support.

Two years after my stroke, I started a blog called Random and Sundry Things. Blogging was considered the modern way for writers, consultants, and other businesses to market online. In starting my blog, I was trying to keep on working as

usual, using a blog to establish an online presence. Although everyone said you needed a niche for your blog, I refused to follow the rules and decided that I was too much of an "unrepentant generalist" to focus on any one subject. And because I had dystonia, I used the blog to raise awareness of the disorder and share resources and information because I could blog about anything there.

Although I started the blog as a place where I could post my thoughts about virtually any subject of interest that I might wish to write about, it became much more than that as time went by. I began expressing my opinion more openly about many subjects, including the failure to find a cure for medical conditions like dystonia.

The blog posts could vary in length and tone from satirical to a simple statement or video or photo. At one point, I was even included on a list of women political bloggers, much to my surprise. Blogging seemed to be a great way of connecting with others and sharing views while getting a benefit in return. To me, it was like a combined form of publishing, marketing, and networking. However, it also turned out to have therapeutic value for me, one I wouldn't realize until many years later.

What happened as a result was that I became increasingly immersed in blogging and when I saw a promising niche, I'd start a new blog to establish my credentials on the subject.

In fact, I decided, at some point, to start a second blog called Writing for Hire. The blog focused on the business aspects of being an independent writer, regardless of the type of writing one did.

This is where the online world put me at an advantage. No one could see my disability, so I could conduct business online as if nothing were wrong. I realize now that creating a wall between my business and personal life was taking a toll on me. However, it took years of working through pain and frustration to reach the point where I knew I had to learn to cope at a much deeper level.

After writing several book reviews on Random and Sundry Things, I started a book review blog called The Book Grrl. I hadn't planned to write reviews for fear of holding back and giving a less than honest opinion. However, I also knew that publishers did a bad job of promoting their mid-list authors and that good word-of-mouth helped sell books. After reviewing a few books on my first blog, I saw an opportunity to establish good will and expertise in the fiction and reviewing arena with a book review blog. This had the added benefit of making me a more discerning reader. I became better at evaluating the essence of each story and how it worked.

In addition, when you read and review lots of books, you develop an appreciation for good writing and a better sense of what works and what doesn't. This gave me insight into what agents must go through in choosing to sign clients. This made me all the more aware of the uphill battle I faced in trying to find agency representation for my novels. I continued to freelance, write novels, submit queries, and get really encouraging rejection letters on top of everything else.

I was blogging every day on all three blogs, along with doing my work and writing fiction. I was also going out to networking events to meet people at writer's conferences, local mixers, and other venues. In this way, I kept busy and didn't allow my dystonia to distract me from the goal of making a living as a writer. My main fear was that I'd be perceived as an object of pity or that if I defined myself in terms of my disability, people would see me as incapable and looking for a handout or a break. I only wanted to be judged on my own merits, like anyone else. Meanwhile, my first blog, Random and Sundry Things, continued to be the one where I could write about anything, including my own occasional news, frustrations, or hopes related to dystonia.

Then, I happened to see the film *Ikiru*, which may have changed my life. Kurasowa's *Ikiru* is about a bureaucrat who sees no point to his existence. He hates his job, one in which he tries and fails to accomplish goals he thinks are important. He's lonely and has no one to turn to until he meets a young woman, who works in a toy factory. It's in the simple task of creating toys for children that she finds her life's meaning. He sees the goodness in her because her nature is essentially so giving.

Then he finds out he has cancer. At this point, he decides he must do something to make his mark and bring joy to the world. He decides he's going to build a public park, no matter what it takes or how much red tape he has to wade through. By the end of the film, the man is dead, but the park is built. The final scene shows him or perhaps his spirit, in his park, on the swing. The film was so beautiful and inspirational that I decided I had to do something, too.

I decided to organize a fundraiser for the Dystonia Medical Research Foundation. This seemed logical because I had ties to the group already and I knew another local dystonia sufferer who held an annual fundraiser. I did this while freelancing and writing fiction, so I was immersing myself in work and philanthropic efforts full-time. I look back on this and realize that doing this was part of my coping process. I had to do something with myself. I couldn't just sit around useless. I was always a busy, productive person before I had dystonia, and I wanted to continue being one.

