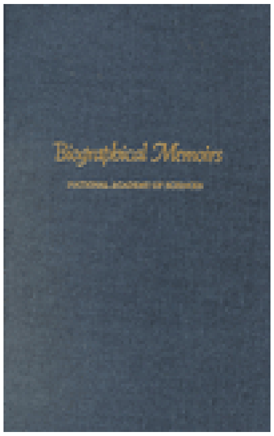

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Biographical Memoirs

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OF THE UNITED STATES OF AMERICA

Biographical Memoirs

VOLUME 79

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PREFACE

On March 3, 1863, Abraham Lincoln signed the Act of Incorporation that brought the National Academy of Sciences into being. In accordance with that original charter, the Academy is a private, honorary organization of scientists, elected for outstanding contributions to knowledge, who can be called upon to advise the federal government. As an institution the Academy's goal is to work toward increasing scientific knowledge and to further the use of that knowledge for the general good.

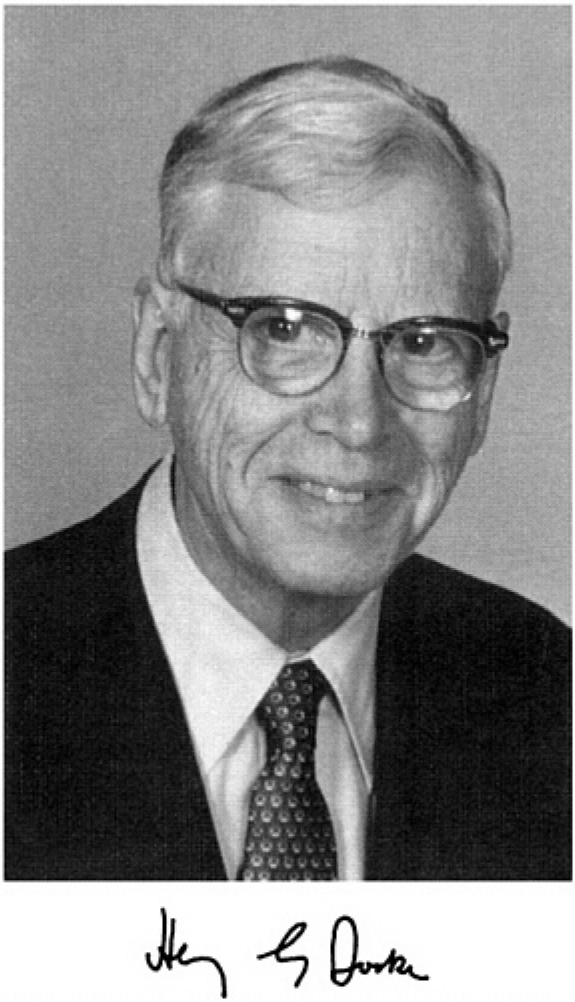
The *Biographical Memoirs,* begun in 1877, are a series of volumes containing the life histories and selected bibliographies of deceased members of the Academy. Colleagues familiar with the discipline and the subject's work prepare the essays. These volumes, then, contain a record of the life and work of our most distinguished leaders in the sciences, as witnessed and interpreted by their colleagues and peers. They form a biographical history of science in America—an important part of our nation's contribution to the intellectual heritage of the world.

R.STEPHEN BERRY

Home Secretary

Biographical Memoirs

VOLUME 79



HENRY G.BOOKER

December 14, 1910–November 1, 1988

BY WILLIAM E. GORDON

HENRY G. BOOKER WAS a superb teacher and insightful researcher: He taught us electromagnetics, radio propagation, and antennas, among other things. He could present an argument in class with apparent simplicity, lulling the students into thinking they had grasped it all. The rude awakening to the complications came when the students on their own tried to reconstruct the argument. It took hours of work. It's the important part of the interaction between teacher and student and it's known as learning. In addition to teaching us the subject matter at hand, more importantly he taught us how to learn and that learning sustains life in its full measure. He was a pioneer in research on the theory of propagation of radio waves in the ionosphere and magnetosphere, and near Earth's surface, on antennas, and on other aspects of electromagnetism.

Henry George Booker was born in Barking, Essex, England, on December 14, 1910, and died in his home at La Jolla, California, from complications of a brain tumor on November 1, 1988. He was survived by his wife of 51 years, Adelaide, now deceased, and four children: John R.Booker, Robert W.Booker, Mary A.Booker, and Alice M.Booker.

Excelling in mathematics, Booker gained entrance to

Cambridge University, where he received a B.A. degree in 1933 and a Ph.D. degree in 1936, specializing in pure and applied mathematics and ionospheric physics. He was awarded the Smith Prize in 1935 and thereafter became a research fellow of Christ's College. Booker first traveled to the United States in 1937 as a visiting scientist at the Carnegie Institution in Washington, D.C. While there, he met and married Adelaide Mary McNish from San Francisco.

His career divides readily into three parts: (1) from 1933 to 1948 in England, largely at Cambridge University, but with an important 5-year segment at the Telecommunication Research Establishment during World War II, (2) from 1948 to 1965 at Cornell University, and (3) from 1965 to 1988 at the University of California, San Diego. The first phase of his career, starting with his education at Cambridge, led to papers concentrating on magneto-ionic theory in prestigious journals even while still a student. The war years left a gap due to military classification in an otherwise continuous publication record spanning 55 years (1934–89).

When Booker started research in 1933, he worked closely with the radio group in the Cavendish Laboratory, Cambridge, under J.A.Ratcliffe. His work was theoretical and concerned with the magneto-ionic theory that Sir Edward Appleton had recently formulated. He published four papers that were models of clear exposition and helped us to understand the physics of radio waves when they enter the ionosphere. The final paper of this group (1939) is still useful reading for students and has been hailed as one of the most important papers ever written on radio wave propagation. It deals with the physics of at least three important concepts: (1) the dispersion relation in a stratified medium expressed as a quartic equation, now called the Booker quartic; (2) the idea that a radio ray can be regarded as the path of a wave packet; and following from this (3) a method of ray tracing in an anisotropic stratified medium known as the Booker method of ray tracing.

Ratcliffe regarded radio science as a branch of physics and rarely used complicated mathematics. He did not want the mathematics to obscure the physics; he wanted it to illuminate the physics. Even though Booker was educated as a mathematician, he adopted Ratcliffe's philosophy. He taught students to try to understand the physics of every line of mathematics that they write down and never unnecessarily to show off the mathematics that they happen to know.

