CHAPTER 40

Leprosy (Hansen's Disease)

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Leprosy, also known as Hansen's disease, is a chronic infectious disease predominantly affecting skin and nerves. The nerve damage occurring in leprosy may result in deformity, disability, and social stigma, creating problems for patients and their families.

The interaction between the patient's immune system and the infection is dynamic, resulting in various clinical forms of leprosy and complications.

Outside endemic areas, doctors often fail to diagnose leprosy, with unfortunate consequences for the patients. In both the United States and the United Kingdom, 40% of new cases have severe neuropathy at diagnosis, reflecting a combination of late presentation and diagnosis. Early recognition of leprosy is important, because the infection is curable and prompt treatment can reduce nerve damage and associated stigma.

ETIOLOGY

Mycobacterium leprae is an obligate intracellular pathogen, first identified in the nodules of lepromatous leprosy patients by Armauer Hansen in 1873. It is a rod-shaped, Gram-positive organism that is acid-fast when stained by the Ziehl–Nielsen or the better Fite methods. Viable organisms stain in a uniform, solid manner. With therapy, most organisms quickly lose their solid staining, appearing beaded or fragmented.

M. leprae has never been successfully grown in artificial media but can be propagated in the mouse footpad and the nine-banded armadillo, which is the only known natural reservoir of the organism. The organism has a long doubling time of 13 days at low temperatures (33-35°C), selectively invading skin macrophages and peripheral nerve Schwann cells. *M. leprae* does not produce any known toxins, and tissue injury is caused by the host's immune response or by the sheer mass of infecting bacilli.

In 2001, the genome of *M. leprae* was sequenced. The organism appears to have undergone extensive reductive evolution with considerable downsizing of its genome compared with *Mycobacterium tuberculosis*. Almost half of the genome is occupied by pseudogenes.

EPIDEMIOLOGY

In 2013, some 215,616 new cases were registered worldwide and reported to the World Health Organization (WHO) by 103 countries. Seven endemic countries reported the most new cases: India, Brazil, Indonesia, Ethiopia, Democratic Republic of the Congo, Nigeria, and Nepal. India reported 59% of the global burden of leprosy.

In the United States, 188 new cases were reported in 2013 by the Centers for Disease Control and Prevention. Immigrants from Mexico, the Philippines, Pacific Islands, and India account for the bulk of new cases. Leprosy has a long incubation period (2-10 years), so patients can present long after leaving endemic areas. However, in recent years 20-25% of new cases have occurred in those who were born in the United States, had not traveled to endemic countries, and were living in Texas, Louisiana, and Florida.

Leprosy affects adult males more than females, with ratios of 1.6:1 to 3:1 in different countries. In children the ratio is 1:1.

The exact mode of disease transmission is unknown. Studies of disease transmission have been hampered by the lack of a culture system, the absence of serologic markers, the latent period of 2-10 years before disease onset, and the high degree of natural immunity in most persons. Tuberculoid leprosy patients shed no demonstrable organisms and are regarded as noncontagious, although this is unproven. Untreated lepromatous patients shed millions of viable-appearing organisms daily, primarily in nasal and oral secretions. Bacilli may also be found in skin scales, sweat, blood, breast milk, and wound exudate. The possibility of animal-to-human transmission is supported by reports of cases in persons handling or consuming armadillos in the Americas.

Transmission is thought to occur mainly through aerosolized nasal droplets, spread when coughing or sneezing takes place. Following contact with an infective dose of *M. leprae*, most people will develop adequate protective immunity and therefore will not develop any clinically detectable signs or symptoms. Only a small percentage of individuals will develop clinical disease. Some literature suggests transmission via contact with broken skin, blood, or soil, as the mycobacteria are known to survive in the environment for up to 46 days.

CLINICAL FEATURES

Leprosy may be considered an immunologic disease. Immunity defines susceptibility to leprosy, type of clinical leprosy, pathology, and major clinical complications of leprosy. Classification of the disease is important to determine prognosis, transmission risk, and selection of treatment. There are two systems used to classify leprosy patients.