The year 2009 ended up being one for the books. The fundraiser took place in May 2009. While I was organizing the fundraiser, I took a screenwriting course and finished a screenplay I had started years before. In June 2009, I re-released my first novel by self-publishing it as an ebook, then as a print book one month later. In September, my husband and I took our first trip overseas. We went to Italy, the country of his ancestors, and a place I'd always wanted to see. Thinking back on it, I realize it was a year of making great things happen because I could. However, at the time, I was simply keeping busy and trying to get things done that I thought were important.

Meanwhile, I kept seeking solutions from different alternative medical providers, but nothing they did seemed to really work. With each attempt, I'd have to ask myself, am I wasting time and money I could be spending more productively? No one had the answers, of course. So, I had to

decide for myself. This was like trying to walk through a maze blindfolded. I had no idea what I was doing or guidelines for how to make the right decisions. And no one could give me any real guidance. This, of course, was terribly frustrating.

What made matters even worse was that my disability went unnoticed. I felt that no one could understand the degree to which I was suffering. But I couldn't go around complaining all the time. That would annoy people. As a result, I kept my frustration bottled up, but allowed it to release through my writing, blogging, and other activities.

Meanwhile, I continued to look for answers and otherwise cope through engaging in my work as if I didn't have a disability. In fact, I tended to downplay it around others for fear of seeming weak or incompetent to do my job. I simply refused to be defined by my limitations. Yet, with no indication that anyone could truly understand what I was going through, I felt cheated. I began to resent people who actually suffered more than me, simply because people noticed their suffering and acknowledged it.

In my heart, I knew this was wrong. I didn't want to be in a wheelchair, nor did I want to suffer more. I also bore no ill will toward people who had suffered. If anything, I felt so bad for them, it began to take a toll on my mental health over time.

My sheer determination to make a living as a writer through freelancing led me to consider a variety of niche subject areas. Over the years, I'd joined a variety of groups and considered specializing in various topics. However, each of these groups involved going to meetings and interacting socially on a regular basis, which was becoming increasingly difficult for me, both physically and mentally.

Nonetheless, because I had both interest and expertise in environmental issues, as a former land use attorney and EPA lawyer, this seemed like a great subject in which to specialize. So, I started a fourth blog called Green Reality Check. Therefore, along with trying to find clients through networking on and offline, I was now posting to four blogs. I was also scanning headlines for news items and blog posts that could provide material for any of the blogs. This kept me well-informed of developments on a wide array of topics, including politics, publishing, bookselling, writing, sustainability, environmentalism, nature conservation, films, book reviews, travel, health news, and dystonia.

Between the onslaught of information I was picking through, the physical demands of all the work and the overall stress of everything, I was already feeling a bit overwhelmed. But I refused to give up. I wanted to make a living as a writer, and I wanted to write fiction and find a publisher and/or an agent. I also planned to write a series, per the terms of my old publishing contract. But I couldn't have imagined making a living as a fiction writer at that point.

One of the most frustrating hurdles I faced when my novel went out of print was that many agents didn't seem interested in representing my out-of-print novel, despite the fact that the book had been well received before the small press went under and there was the potential to create a whole series of books based on the protagonist, which was what mystery readers tend to like.

Despite this, I revised a previous novel to make it the sequel and wrote the third novel in the series. Then, at the suggestion of various agents, I wrote two stand-alone novels. I was at a loss for where to go next, so I just kept writing, submitting queries and getting rejections. The process reminded me of the old maxim: "Insanity is doing the same thing over and over and expecting a different result."

I learned over time that I had to conserve my strength and focus on the positive things in life. I had to stay focused on getting the job done and not be distracted by wasted gestures and activities. I believe that over time this failure to acknowledge my own frustration and rage at my situation ultimately hurt me. I was so focused on proving to myself that I still had what it took to succeed that I needed a way to ridicule myself for lack of other outlets.

Hell, there were nights I'd pray (even though I didn't believe in god and cursed the nonexistent god's name on more than one occasion), "Please, let me die in my sleep tonight." But I didn't, nor did I kill myself because I felt I had a mission. And killing myself would be a waste of my potential. My life would've amounted to nothing. And my husband and family would suffer.