During World War II Booker was in charge of theoretical research at the Telecommunications Research Establishment in England, where he was involved in development of new ideas on antennas, electromagnetic wave propagation, and radar systems, all of which were critical to the defense of Britain. During this period he conducted radio meteorological investigations in England, India, Australia, and New Zealand on the phenomenon known as anomalous propagation or super-refraction. In some conditions the troposphere can act as a reflector of radio waves and with Earth's surface it forms a wave-guide in which radio waves can travel abnormally large distances. The paper by Booker and Walkinshaw (1946) extended the theory to deal with other types of guided wave propagation and is about the best of many papers on this subject written at that time. Booker maintained his interest in guided waves and published further papers on it.

For three years after the war Booker was university lecturer in mathematics at Cambridge producing, among others, classic contributions on slot aerials and their relation to complementary wire aerials (1946); the elements of wave propagation using the impedance concept (1947,1); the mode theory of tropospheric refraction and its relation to wave guides and diffraction (1947,2); and diffraction from an irregular screen with applications to ionospheric problems (1950).

At the end of 1948 at the invitation of Charles R.Burrows, director of the School of Electrical Engineering and well-known researcher in radio propagation, Booker moved to Cornell and shifted his interest from smoothly varying media to irregular media; at Cornell he provided the stimulation for creative work by students and colleagues, while he moved a school of electrical engineering built on power generation and vacuum tubes into the postwar era of communications and information. His work at Cornell emphasized propagation through irregular media beginning with the troposphere and extending through the stratosphere and the ionosphere and into the magnetosphere. In each he made major contributions to the theory and usually joined with others in applying the results to practical communication systems. The paper "A New Kind of Radio Propagation at Very High Frequencies Observable over Long Distances" (1952) stands out not only because it led to ionospheric-forward-scatter communication, the mainstay of the Defense Early Warning System, but also because of the number of its authors (eight—a record for Henry).

Henry's research was elegant. That is not a word he would have used or that is used very often to describe research, but it fits. His work had beauty and style, and it was widely admired by those who understood it. He created ideas as a composer creates music or a sculptor creates art. All can be elegant. His teaching at Cornell was widely admired for its clear exposition, even of complicated subjects. Typical of his students' comments is that by Ken Bowles: "The best university level teacher that I ever experienced."

Two of his four books *An Approach to Electrical Science* (1959) and *A Vector Approach to Oscillations* (1965) were published while at Cornell. He also found time to write many memos on what was wrong with engineering education. Some of those appeared in print and many unpublished ones stimulated the faculty.

From 1958 until 1965 he was deeply involved in the Arecibo radar project and the incoherent radio scattering. In 1965 he was lured to the University of California, San Diego (UCSD), by the challenge of building a department of applied electro-physics as a part of the grand California master plan for higher education supported generously by then Governor Pat Brown. The plan included the creation of four major campuses, of which UCSD was one. It was to grow rapidly to 12 colleges, 27,000 students, and a faculty of world-class researchers using a combination of state and federal funds. When Reagan replaced Brown the master plan lost its energizer, the shrinking state funds were subject to higher education competition from stalwarts Berkeley and Los Angeles, and UCSD settled for 5, not 12, colleges. The faculty recruited by Booker, described by historian of science George Gilmore as “the finest ionospheric group ever assembled,” became easy targets for other universities, and several left UCSD, a great frustration for Booker. The development of the new department was a remarkable success measured in terms of scholars attracted (e.g., Ken Bowles, Ian Axford, Peter Banks, Marshall Cohen, Vic Rumsey). This did not, however, interfere with Booker’s scientific productivity. He wrote papers on the ionosphere, on irregularities, on wave propagation, two books, and a criticism of electrical engineering education. The department has evolved into electronic devices and communications theory and more recently into wireless communications with the title of Department of Applied Physics and Information,

Both the University of California and the economy of the San Diego region have benefited greatly as a result of

Henry's attracting faculty to UCSD during that early period. Part of the master plan envisioned strong ties with industry. Several of the faculty and their students have founded high-tech companies (e.g., Linkabit, Qualcomm). While the department did not develop as Henry had expected, it has become a highly ranked department with a significant impact on the region.

If Booker's scientific output can be characterized, it has an underlying theme of ionospheric physics with smoothly varying media being replaced by irregular media and with the irregularities, excursions into the troposphere, the stratosphere and the magnetosphere. There were early encounters with antennas and radio ducting, the latter stimulated by wartime radar operations (radio super-refraction, radio mirage).

Booker's work has set a pattern of clear thinking for which his numerous colleagues and research students will be grateful, and this will benefit the subject of radio propagation for many years to come.

The International Union of Radio Science has a major international scientific meeting every three years, the general assembly. For the past seven meetings one or more Henry G.Booker fellows has attended the assembly covered by the fellowship, and this will continue. It is assured by an endowment established by Henry's admirers, bearing the distinctive title, Henry G.Booker Fellow. That the fellows represent bright talent with promising futures is fitting, for Henry had always attracted the brightest young students.

Let me close on a more personal note by quoting from a speaker at Booker's memorial service. "He was a person who could both be close to you as a friend and at the same time inspire a feeling of awe. You knew that his mind was ranging somewhere between the Milky Way and the mysteries of subatomic physics while ordinary people were passing hors d'oeuvres and talking about the weather. He was a very hard man to preach to. Always sitting, as I recall, somewhere to the preacher's left and halfway back in the congregation, he would fix his gaze on the ceiling and take off into outer space, though probably a week later he could remember more of the sermon than anyone else. His mind was truly awe-inspiring."

My own warm feelings for Henry come in part from having known a very modest man and good friend and in part from having shared with him the joy of discovery—the discovery of ideas new to us and less frequently new to science. That joy was deep, spiritual, and exhilarating. All of us should have experienced it, and my hopes are that the Henry Booker fellows have the experience many times.

Booker received many awards and national and international recognition for his academic and scientific achievements (see list). Additionally, he was elected a fellow of the Institute of Electrical and Electronics Engineers in 1953 and a member of the National Academy of Sciences in 1960. For his activity in the International Union of Radio Science he was elected honorary president in 1978.

Throughout his life Professor Booker was most dedicated to the education of undergraduate and graduate students, many of whom are now eminent scientists and educators in their own right. In 1979 his former students, colleagues, and friends honored him with the establishment of a fellowship in his name at the National Academy of Sciences to support participation of "a young scientist of promise" at the general assembly of International Union of Radio Science. As emeritus professor he continued to teach full time and conduct research at the University of California and to consult with the RAND Corporation until the last few months of his life.