The Ridley–Jopling system uses clinical and histopathologic features and the bacteriological index (**Fig. 40.1**). Leprosy manifests in a spectrum of disease forms, ranging from the tuberculoid to the lepromatous.

The WHO classification is a simplified version depending on the number of skin lesions, which can be used in the field when slit skin smears or biopsies are not available. Patients with one to five skin lesions are classified as paucibacillary and those with six or more lesions as multibacillary. Up to 60% of patients classified as multibacillary are smear negative.

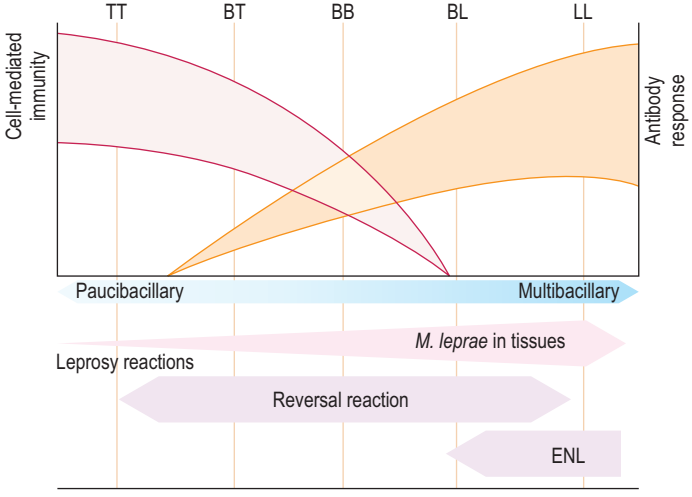

Fig. 40.1 **The Ridley–Jopling Classification and the relationship with host immunity. *BB*, Borderline; *BL*, borderline lepromatous; *BT*, borderline tuberculoid; *ENL*, erythema nodosum leprosum; *LL*, lepromatous; *TT*, tuberculoid.**

Clinical features of leprosy are a continuum between the tuberculoid and lepromatous forms of disease. There is substantial overlap in the appearance of the different forms, and careful assessment of clinical and histologic parameters is needed for accurate diagnosis. Important clinical features include (1) number of skin lesions, (2) size and morphology of skin lesions, (3) presence of neuropathy, and (4) presence of reactional states.

Indeterminate leprosy is the earliest recognizable form of the disease and may be extremely difficult to diagnose. There is typically a single hypopigmented or erythematous macule without abnormal sensation or sweating. There is no nerve enlargement. It is commonly seen in children. Biopsy is nonspecific and shows few or no organisms. Most heal without treatment, but 25% may progress to established leprosy.

Table 40.1 describes the varied clinical manifestations of leprosy. These are determined by the host's response to the leprosy bacillus: tuberculoid (TT) patients have a uniform clinical, histologic, and immunologic response manifesting as limited clinical disease, granuloma formation, and active cell-mediated immunity (**Fig. 40.2**); lepromatous leprosy (LL) patients have multiple clinical signs, a high bacterial load, and low cell-mediated immunity (**Fig. 40.3**). Between these two extremes there is a range of variations in host response; these comprise borderline cases (BT, BB, BL) (**Fig. 40.4**). Immunologically, borderline cases are unstable, while polar tuberculoid and lepromatous cases are stable.

Neural involvement in leprosy is due to selective proliferation of *M. leprae* in superficial peripheral nerves. Nerve destruction occurs either from inflammation or from infiltration by masses of infecting organisms. Inflammation in the nerves may result in nerve entrapment. Damage to peripheral nerve trunks produces sensory loss and weakness of the muscles supplied by the affected peripheral nerves. Sensory function is the earliest affected in leprosy; sensory impairment can occur alone without motor involvement. Autonomic nerve damage results in dryness of the hands and feet. The ulnar, median, posterior tibial, common peroneal, and radial nerves are most commonly involved. The central nervous system is never involved, and *M. leprae* does not usually propagate within internal organs due to high human core body temperature.