But I couldn't talk about it for fear of sounding ungrateful. Dystonia sufferers all differ, so I could truly empathize with them, but it was hard to explain my particular predicament. None of my writer friends truly understood my pain. On top of which, I felt guilty, because I knew others suffered much more than I did.

When I decided to self-publish my out-of-print novel, I hit upon an idea for a blog to market myself as an author. I called the blog, My Life on the Mid-List, in homage to Kathy Griffin. I thought it was because Kathy Griffin was doing the kinds of things authors did all the time to promote themselves—events and so on. She made a joke of her own life and it worked out for her. I thought that idea had possibilities, though I wasn't sure how well it would work for a writer.

However, I'd reached the point where my own life seemed so ridiculous, the only thing I could think to do was laugh at my calamities. And so I began my fifth blog. Significantly, the very first thing I posted after the initial post was called "There's No Crying in Publishing." Essentially, it was a humorous diatribe that said, "You think you have problems? Try being me." I look at that now and realize I was a very angry person, who had to laugh at her own life or go mad. However, at the time, I was so consumed with presenting myself as being strong and capable despite my disability, I failed to address the now obvious emotional issues I was burying beneath the humor.

All the while I'd been freelancing, I was writing fiction and sending queries to agents and reputable small publishers. I started my fifth blog in June 2009, along with self-publishing my out-of-print first novel, in a bid to establish a readership while I was seeking an agent or new publisher. The book had received a handful of great reviews from various publications. It also got some rave online reviews from readers.

My blog became my forum for sending up the bizarre nature of the publishing world. Self-publishing my work as ebooks wasn't part of a big plan on my part. I stumbled across the information by reading blogs about the subject while writing posts for Writing for Hire. As a writer seeking a readership, it only made sense to me to take advantage of new technology to create, market, and sell my books.

It didn't take long for me to figure out that, if I priced my ebooks low, I could make more money from volume sales. So I took this approach in the hope that selling my ebooks cheaply would generate more sales, which hopefully would lead to more and better word of mouth about the books. When I started to see significant financial results, I threw myself even harder toward succeeding as a fiction writer. Based on my writers group's suggestion, I revised the third novel in the series and made it the sequel. I also wrote occasional short stories, some of which were published in anthologies.

Eventually, my husband could see I was wearing myself out, and he suggested that I focus solely on fiction writing. I also grew tired of waiting for the publishing world to accept me. So I decided to take the leap to self-publishing all my novels.

This felt like a huge gamble. Up until then, I would never have thought to self-publish all my work, let alone start trying to earn a living from fiction writing, before I'd had time to build a more substantial readership. However, once I saw how well self-publishing ebooks could pay, if you played your cards right, I figured all the effort I was putting toward freelancing could be better spent establishing my credentials as an author.

So, I approached fiction writing and marketing the same way I did when I was freelancing. I looked for ways to sell my work, on- and offline. In the process, I discovered that many approaches authors took to marketing their work were time-consuming and required both physical stamina and social skills, both of which I was pushing to the limit. My secret disorder made it all the harder to keep going to events that didn't pay off financially or doing things the old-fashioned way, such as driving all over creation to book signings, book festivals, and other traditional selling venues.

Along with that, although I didn't realize it, blogging was therapeutic for me. The Internet and social media provided a way to market my work more easily than in the past. This way I could continue to do my work while being relieved of the stress created by social interaction. The only problem with this approach was that the more dependent I became on it, the less I stepped away from my computer. The effect was to isolate me, which wasn't healthy.

I began to rely increasingly on technology, the Internet, blogging, and Twitter to sell my work. Because writing takes time and more effort when you have a condition like dystonia, the less physical strain and time I put into marketing, the better off I was. Or so it seemed. Online marketing required far less time and was much more cost-efficient than the usual ways of getting the work out there.

Although I gained financially, having hit the ebook market early enough to avoid the huge competition new authors face now, I lost touch with people. At least, my face-to-face dealings with them were minimized so much, I began to feel like a hermit. However, I got to know people online, which seemed like enough for a while.