AWARDS

1934–35	Allen Scholarship, Cambridge University
1935	Smith Prize, Cambridge University
1947	Duddell Premium, Institution of Electrical Engineers
1948	Kelvin Premium, Institution of Electrical Engineers
1954–55	Guggenheim Fellowship
1970	50th Anniversary Medal, American Meteorological Society
1981	Honorary professor, Wuhan University, Hubei, China
1984	Centennial Medal, Institute of Electrical and Electronics Engineers

SELECTED BIBLIOGRAPHY

1934 Some general properties of the formulae of the magneto-ionic theory. *Proc. R. Soc. A* 147:352–82.

1938 With L.V.Berkner. An ionospheric investigation concerning the Lorentz polarization-correction. *Terr. Mag. Atmos. Electr.* 43:427–50.

1939 Propagation of wave-packets incident obliquely upon a stratified doubly refracting ionosphere. *Phil. Trans. R. Soc. A* 237:411–51.

1946 Elements of radio meteorology: How weather and climate cause unorthodox radar vision beyond the geometrical horizon. *J. Inst. Electr. Eng.* 93:69–78.

Slot aerials and their relation to complementary wire aerials (Babinet's principle). *J. Inst. Electr. Eng.* 93:620–26.

1947 The elements of wave propagation using the impedance concept. *J. Inst. Electr. Eng.* 94:171–202.

With W.Walkinshaw. The mode theory of tropospheric refraction and its relation to wave-guides and diffraction. *Phys. R. Meteorol. Soc. Rep.* pp. 80–127.

1948 A relation between the Sommerfeld theory of radio propagation over a flat earth and the theory of edge-diffraction. *J. Inst. Electr. Eng.* 95:326–27.

1950 With P.C.Clemmow. The concept of an angular spectrum of plane waves, and its relation to that of polar diagram and aperture distribution. *Proc. Inst. Electr. Eng.* 97:11–17.

With J.A.Ratcliffe and D.H.Shinn. Diffraction from an irregular screen with applications to ionospheric problems. *Phil. Trans. R. Soc. A* 242:579–607.

With W.E.Gordon. A theory of radio scattering in the troposphere. *Proc. Inst. Radio Eng.* 38:401–12.
1952 With D.K.Bailey, R.Bateman, L.V.Berkner, G.F.Montgomery, E. M.Purcell, W.W.Salisbury, and J.B.Wiesner. A new kind of radio propagation at very high frequencies observable over long distances. *Phys. Rev.* 86:141–45.
Morphology of ionospheric storms. *Proc. Natl. Acad. Sci. U. S. A.* 40:931–43.
1954 What is wrong with engineering education? *Proc. Inst. Radio Eng.* 42:513.
1955 With J.T.deBettencourt. Theory of radio transmission by tropospheric scattering using very narrow beams. *Proc. Inst. Radio Eng.* 43:281–90.
1956 Turbulence in the ionosphere with applications to meteor-trails, radio-star scintillations, auroral radar echoes and other phenomena. *J. Geogr. Res.* 61:673–705.
1957 With W.E.Gordon. The role of stratospheric scattering in radio communications. *Proc. Inst. Radio Eng.* 45:1223–27.
1959 *An Approach to Electrical Science.* New York: McGraw-Hill.
Radio scattering in the lower ionosphere. *J. Geogr. Res.* 64:2164–77.
1962 Guidance of radio and hydromagnetic waves in the magnetosphere. *J. Geogr. Res.* 67:4135–62.
1963 Proposal for an international union of solar system physics. *Science* 141:673–74.

1965 With R.B.Dyce. Dispersion of waves in a cold magnetoplasma from hydromagnetic to whistler frequencies. *Radio Sci.* 69D:463–92.

A Vector Approach to Oscillations. New York: Academic Press.

1973 The ionosphere as the secondary conductor of a transformer for ELF. *Radio Sci.* 8:757–62.

1974 International scientific organization in telecommunications and remote sensing. *Commun. Soc.* 12:8–10.

1975 Electromagnetic and hydromagnetic waves in a cold magnetoplasma. *Phil. Trans. R. Soc. Lond. A* 280:57–93.

1977 Is the teaching of electricity and magnetism in need of change? *IEEE Trans. Educ.* 20:126–30.

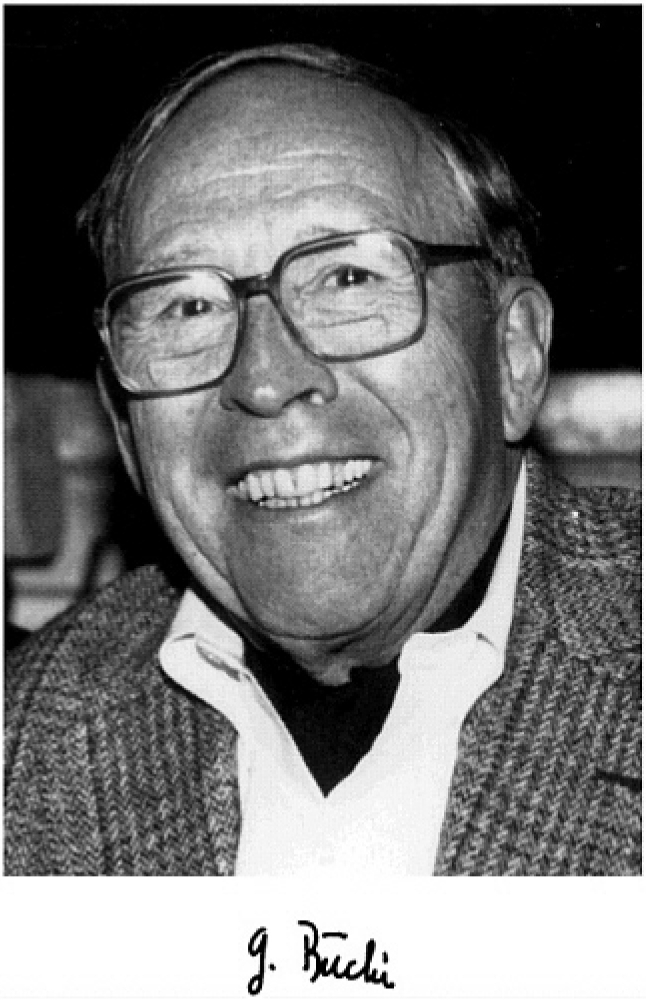
1979 The role of acoustic gravity waves in the generation of spread F and ionospheric scintillation. *J. Atmos. Terr. Phys.* 41:501–15.

1981 *Energy in Electromagnetism.* London: Peregrinus Press.