DIAGNOSIS

A clinical diagnosis of leprosy is made by considering key features associated with the disease (the presence of characteristic skin lesions with anesthesia, and thickening of one or more peripheral nerves), supported by skin smears and biopsy. A patient may present with a macular hypopigmented skin lesion, weakness or pain in the hand due to nerve involvement, facial palsy, acute foot drop, or a painless burn or ulcer in an anesthetic hand or foot. Patients may also present with painful eyes as a first indication of lepromatous leprosy. The diagnosis of leprosy should be considered in anyone from an endemic area who presents with typical skin lesions, neuropathic ulcers, or a peripheral neuropathy. In leprosy-endemic settings, a typical skin lesion that is also anesthetic is said to be 70% sensitive for the diagnosis of leprosy, and has been recommended by the WHO as sufficient for leprosy diagnosis by knowledgeable health providers. Clinicians need to have a high index of suspicion when dealing with patients from endemic areas.

Evaluation of patients should include the following:

1. A careful inspection of the skin with diagrams or photography of lesions should be carried out.
2. Areas of anhidrosis should be noted, because this correlates with loss of protective sensation.
3. Superficial nerves should be palpated for enlargement and tenderness.
4. Detailed sensory testing should be carried out to define deficits. This can be done with graded nylon monofilaments or a ball-point pen.
5. Motor testing and nerve conduction studies should be performed.
6. Examination of insensitive extremities for areas of trauma or pressure injury is important, as is assessment of the adequacy of footwear.
7. Ophthalmologic evaluation is indicated for patients with facial or ocular involvement.

TABLE 40.1 Major Clinical Features of the Disease Spectrum in Leprosy

Clinical Features	CLASSIFICATION				
	Tuberculoid (TT)	Borderline Tuberculoid (BT)	Borderline (BB)	Borderline Lepromatous (BL)	Lepromatous (LL)
	WHO PAUCIBACILLARY			WHO MULTIBACILLARY	
Skin					
Infiltrated lesions	Defined plaques, healing centers	Irregular plaques with partially raised edges	Polymorphic, "punched out centers"	Papules, nodules	Diffuse thickening
Macular lesions	Single, small, but can be large	Several, any size, "geographical"	Multiple, all sizes, bizarre	Innumerable, small	Innumerable, confluent
Nerve					
Peripheral nerve	Solitary enlarged nerves	Several nerves, asymmetrical	Many nerves, asymmetrical pattern	Late neural thickening, asymmetrical, anesthesia and paresis	Slow symmetrical loss, "glove and stocking" anesthesia
Microbiology					
Bacterial index	0-1	0-2	2-3	1-4	4-6
Histology					
Lymphocytes	+	++	+/–	++	+/–
Macrophages	–	–	+/–	–	–
Epithelioid cells	++	+/–	–	–	–
Antibody, anti-*M. leprae*	–/+	–/++	+	++	++

WHO, World Health Organization.

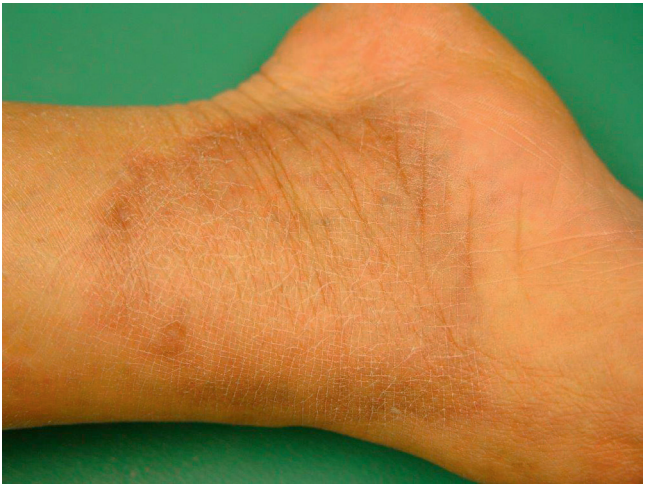

Fig. 40.2 **Tuberculoid leprosy.** Tuberculoid leprosy plaque, which is anesthetic and granulomatous, often with no bacilli on biopsy. (Courtesy of James P. Harnisch, MD.)