Furthermore, my ebook sales were far greater than I could have ever imagined possible, not only in the United States, but also in the United Kingdom. Many authors asked how I was doing this, and I had no idea. I just assumed my author blog and perhaps my interactions on Twitter with people in England and Ireland were helping. And I had gotten to know one reader in particular in England through blogging as well as an author who had been kind enough to leave a comment on my blog suggesting the names of two agents in the United Kingdom I could try to approach if I wanted to.

It soon got to the point where the only times I stepped away from the computer were on weekends, at writers conferences, and for the odd special occasion. I literally had to pencil in relaxation time. I forced myself to do other things, because I feared becoming a complete shut-in. I yearned for the time when relaxation and fun came so simply. Yet going out to parties and other social events requires that you always be on. I had to bite my tongue many times to keep from shouting my frustration to one hapless person or other who couldn't see the ordeal all the fun was for me.

Clearly, I was becoming consumed by my work and Internet interactions to the point where I was losing touch with people right in my own backyard. It's hard not to seek release through losing yourself in creative work and the freedom of speech the Internet grants you when you're suffering and you have no idea if it will ever stop.

For nearly seven years, I conducted business this way. I kept writing, blogging, and suffering silently. I think I found meaning and purpose in doing things for people online. Engaging in random acts of kindness on the Internet seemed to help me work through my own sorrows. It was also smart marketing and networking, in my opinion. And I could do it from home without worrying about how happy I looked, whether I was responding appropriately on the fly, how the exertion would affect me physically, and myriad other things I'd always taken for granted before I developed a movement disorder.

To complicate matters, I started to see and feel changes in my body because of my movement disorder. My balance was affected. I'd developed a bunion-like growth on my hand. This worried me on top of everything else.

Eventually, my work wore me down so much, I had to face my demons. The turning point may have come while I was attending a regional dystonia conference. I was fast reaching the end of my rope when I heard a speaker talking about acupuncture.

I'd done acupuncture before, so I wasn't terribly hopeful when I sat in on the session. However, the presenter got me thinking about it again. His position was that you needed to see a practitioner that knew dystonia and was right for you. Acupuncture takes a highly subjective approach to treatment and cure. Not only is it more holistic than Western

medicine, but it also emphasizes individualized care, based upon factors specific to each patient.

In other words, the only way to find out if acupuncture could help me was to find the right practitioner and give it a real shot. This had to be with the understanding that each patient requires a different approach. Each acupuncturist takes a different approach to the same set of symptoms. I think it's this lack of standardized care that makes acupuncture so suspect or seemingly unworthy of being taken seriously by Western medicine and traditional physicians.

However, I'd arrived at the point where I had to take responsibility and change the way I was treating and coping with my health problems. Simply writing, blogging, and marketing weren't cutting it anymore.

So, between my husband's and my efforts, we were able to find an acupuncture clinic that treated stroke and movement disorders right at the hospital where I was going for traditional medical care. After a time, I noticed acupuncture seemed to provide small amounts of relief. Although it didn't fix the problem, I could feel a difference in my capabilities. These benefits took time to register on my radar. In addition, when my acupuncturist tested my grip after I underwent several months of treatment, even I could tell there were small improvements that I hadn't noticed and wouldn't have if he hadn't bothered to check for them.

On top of this, acupuncture helped my overall relaxation and improved my mood to an extent. I'm assuming that the theory would be that by balancing my body's *chi*, acupuncture was treating my problems overall at both a physical and emotional level.

I began to notice that after a session, I'd have thoughts that seemed almost revelatory. I started blogging about my postacupuncture thoughts because they seemed important, and I wanted to share information, as usual.

These were thoughts I posted on my first blog because I could write about anything there. So, in effect, that blog became like an online shrink, a place where I could vent about my problems and breakthroughs. However, I didn't limit myself to talking about dystonia. I continued to fear being shunned or categorized, based upon my health problems. Further, I'd reached a point in my writing career where I had achieved enough success that I was being taken seriously by my peers in the business. So I worried about making too much of my condition on one blog while marketing myself as an author on another. Given the still unhappy state of my physical and mental health, I'd begun discussing my problems more openly on my author blog. Always I would turn my problems into a joke, because the whole purpose of the blog was to laugh at my own misfortunes. This approach worked until it didn't.