Application of refractive scintillation theory to radio transmission through the ionosphere and the solar wind, and to reflection from a rough ocean. *J. Atmos. Terr. Phys.* 43:1215–33.

1984 *Cold Plasma Waves.* The Hague: Martinus Nijhoff.

1985 With H.O.Vats. Application of refractive scintillation theory to laser transmission through the atmosphere near ground level. *Radio Sci.* 20:833–41.



GEORGE HERMANN BÜCHI

August 1, 1921–August 28, 1998

BY GLENN A. BERCHTOLD AND LOUISE H. FOLEY

MASSACHUSETTS INSTITUTE OF TECHNOLOGY Professor Emeritus George H.Büchi of Cambridge, Massachusetts, and Jackson, New Hampshire, one of this century's foremost organic chemists, died of heart failure while hiking with his wife in his native Switzerland on August 28, 1998, at the age of 77. Throughout his life he was an avid hiker, hunter, skier, and fisherman whose fondness and appreciation of the outdoors rivaled his love of science.

Büchi was born in Baden, Switzerland, on August 1, 1921. He received a diploma in chemical engineering from the Eidgenössische Technische Hochschule (ETH) in Zürich in 1945. He received the D.Sc. in organic chemistry from the ETH in 1947, while working in the laboratory of Professor Leopold Ruzicka. Even in the 1940s the ETH was the center of organic chemistry in Europe, and Büchi's education and love for the chemistry of natural products was heavily influenced by close association with distinguished faculty, including not only Ruzicka but also V.Prelog, O. Jeger, and P.A.Plattner. Early in his graduate days George Büchi completed a synthesis of 1-methylazulene. The area of research was of active interest to Professor Plattner, and it was agreed that the work would be published with Plattner as coauthor.[1] This one publication became the source of an error begun in *Topics in Organic Chemistry* by L.F.Fieser and M.Fieser,[2] which persisted most of his career. Because of this one paper Büchi was often introduced as a doctoral student of Plattner and, as was his style, he never corrected the introducer.

Büchi left the ETH and came to the United States as a Firestone postdoctoral fellow in the laboratory of Professor M.Kharasch at the University of Chicago. During his three-year tenure in Kharasch's laboratory Büchi's systematic investigations of free-radical chemistry augmented his curiosity in the potential utility of organic photochemistry.

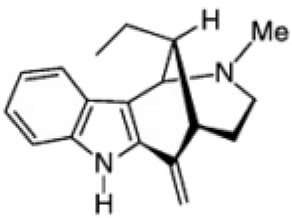
In 1951 Büchi accepted an offer from the late Arthur C. Cope to join the faculty of the Chemistry Department at the Massachusetts Institute of Technology. He was promoted to associate professor in 1956 and to full professor in 1958. He was appointed the Camile and Henry Dreyfus professor of chemistry in 1969, a position he held until his retirement in 1991. During his 40 years of service at MIT, Büchi trained 70 doctoral students and more than 130 postdoctoral students. Many of his former coworkers have gone on to leadership positions in academia and industry throughout the world. George Büchi's research accomplishments, reported in over 200 publications, made significant contributions in diverse areas of organic chemistry, including organic photochemistry, structure elucidation of natural products, synthesis of natural products, toxicology, and the development of new synthetic methods. What makes the number of publications even more impressive was that George's high standards did not allow him to publish anything but a complete work: a complete structure, a total synthesis, a novel synthetic method. He often suggested to the students whose synthetic work did not lead to the total synthesis but contained interesting chemistry that they publish the work on their own.

In addition to contributions from his own research and teaching, George's originality, thorough knowledge of organic chemistry, and its literature made him a highly respected and prized consultant to Pfizer (1956–63) and Hoffmann-La Roche (Nutley, New Jersey, and Basle, Switzerland, 1963–91) and throughout his career to Firmenich, S.A. (Geneva, Switzerland, 1954–91). It was rare that he could not recite on the spot where, when, what journal, and the author for a critical reference or procedure. His consulting contributions, like his research, were not just to reproduce the literature but rather to come up with novel uses of a method or a totally new method to accomplish a critical step in a synthesis. One of his suggestions resulted in a new route to vitamin K patented by Roche and Büchi. Many of his contributions to flavor and fragrance chemistry have been patented by Firmenich, S.A., and Büchi, and most with coinventor and nearly career-long coworker Hans Wüest.

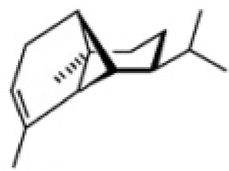
Prior to the 1950s, the photochemistry of organic compounds was a rarely investigated and poorly understood field of endeavor. Büchi's accomplishments in this area in the 1950s were instrumental in converting this latent field into an understandable and useful synthetic tool, and they laid the groundwork for what is now modern organic photochemistry. The light-catalyzed addition of carbonyl compounds to olefins had been observed by E.Paterno in 1909, but the structure of the oxetane products remained a mystery until elucidated by Büchi and coworkers in 1954. The reaction is now known as the Paterno-Büchi reaction, and its scope was extended in Büchi's laboratories to include the addition of carbonyl compounds to alkynes and alkenes. Over a 10-year period new photochemical reactions and structural work in Büchi's laboratory, coupled with his mechanistic insights provided a detailed understanding of numerous fundamental photoreactions, all of which were unprecedented at the time.

At about the same time, Büchi began structural work in natural products that led to the structure determination of more than 55 natural products. During this era, prior to the routine use of X-ray crystallographic methods for organic structure determination, his accomplishments have been described by his peers as among the finest examples of structure elucidation by classic degradation and spectrometric techniques. The structures of the sesquiterpenes patchouliol (with J.Dunitz), maaliol, aromadendrene, valerenic acid, calarene, and copaene (with P.de Mayo), all containing novel skeletons, were disclosed in succession. Work on the complex alkaloids (uleine, flavocarpine and aconitine), the latter with K.Weisner, led to the structures through ingeniously conceived degradative studies. A study on the bis-indole alkaloid voacamine suggested to Büchi that the antitumor alkaloids vinblastine and vincristine were structurally similar bis-indoles. This suggestion was confirmed in collaboration with Klaus Biemann (MIT) and N.Neuss and M.Gorman (both of Eli Lilly).