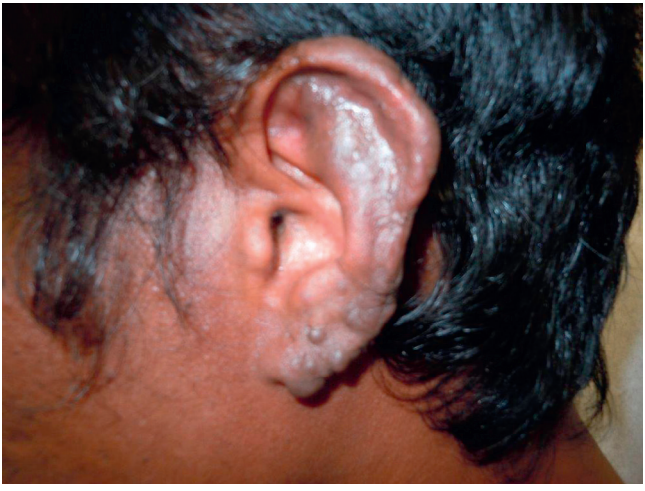

Fig. 40.3 **Lepromatous leprosy.** Classic nodules of lepromatous leprosy on the cool surface of the ear. Many bacilli seen on biopsy. (Courtesy of James P. Harnisch, MD.)

The differential diagnosis of leprosy is wide due to its protean manifestations. Individuals found to have granulomatous pathology on skin or nerve biopsy, peripheral neuropathy, mononeuritis, or mononeuritis multiplex may have leprosy. Examples of other diagnoses that may enter the differential diagnosis depending on the type of leprosy include superficial fungal infections of the skin, such as tinea corporis, pityriasis versicolor, or pityriasis alba; vitiligo; sarcoidosis; secondary and tertiary syphilis; mycosis fungoides; and psoriasis. Other

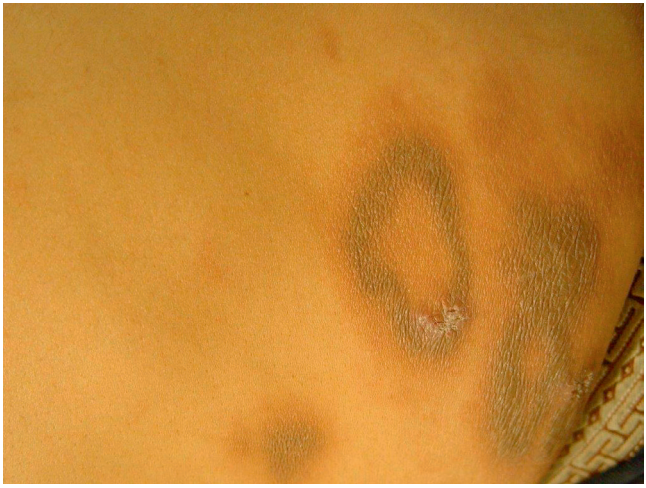

Fig. 40.4 **Borderline leprosy.** Target-like plaques of borderline leprosy. Always biopsy the peripheral border. (Courtesy of James P. Harnisch, MD.)

mycobacterial infections such as *Mycobacterium tuberculosis* and *Mycobacterium ulcerans* may also cause diagnostic confusion.

BACTERIOLOGICAL AND HISTOLOGICAL EXAMINATION

Slit skin smears should be taken to look for acid-fast bacilli. *M. leprae* on the smears are counted and the bacterial index calculated on a semi-quantitative scale. A negative result does not exclude leprosy, as TT and BT lesions may contain no detectable bacteria.

Histopathological evaluation is essential for accurate classification of leprosy lesions and is the best diagnostic test in a well-resourced setting, both for confirming and for excluding the diagnosis of leprosy. The presence of granulomata and lymphocytic infiltration of dermal nerves and skin adnexal structures such as sweat glands in skin lesions confirms the diagnosis. Biopsy should be taken from the active border of a skin lesion and stained with a Fite stain in addition to routine stains. A nerve biopsy may be required in cases with no visible skin lesions. A cutaneous sensory nerve is selected in an area of neuropathy and examined histologically for organisms and typical granulomas.