I eventually became so worn down by exertion and emotional baggage that I became depressed. When it reached the point where I couldn't bear to move or do anything, I realized I needed more help than acupuncture alone could provide. However, I think acupuncture helped me understand that my moods were my responsibility. Thus, by blogging and getting acupuncture, I was realizing things about myself and sharing those thoughts online. In this way, my Random and Sundry Things blog became a virtual sounding board in which I did a slow turnaround in my mood and coping with my condition. However, this took time.

By the end of 2011, I'd reached an epic low outlook when I decided to start taking antidepressants. I'd tried them before and, for some reason, chose not to keep taking them. However, when I realized that I'd become so depressed that I could barely muster the strength to get up in the morning, I knew I had to do something. So, I took another crack at managing my moods through pharmaceuticals.

A few things happened, all at once, that turned me around. The first thing I noticed was that I was willing to try new approaches to my work. In fact, I seemed to find new resolve. But the drugs weren't the only thing that changed my outlook. The acupuncture was bringing out long-buried thoughts and feelings that I needed to work through, as well as providing some relief from my physical symptoms.

By that time, I'd enjoyed more financial success as a fiction writer than I'd ever have thought possible as a new author with two novels and a handful of short stories. I was on the cusp of publishing my third novel in an increasingly competitive fiction writing market. And I could already read the writing on the wall. The boom days of self-publishing ebooks were over. My huge success the previous year, along with making the *New York Times* ebook bestseller list, were temporary states of being for an author who couldn't or wouldn't crank out books as fast as possible or, in essence, sell out to Amazon, a company that was poised to monopolize the publishing business.

The publishing world had changed in both good ways and bad. Now, everyone was jumping aboard the self-publishing bandwagon. This made it much harder for any one author to stand out, especially one without much name recognition unless you were willing to self-publish exclusively for limited periods with Amazon, which I chose not to do. Frankly, I believed the long-term effect of Amazon's limited exclusivity program would be to devalue our work to the point where fiction writers would be back to where they were when they were accepting terrible deals to land a publisher.

The pressure was on for me to adjust to changing times, even as I struggled with my own physical and emotional problems. This made my decision not to publish exclusively with Amazon all the tougher because I had so much to lose financially. However, I refused to compromise the value of my books or my personal values while making those adjustments.

By the time I started taking antidepressants, I was looking for new outlets: something to rejuvenate my passion for my work. I'd already focused more on improving my blogging and was seeing results in terms of attracting new followers and other bloggers who liked what they saw or left comments. At that point, I realized that blogging was like publishing, but different. Bloggers could gravitate toward one another, based on their shared interests, passions or other commonalities. They could, in essence, be like an online support group.

In January 2012, I registered for an indie film seminar that covered all the details of planning, financing, and creating films as an independent producer. Even though I'd never thought about producing films, the seminar seemed like a good way to step away from my computer, meet new people, and learn the ropes of the film business. I also had not only a feature film script but hopes that someday my novels might be turned into movies.

In short, I fell back upon what I knew about personal networking. In my opinion, there's no substitute for going places and actually meeting people. I'd found this to be true before I got dystonia when I attended more writer's conferences and events.

So I attended the seminar and learned about film production. I even realized that I could be a film producer if I chose to be because it entailed using the same skills I used when organizing the fundraiser. This realization was such a positive affirmation in itself that I blogged about it and even attributed my dystonia as the spark that set things in motion.

My thinking was that if not for getting dystonia, I wouldn't have organized the fundraiser; thus I never would have realized my own ability to be a producer. However, this epiphany was just one of many related to my dystonia.

Shortly after I took the seminar, I read a self-help book on happiness. I'll admit I wasn't expecting it to be much more than a lot of pop psychology. However, there was a reference in the book to Viktor Frankl's theory about the gap between stimulus and response. Basically, the theory was that we could all choose to be happy despite our circumstances. I thought, "Can it really be that simple?" Then, I realized that these were the thoughts of a Jewish man who'd lost his family and been tortured by Nazis in a concentration camp. I knew then that I could choose happiness too.