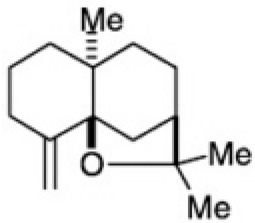
Patchouliol



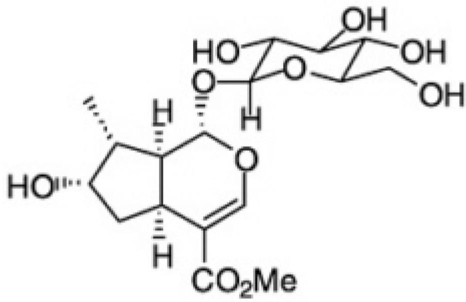
Uleine


Copaene

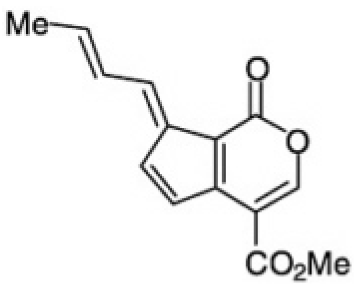
The synthesis of over 75 complex natural products came from Büchi's laboratory. His peers considered his syntheses creative, elegant, and original. Typically his syntheses were very efficient in producing quantities of the target compound in very few steps. The first syntheses of many sesquiterpenes (e.g., patchouliol, maaliol, aromadendrene, agarofuran), iboga alkaloids, iridoid glucosides (loganin), fulvoplumierin, aflatoxins, and their metabolites were accomplished. Both vindoline and catharanthine first yielded to synthesis in his laboratory; these two alkaloids were subsequently combined by Potier to produce the antitumor drug, vinblastine. Neolignans (burchellin, guianin, futoenone) and several marine natural products, including parazoanthoxanthin and dibromophakellin, were synthesized



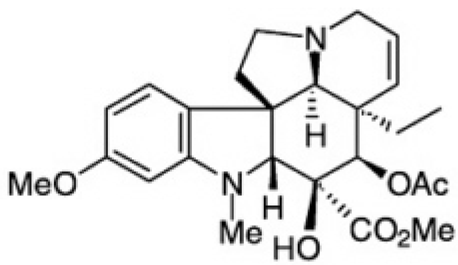
ß-Agarofuran



Loganin

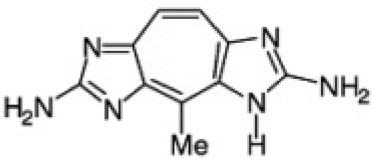


Fulvoplumierin

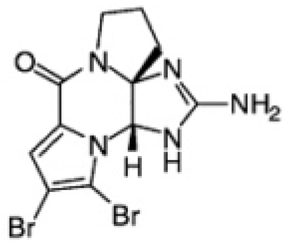


Vindoline

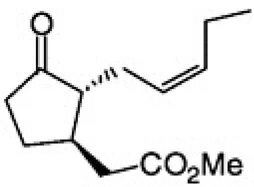
by elegant biomimetic routes. Throughout his career Büchi maintained a strong interest in flavor and fragrance principles, and many were synthesized in his laboratory. They include damascenes (rose), methyl jasmonate (jasmine), muscone (musk deer), sinensals (orange), khusimone (vetiver), khaweofuran (coffee), furaneol (strawberry), and muscopyridine.



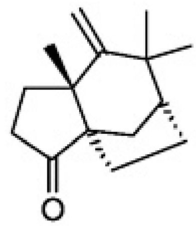
Parazoanthoxanthin



Dibromophakellin



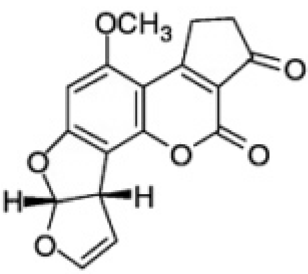
Methyl Jasmonate



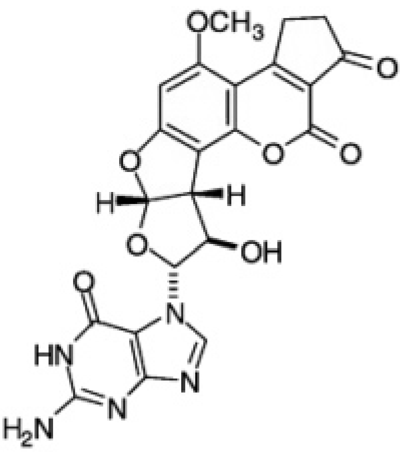
Khusimone

Many important contributions to synthetic methodology were developed in Büchi's laboratory. They include numerous methods for new and convenient preparations of olefins, carbonyl compounds, macrocycles, tropolones, and heterocycles. A new synthesis of allylic sulfones and their conversion to polyolefins provided for an elegant synthesis of β-carotene from vitamin A.

In 1962 Büchi and MIT colleague Professor Gerald N. Wogan initiated a collaborative effort that ultimately established molecular toxicology as an important scientific discipline. Their experimental evidence concerning carcinogens provided fundamental chemical, biological, and epidemiological correlations that are a paradigm for modern toxicological studies. They were first concerned with establishing the structures of the aflatoxins, fungal metabolites that had been isolated from moldy peanuts and found to be responsible for a mass outbreak of poultry disease. Aflatoxin $B_{1,}$ the major metabolite, is a potent carcinogen, and its consumption is associated with primary liver cancer. Büchi deduced the structure of aflatoxin B_1 by ingenious application of spectroscopic information. Subsequent work resulted in the isolation and structure identification of other aflatoxin metabolites ($M_{1,}$ $P_{1,}$ Q_1) and a number of other mycotoxins (rubatoxins, tryptoquivalines, mollicellins, malformin C). In a series of brilliant synthetic studies, he devised methods for their total synthesis. Several of these syntheses provided the quantities of aflatoxin metabolites needed for essential toxicological investigations. Later work established the structure of the major adduct formed between aflatoxin B_1 and DNA. The isolation and identification of the DNA-

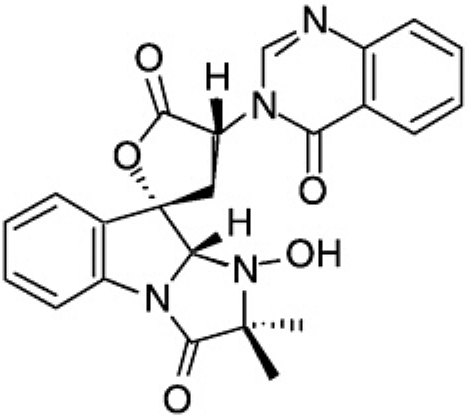


Aflatoxin B_1



Aflatoxin B_1 - guanine adduct

aflatoxin-derived adduct as a 3-hydroxyaflatoxin linked via C-9 to the N-7 atom of a guanine of DNA was a milestone in toxicology. It provided the first definitive molecular structure for a carcinogen-induced covalent modification of a mammalian DNA.