Skin smears aid in diagnosis, in assessment of bacillary load, and in following response to therapy. The bacteria should diminish within the smears or biopsies during therapy unless there is an issue of compliance or resistance. In multibacillary patients the reduction of bacilli is often slow, over many years.

SEROLOGICAL TESTS AND POLYMERASE CHAIN REACTION

Recent advances have been made in serological diagnostic testing. Antibodies to the *M. leprae*–specific PGL-1 (antiphenolic glycolipid) are present in 90% of patients with untreated lepromatous disease, but only 40-50% of patients with paucibacillary disease and 1-5 % of healthy controls. A negative test does not exclude diagnosis. This test is not available in the United States.

PCR for detection of *M. leprae* encoding specific genes or repeat sequences is potentially highly sensitive and specific, since it detects *M. leprae* DNA in 95% of multibacillary and 55% of paucibacillary patients. However, PCR is not currently used in routine clinical practice.

TABLE 40.2 Current Hansen's Disease Treatment Regimens

Type of disease	NHDP regimen	WHO regimen
Paucibacillary	Dapsone 100 mg/day plus rifampin 600 mg/day for 12 months	Dapsone 100 mg/day (unsupervised) plus rifampin 600 mg once monthly (supervised) for 6 months
Multibacillary	Dapsone 100 mg/day plus clofazimine 50 mg/day plus rifampin 600 mg/day for 2 years (May substitute daily minocycline for clofazimine)	Dapsone 100 mg/day plus clofazimine 50 mg/day (both unsupervised) plus rifampin 600 mg and clofazimine 300 mg once monthly in supervised setting; continue regimen for 12 months of therapy

NHDP, National Hansen's Disease Program; *WHO*, World Health Organization.

TREATMENT

Multidrug therapy with a combination of dapsone, rifampicin (rifampin), and clofazimine is the current treatment for infection with *M. leprae*. Multidrug therapy is very successful, with a high cure rate, few side effects, and low relapse rates. WHO studies have reported a cumulative relapse rate of 1.1% for paucibacillary leprosy and 0.8% for multibacillary leprosy at 9 years after completion of multidrug therapy. Patients with a high initial bacillary load are thought to be at higher risk of relapse, thus treatment for at least 24 months is advocated by some.

Treatment recommendations are divided into paucibacillary or multibacillary therapy. Patients with paucibacillary leprosy require treatment for shorter periods. Treatment regimens recommended by the US National Hansen's Disease Programs and the WHO are summarized in **Table 40.2**.

Patients should be warned that rifampicin will turn their urine, sweat, semen, and tears orange/red for 48 hours post-dose. Rifampicin may decrease the efficacy of oral contraceptives and other medicines, including prednisolone. Clofazimine skin pigmentation may be very troublesome and particularly affects the actual lesions. Patients can be reassured that the pigmentation will fade after stopping multidrug therapy, but it may take many months. Dapsone is a sulfa drug that often causes mild anemia but may also cause severe hemolysis in individuals with glucose 6-phosphate dehydrogenase (G6PD) deficiency. For this reason, it is standard of care to obtain a G6PD activity level before initiating dapsone therapy. Patients should be specifically warned about dapsone allergy, which may be severe and life threatening. It usually starts 3-6 weeks after starting the drug and presents with fever, rash, and pruritus. If the drug is not stopped, the reaction may progress to an exfoliative dermatitis, hepatitis, pneumonitis, albuminuria, and death. Dapsone should be stopped immediately and medical advice sought at the first sign of any rash or unexplained fever. The role of corticosteroids in the management of severe dapsone allergy is unclear.

A number of other antibiotics are active against *M. leprae* and may be useful in combination as second-line therapy in the setting of drug intolerance or documented drug resistance. Such antimicrobials include minocycline 100 mg daily, ofloxacin 400 mg daily, and clarithromycin 500 mg daily.