Even so, it helped immeasurably when my doctor had a talk with me about my feelings. He said that I sounded guilty. I realized that I was letting guilt ruin my happiness. In fact, instead of choosing to be happy, I had been allowing guilt and anger to make me unhappy.

I also realized that no one could really judge another person's pain. I decided that from then on, I wouldn't compare myself to anyone or engage in senseless arguments because neither were worth it. Humor, on the other hand, made the world bearable. As long as I could laugh at life on my blogs, I felt better about everything. This actually attracted new followers, which helped even more. At that point, I realized that coping with a bad condition was up to me. I realized that I could adapt and thrive, despite everything, if I wanted to. I might never have reached this point if it hadn't been for friends in my day-to-day life as well as those I made online. Whereas traditional medicine hasn't provided all the solutions for my problem, blogging and social media have actually helped.

Given what I'd learned about film production, it was only a matter of time before I realized that the same skills applied to producing books. And because I was actually a book producer, because I published my books under my own publishing imprint, all I had to do was use Internet resources to distribute them.

At the film seminar, I learned about crowdsourcing. This gave me an idea that I thought could result in a win for me, for readers, bookstores, and authors. And I thought it was the perfect solution for self-published authors—one that could allow me to earn a living as a writer despite my disability.

Part of the reason I thought this could work is that I had previously sold and donated books on the Internet to places as far away as England and Australia because I'd gotten to know people living in those countries through blogging and social media.

This knowledge in itself was a powerful affirmation of what anyone could do on the Internet. However, I also realized that I needed to get out more and spend quality time in the real world more often. So, in the summer of 2012, I decided we should take another overseas trip. This time, my husband and I went to Ireland and the United Kingdom. I left my laptop behind and made plans to meet people I'd gotten to know only online.

As with the trip to Italy, it was an unforgettable experience. However, meeting people I'd only gotten to know because of Twitter or blogging made it all the more special. This included not only an author in Ireland but also a reader in England, who I'd gotten to know through blogging and a shared love of Bond movies and *Doctor Who*. Not many authors get to both find and actually meet one of their own readers, in such an unusual way.

On top of all that, the salutary effects of traveling and experiencing other cultures cannot be understated. I came back from that vacation feeling reinvigorated and more confident that I could accomplish my goals despite whatever setbacks I might experience trying to reach them.

That year, I also submitted the screenplay I'd finished in 2009 to a contest and made the quarterfinals cut. As a result, I attended the Austin Film Festival as well as the mystery convention Bouchercon in Cleveland, OH. Both events took place in October 2012. Much as I love to travel, this tested my endurance some. But I think coping with dystonia or any poststroke chronic condition is a matter of choosing to focus on the positive and testing the boundaries of one's abilities. Both experiences were well worth the effort, and I couldn't be happier for having chosen to take the challenge of going to both events.

And so I continue to write novels and short stories and, with any luck, will write more screenplays. I have high hopes that someday one of my books might even be adapted into a film. I try to take my life one day at a time, one step at a time.

If I were asked to provide a wish list to the medical community about what they might want to do for stroke survivors with movement disorders, I'd include the following:

1. Talk to your patients and encourage them to talk to you about their feelings.
2. Encourage your patients to engage in life activities and not to shut the world out. Suggest therapy, where it seems appropriate. The online world can provide support in many cases, as I've discovered.

3. Keep doing research on better methods to treat movement disorders like dystonia and, ideally, find a cure.
4. Coordinate your research and treatment with acupuncture and other nontraditional methods.
5. Find ways to raise awareness of poststroke movement disorders so that the general public is more aware of them.

Learning to cope with poststroke dystonia has been and continues to be a process. The details of each person's coping process will differ, but the secret lies in one's attitude. Be grateful for what you can do and keep doing it. Whatever happens, choose to be happy.

I'm not perfect at doing this, but I'd like to think of myself as a work in progress. As long as I can keep my spirits up and keep my work, play, and life balanced, I figure I'll be okay.

In my wildest dreams, I would love to meet with the Dalai Lama and tell him about dystonia so the subject could be covered at one of his neurological conferences. I also wish that Western and Eastern medicine would combine forces to find more effective ways to deal with dystonia and, ideally, find a cure for it.

Index