Tryptoquivaline G

George did not become the "head" of organic chemistry at MIT; academic administration was not his style. Yet he influenced organic chemistry at MIT in many ways. In the 1970s he believed that organic chemistry at MIT should develop with a more significant bioorganic component. He and a few colleagues led the department in that direction and thus had an impact on the future thrust of the department. George nurtured the highly talented young faculty in organic chemistry and biochemistry. He was excited by the arrival of new faculty members, and he made a significant effort to help their careers both inside and outside MIT. His presence provided a magnet that attracted excellent graduate students and young as well as established organic faculty to MIT.

One of us (L.H.F.) was drawn to the Büchi group as a graduate student after reading his papers and seeing the insights and knowledge each paper contained. Clearly here was someone with knowledge to share, and share he did with his students and other coworkers. Up until the late 1970s he could be expected to come in to talk with his students and coworkers several times a day and during nights and weekends. How many of us recall working long hours trying unsuccessfully to determine a side product's structure only to have GB or "the boss," both of which his students called him, come in, sit down, and in minutes (if not seconds) figure it out and then share with all how he had deduced it? In their first years, graduate students could count on George for numerous suggestions of things to try when problems occurred. In the last years of their studies, when things went wrong, students often found themselves on their own for a period of time. During this time George watched from a distance to see if the students were searching for solutions on their own. If he saw they were and still were not making progress, he would step back in with suggestions of things to try or papers to read. This approach made his students very self-sufficient and ready for the "real world," where he knew they would be expected to "sink or swim" on their own.

George's high standards also applied to his teaching. In his early career at MIT he taught a basic organic chemistry course and a graduate course in natural products. It was the natural products course that was *his* course and the course for which most MIT organic graduate students and postdocs will remember George. All who attended will recall the impeccable chalk talks; each structure was drawn with care and clarity and a lecture was full of insights on structure determination and synthetic methods. Each year George analyzed recent publications in structure elucidation and synthesis of natural products, and in this course he provided his evaluation of the work reported. This course taught one how to read the literature and how to analyze what was presented, not to just accept it as fact; no better education was available anywhere.

George had a wonderful sense of humor, and as a graduate student I (L.H.F.) was continually coming up with tricks to play on him, often enlisting other graduate students to share in the fun. One could be sure that he would both enjoy the joke and at some later point extract some revenge. This continued even after I left MIT. On one occasion I gave him a $1.99 bottle of New Hampshire wine saying that I thought as a wine connoisseur and a New Hampshire resident he should have at least one bottle of New Hampshire wine in his wine cellar. Sometime later I was invited to share one of Anne Büchi's fine dinners, and I alone was served the New Hampshire "fine wine." The face I made on taking the first sip was sufficient to make George's day.

One of the fascinating delights of being a colleague of George Büchi was to experience his expression of the unique insight into structure and synthesis that he possessed. His critical evaluation of the works of others, not only in his graduate course but also during the daily course of events, was truly a work of art. He genuinely praised the work of high intellectual talent; he quickly discovered, and often corrected, the mistaken approach or conclusions. Although others grasped the opportunity to correct even the smallest errors in recent literature, to his credit, he was above this. His published corrections were only those of major works, and they were done in a gentlemanly fashion—a characteristic of the man.

Yes, we all knew and respected George as a gentleman and a perfectionist in everything with which he was associated. Dinner with George was always a special treat. The food, the wine, the ambiance had to be perfect—it was special. But then again, a late evening dinner on the banks of the Stewart River in the Yukon Territory, where the appetizer was fire-roasted beaver tail on a stick followed by duck or goose prepared and presented in similar fashion was, I (G.A.B.) believe, one of the most enjoyable meals George and I shared: not the ambiance of Lock-Ober but a gastronomical delight. He knew how to get the most out of life, and he certainly did that.

George's love of the outdoors began in early life and continued throughout his life with alpine skiing up until 1995 and cross-country skiing, hiking, hunting, and fly fishing up until the time of his death. He began alpine skiing (often using skins to climb uphill) as a youngster in Switzerland. His characteristic limp was the result of a collision he had as a teenager. This collision resulted in a number of broken bones and damage to his hip, the pain from which he endured up until its replacement in 1980. Following hip replacement he was told he should not alpine ski, but since it was one of his loves, he continued to ski. At each checkup his orthopedic surgeon would report the hip was as good as when it was put in. This prompted the doctor to say, according to George, that he was going to suggest that all his hip replacement patients should continue to ski and those who did not already ski should take it up: a story told with George's characteristic humor.

George's insights into organic chemistry continued right up until his death. One of us (L.H.F.) had the pleasure to spend George's last birthday with him and Anne in New Hampshire. Along with hiking and wonderful cuisine that weekend, there was a discussion of a natural product synthesis. As was so characteristic of George, midway through our discussion he stopped and began to write down a new route to the final compound involving a novel rearrangement.

George's contributions to chemistry were recognized by election to the National Academy of Sciences in 1965, and numerous awards, honorary degrees, and over 30 honorary lectureships around the world. Among the awards he received were the J.R.Killian Faculty Achievement Award (MIT's highest faculty award), the Order of the Rising Sun from the Government of Japan, the American Chemical Society Award for Creative Work in Synthetic Organic Chemistry, the first Ruzicka Prize, and the Fritzche Award of the American Chemical Society.

One of his former colleagues in describing George wrote, "He was one of the most balanced and influential chemists of his day. More to the point, he embodied a style of chemistry—excellence in science, breadth, curiosity, and enormous joie de vivre—that made him a symbol for organic synthesis at its best and most sane. He was a remarkable man, who embodied a remarkable era, and did so in a way that made the whole enterprise human."[3] George died as he would have preferred: out-of-doors doing something he loved, but for his wife and his many friends it was much too soon.

George is survived by his wife of 43 years, Anne Barkman Büchi of Cambridge, Massachusetts, and Jackson, New Hampshire; a brother, Heinrich, of Berne, Switzerland; and three nephews, all of whom live in Switzerland.

THE AUTHORS GRATEFULLY acknowledge Anne Büchi, Satoru Masamune, Gerald Wogan, and Hans Wüest for their help in the preparation of this memoir.

NOTES

1. P.A.Plattner and G.Büchi. Uber eine einfache, von Cycloheptanon ausgehende Azulen-Synthese. *Helv. Chim. Acta* 29(1946):1608–11.

2. L.F.Fieser and M.Fieser. *Topics in Organic Chemistry.* New York: Reinhold, 1963, p. 161.

3. Personal communication from Professor George Whitesides, Department of Chemistry, Harvard University, Cambridge, Mass.