LEPROSY REACTIONS

Leprosy is complicated by immunological phenomena called reactions: reversal reactions (RR), or type 1 reactions, and erythema nodosum leprosum (ENL), or type 2 reactions. Leprosy reactions are the main cause of nerve damage in leprosy. The inflammation is due to immune reactions against *M. leprae* antigens. Patients can present in reaction before multidrug therapy treatment, and a significant proportion of patients develop reactions

TABLE 40.3 Comparison of Clinical Features of Type 1 and Type 2 Leprosy Reactions

Parameter	Type 1 (RR)	Type 2 (ENL)
Patients at risk	All types but particularly BT, BB, BL	LL, BL
Onset of reaction	Usually gradual, over a few weeks but may be sudden	Sudden, "overnight"
Cutaneous lesions	Increased erythema and induration of previously existing or new lesions	Numerous erythematous, tender nodules on face, extremities, or trunk, without relationship to prior lesions
Neuritis	Frequent, often severe	Frequent, often severe
Systemic symptoms	Afebrile, mild malaise, edema	Fever, malaise, lymph node enlargement, arthritis, iritis, orchitis
Histopathological features	↑CD4 cell, granuloma edema, ↑giant cell size and numbers, dermal edema, and HLA-DR expression	Polymorphonuclear cell infiltrates in lesions <24-h old, ↑TNF-α
Treatment	Corticosteroids	Corticosteroids, thalidomide
Recurrence	30-50%	~65%

BB, Borderline; *BL*, borderline lepromatous; *BT*, borderline tuberculoid; *ENL*, erythema nodosum leprosum; *LL*, lepromatous; *RR*, reversal reactions; *TNF-α*, tumor necrosis factor α; *TT*, tuberculoid; *HLA-DR*, Human Leukocyte Antigen-antigen D related.

within the first 6 months of treatment. There is also an increase in the incidence of reactions in women during the postpartum period. However, reactions can also occur after successful multidrug therapy treatment and are probably due to persistence of *M. leprae* antigens. Patients may suffer from recurrent reactions or repeated reactions after treatment, resulting in increased suffering and disability. The clinical features of these reactions are listed in **Table 40.3**.

Management of Type 1 Reactions

The clinical manifestations of these reactions are painful, edematous, erythematous skin lesions, neuritis, and facial and peripheral edema. Acute neuritis (defined as spontaneous nerve pain, paresthesia, or tenderness with new sensory or motor impairment of recent onset) may also occur without evidence of skin inflammation. Nerve function impairment is defined as clinically detectable impairment of motor, sensory, or autonomic nerve function. Nerve function impairment may occur in the absence of symptoms and may go unnoticed by the patient—"silent neuropathy."

Type 1 reactions are treated with corticosteroids. High doses of prednisolone 40-60 mg daily should be started, depending on severity, and tapered down after clinical improvement to the minimal effective dose until the reaction subsides. Treatment should last 5-6 months

Patients seen with nerve function impairment of recent onset (within 6 months) should be given a trial of prednisolone therapy and physiotherapy. Some of these patients will recover function of the affected part.

Management of ENL Reactions

ENL reactions present as a systemic illness: a patient with ENL may be very sick with high fever, painful cutaneous and subcutaneous nodules, peripheral edema, and inflammation of the nerves, eyes, joints, muscles, bones, and testes. The onset of ENL is acute, but it may pass into a chronic or recurrent phase.

For very mild cases aspirin may be used. Severe cases require hospitalization and treatment with high doses of prednisolone (starting at 60 mg). The efficacy is variable, and some

patients with chronic or recurrent ENL may need to take prednisolone for several years. These prolonged, high doses of corticosteroids are associated with adverse effects. In patients on prolonged corticosteroid courses, consider adding daily calcium carbonate and vitamin D3 for bone protection and trimethoprim-sulfamethoxazole 400/800 mg daily for *Pneumocystis jiroveci* pneumonia prophylaxis.

Thalidomide, starting at 300-400 mg daily and tapering down, is the treatment of choice for severe ENL. It has a dramatic effect in controlling ENL and preventing recurrences, but its use is strictly regulated because of teratogenicity. However, it is ineffective in the management of neuritis associated with ENL. Patients may experience sedation, and there is an increased risk of thromboembolism when used in conjunction with corticosteroids. Thalidomide has been shown to be neurotoxic when used in patients with a wide range of dermatologic conditions, but there are no studies demonstrating this in patients with leprosy. In the United States, thalidomide must now be obtained through the Celgene REMS program (1-888-423-5436).