SELECTED BIBLIOGRAPHY

1954 With C.Inman and E.S.Lipinsky. Light catalyzed organic reactions. 1. The reaction of carbonyl compounds with 2-methylbutene-2. *J. Am. Chem. Soc.* 76:4327.

1956 With J.T.Kofron, E.Koller, and D.Rosenthal. Addition of aromatic carbonyl compounds to a disubstituted acetylene. *J. Am. Chem. Soc.* 78:876.

1959 With K.Wiesner, M.Götz, D.L.Simmons, L.R.Fowler, F.W.Bachelor, and R.F.C.Brown. The structure of aconitine. *Tet. Lett.* 2:15.

With E.W.Warnhoff. The structure of uleine. *J. Am. Chem. Soc.* 81:4433.

1963 With T.Asao, M.M.Abdel-Kade, S.B.Chang, E.L.Wick, and G.N. Wogan. Aflatoxins B and G. *J. Am. Chem. Soc*. 85:1706.

With M.Dobler, J.D.Dunitz, B.Gubler, H.P.Weber, and J.Padilla O. The structure of patchouli alcohol. *Proc. Chem. Soc., Lond.* 383.

1964 With N.Neuss, M.Gorman, W.Hargrove, N.J.Cone, K.Biemann, and R.E.Manning. The structure of the oncolytic alkaloids vinblastine and vincristine. *J. Am. Chem. Soc.* 86:1440.

With W.D.MacLeod, Jr., and J.Padilla O.Terpenes. XIX. Synthesis of patchouli alcohol. *J. Am. Chem. Soc.* 86:4438.

With R.E.Manning and S.A.Monti. Voacamine and voacorine. *J. Am. Chem. Soc.* 86:4631.

1966 With D.L.Coffen, K.Kocsis, P.E.Sonnet, and F.E.Ziegler. The total synthesis of iboga alkaloids. *J. Am. Chem. Soc.* 88:3099.

1967 With D.M.Foulkes, M.Kurono, G.F.Mitchell, and R.S.Schneider. The total synthesis of racemic aflatoxin B_1. *J. Am. Chem. Soc.* 89:6745.

1969 With J.A.Carlson. The total synthesis of fulvoplumierin. *J. Am. Chem. Soc.* 91:6470.

1970 With J.A.Carlson, J.E.Powell, Jr., and L.F.Tietze. The total synthesis of loganin. *J. Am. Chem. Soc.* 92:2165.

1971 With S.M.Weinreb. Total synthesis of aflatoxins M_1 and G_1 and an improved synthesis of aflatoxin B_1. *J. Am. Chem. Soc.* 93:746.

With K.E.Matsumoto and H.Nishimura. The total synthesis of vindorosine. *J. Am. Chem. Soc.* 93:3299.

1974 With R.Friedinger. A new synthesis of allylic sulfones and their conversion to polyolefins, β-carotene, and vitamin A. *J. Am. Chem. Soc.* 96:3332.

1975 With M.Ando and T.Ohnuma. The total synthesis of racemic vindoline. *J. Am. Chem. Soc.* 97:6880.

1977 With J.M.Essigmann, R.G.Croy, A.M.Nazdan, W.F.Busby, V.N. Reinhold, and G.N.Wogan. Structural identification of the major DNA adduct formed by aflatoxin B_1 in vitro. *Proc. Natl. Acad. Sci. U. S. A.* 74:1870.

With A.Hauser and J.Limacher. The synthesis of khusimone. *J. Org. Chem.* 42:3323.

1979 With P.R.DeShong, S.Katsumura, and Y.Sugimura. Total synthesis of tryptoquivaline G. *J. Am. Chem. Soc.* 101:5084.

With H.Wüest. Macrocycles by olefination of dialdehydes with 1,3-bis(dimethyl-phosphone)-2-propanone. *Helv. Chim. Acta.* 62:2661.

With H.Wüest. New synthesis of β-agarofuran and dihydroagarofuran. *J. Org. Chem.* 44:546.

1981 With P.-S.Chu. A synthesis of gymnomitrol. *Tetrahedron.* 37:4509.

With L.H.Foley. A biomimetic synthesis of dibromophakellin. *J. Am. Chem. Soc.* 104:1776.

1986 With J.C.Leung. Total syntheses of atrovenetin and scleroderodione. *J. Org. Chem.* 51:4813.

1989 With H.Wüest. The synthesis of racemic ambrox. *Helv. Chim. Acta.* 72:996.

1994 With D.A.Home and K.Yakushijin. A two-step synthesis of imidazoles from aldehydes via 4-tosyloxyazolines. *Heterocycles* 39:139.

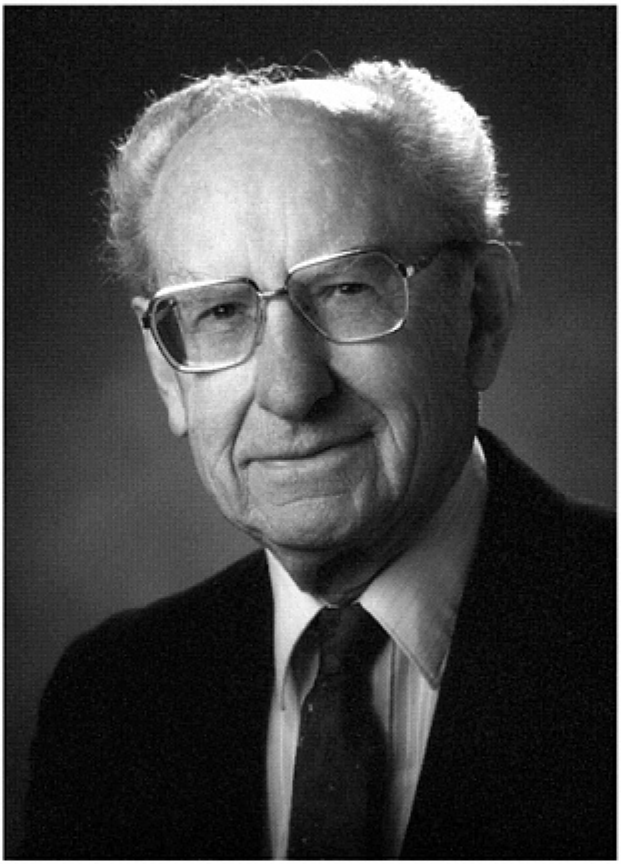


Photo by Alex Jauregd

Horace R. Byers

HORACE ROBERT BYERS

March 12, 1906–May 22, 1998

BY ROSCOE R. BRAHAM, JR., AND THOMAS F. MALONE

HORACE ROBERT BYERS was a pioneer in aviation meteorology, synoptic weather analysis, severe storms, cloud physics, and weather modification—an educator, an organizer and communicator for meteorology, a scientist, author of one of the most widely used textbooks in meteorology, a university administrator, and a quietly effective scientific statesman. The hallmark of his scientific career was his ability to organize groups and activities for meteorological research and his ability to identify and provide opportunities for developing scientists with whom many of his papers were co-authored. During his long career at the University of Chicago, Professor Byers taught and helped to supervise the training of a large number of Ph.D. students, many of whom became distinguished leaders in meteorology. The pinnacle of his scientific career, and the thing for which he is most noted, came with the Thunderstorm Project, the first comprehensive investigation of the turbulence and vigorous vertical motions inside thunderstorms.