In chronic ENL, clofazimine 100-300 mg daily may be helpful. This medication takes approximately 6 weeks to reach full efficacy. Side effects include hyperpigmentation of the skin and sclera. At prolonged high doses, nausea or intestinal obstruction can occur, which may lead to unnecessary surgical intervention.

Lucio phenomenon (erythema necroticans) is a rare reactional state seen mainly in patients from Mexico, Cuba, Brazil, or Costa Rica. This has been associated with *Mycobacterium lepromatosis*, a recently discovered acid-fast bacillus linked to diffuse lepromatous disease. Histopathologic examination reveals profound bacterial load with endovascular invasion, vasculitis, and intravascular thrombosis. The necrotic skin lesions begin as irregular or stellate macules and papules that become purpuric and ulcerate. Widespread cutaneous necrosis may occur, leading to secondary bacterial infection, sepsis, and death. Survival depends on supportive care combined with steroids and, if necessary, the addition of cyclophosphamide and treatment of the underlying infection.

MANAGEMENT OF LEPROSY

The treatment of leprosy has six main components:

- Chemotherapy
- Patient education
- Management of reactions and neuritis
- Prevention of disability
- Management of ulcers
- Social and psychological support.

All patients with leprosy need education regarding the nature of their disease. An independent interpreter may be invaluable. Fears of contagion and social rejection must be dealt with directly. Patients should be assured that *therapy will make them non-infectious* and that family and social relationships need not be altered. An attitude of openness and reassurance is important. A multidisciplinary approach is ideal, and establishing a good relationship with affected individuals and identifying and addressing their concerns is vital.

Information about mode of transmission, treatment, and complications—including the recognition and risk of leprosy reactions—is essential for patients and health providers. Patients should be taught self-examination of the hands and feet and to seek medical care immediately if signs of inflammation or trauma occur. Adequate footwear such as extra-deep shoes with a wide toe box and inserts or other protective devices should be made available to those with insensitive or deformed feet. Appropriate early physiotherapy must be instituted in cases of motor neuropathy, and patients should be referred to an appropriate specialist for evaluation and correction of ulcers and deformities. Acquired ichthyosis is common in multibacillary leprosy and with clofazimine treatment. Strong emollients such as 12% ammonium lactate lotion or 40% urea lotion should be used to prevent excessive cracking/fissuring of the skin, which can lead to secondary bacterial infection.

Having regular ophthalmic examinations will minimize the risk of visual impairment. Loss of corneal sensation and lagophthalmos from denervation are most typical of the tuberculoid end of the spectrum and can lead to exposure keratitis. Bacillary infiltration of the anterior eye occurs in borderline and lepromatous patients, causing nodular keratitis and episcleritis. ENL may cause iridocyclitis and secondary glaucoma leading to blindness. The sensory denervation of the eye results in the absence of symptoms despite progressive ocular injury, thus contributing to vision loss. Patients with corneal anesthesia need counseling and measures to prevent exposure injury such as eye covers at night and sunglasses in the day. Surgery may be useful in lagophthalmos. Inflammatory conditions associated with reactions are managed with steroids. The commonest cause of visual impairment in leprosy is cataract due to long-term steroid use.

Therapy of Contacts

No satisfactory method has been established for managing household contacts. Current practice involves a full examination of all household contacts.

Management of Complicated Cases

Consultation in the management of leprosy can be obtained by contacting the US National Hansen's Disease Program at 800-642-2477 (http://www.hrsa.gov/hansensdisease/). Additional information can be obtained through the World Health Organization website (http://www.who.int/lep/).

Availability of Clofazimine

Clofazimine is distributed worldwide though the WHO by donation of Novartis Foundation for Sustainable Development. In the United States, the drug was no longer commercially distributed as of November 2004 but is available from Novartis through the National Hansen's Disease Programs for use in treatment of leprosy under an investigational protocol. Contact the National Hansen's Disease Program for assistance in obtaining clofazimine for use in treatment of leprosy.

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