EARLY YEARS

Horace R.Byers was a son of Charles H. and Harriet (Ensminger) Byers with ancestral lines back to the early colonial period in Pennsylvania. His parents met and married in Kansas City. His father was a civil engineer employed in constructing new lines as the railroad system advanced westward. As a consequence of this employment, the family migrated westward, ending up on the West Coast.

Horace R.Byers was in born in Seattle on March 12, 1906. He had an older brother, Fred, a younger sister, Louise, and a younger brother, Lyle. When he was nine years old, his father accepted a position in San Francisco as assistant chief engineer, western district, of the Interstate Commerce Commission's Bureau of Valuation, and the family moved to Berkeley, California. Here Horace grew up and went to college. He described this period in autobiographical statements on file at the National Academy of Sciences, from which we quote the following:

> My mother had an artistic bent, painted, and [was] also quite musical as an amateur pianist and singer, while my father was almost a caricature of the practical-minded engineer… Our home had a cultural atmosphere, with many books… My mother sponsored musical evenings in our home where accomplished Berkeley musicians performed for up to fifty guests….
>
> In high school I developed a passionate interest in journalism, became editor of the school paper and had a summer job as a reporter [of] high school activities for the Berkeley Daily Gazette… Upon graduation I took a job as a newspaper reporter and worked full time for a year before entering the University of California, after which I worked part-time at this job, advancing to reportorial positions on various newspapers of the San Francisco Bay region.

In the geography department at the University of California, Berkeley, he became acquainted with the world of science and decided to make meteorology his life work. His mentors were Richard J.Russell, a physical geographer, and John B.Leighly, a climatologist. While an undergraduate, Byers was appointed meteorological observer at the university. His twice-daily observations were published by the geography department in a monthly bulletin over his name. This bulletin was distributed to several places, including the Port of Oakland, which had jurisdiction over the Oakland airport.

BYERS MEETS ROSSBY

In the spring of 1928, his junior year, Byers received a call from the chief engineer of the Port of Oakland stating that a representative of the Daniel Guggenheim Fund for the Promotion of Aeronautics was looking for a meteorological assistant to help operate an experimental “airway weather service” to assist a fledgling airline operating between the Oakland airport and Vail Field, near Los Angeles. The airline would later become Transcontinental and Western Airways, Inc. (TWA). The Guggenheim representative was Carl-Gustaf Arvid Rossby.[1] This was the beginning of a long and fruitful association between these two men. It would be hard to overestimate the impact this association had on subsequent developments in meteorology. Later that summer, operation of the experimental airway weather service was turned over to the U.S. Weather Bureau. Byers returned to school and Rossby departed to head a new meteorology program in the Department of Aeronautical Engineering at the Massachusetts Institute of Technology.

After graduation from Berkeley in 1929 with an A.B. degree in geography, Byers received a fellowship from the Daniel Guggenheim Fund to attend MIT, where he studied meteorology under Rossby and Hurd C.Willett. When he completed his M.S. degree in 1932 the country was in a serious economic depression and jobs in meteorology were scarce. Byers returned to California as a research assistant at the Scripps Institution of Oceanography. This was followed by a period at TWA, where he instructed flight crews and other company personnel in the new concepts of weather fronts and air masses. These classes were held in Kansas City, Newark, New Jersey, and Glendale, California. His lecture notes formed the basis for his first textbook, *Synoptic and Aeronautical Meteorology,* published in 1937.

In the meantime, General Motors had acquired TWA, and Byers became eligible for the Alfred P.Sloan Fellowship in meteorology at MIT. With this financial assistance he returned to MIT in 1934 and obtained his Sc.D. degree in 1935. His thesis was entitled "The Changes in Air Masses During Lifting." Upon completion of the Sc.D. degree, he was appointed to the U.S. Weather Bureau as an associate meteorologist and was placed in charge of the newly created Air Mass Analysis Section with responsibility for developing new methods of weather forecasting. This period has been described as one of great change and reorientation in the U.S. Weather Bureau. The polar front theory of weather disturbances, developed by Vilhelm Bjerknes and colleagues at the Bergen Geophysical Institute, Bergen, Norway, was just coming into use by the Weather Bureau in the analysis of weather observations and making of weather forecasts.

In 1935 the Weather Bureau instituted a program whereby employees were brought into the Washington, D.C., central office in small groups for two months of training and practice in air mass analysis and the use of frontal maps in forecasting. As head of the Air Mass Section, Byers was in the forefront of this activity. The Weather Bureau's in-house training program continued to expand, and by 1940 plans were underway for five such units (Chicago, Washington, New Orleans, Denver, and San Francisco). Byers volunteered to head up the unit in the Chicago District Forecast Office on the top floor of the old post office building in downtown Chicago.

BYERS AT THE UNIVERSITY OF CHICAGO

At the University of Chicago, Byers's career flowered. In the fall of 1940 he persuaded the university to set up an Institute of Meteorology in the physics department (with financial support from Sewell Avery, chief executive officer of Montgomery Ward Co.).[2] This event took advantage of the launching of programs at several universities to train meteorologists for the U.S. Navy and Army Air Corps. Rossby was designated head of the Chicago program, but responsibility for most of its operations fell to Byers. "He was the balance wheel in the administration of one of the greatest meteorology programs the world has ever known; a spirited, if at times unruly, department energized in its early days by the creative genius of Carl Rossby. The low profile he played in that milieu prevented widespread recognition…." (H.R. Simpson, e-mail message, August 8, 1998). The institute evolved into a separate Department of Meteorology. Byers was appointed associate professor (1940–45), professor (1945–65), and department chairman (1948–60). In 1944 he published his textbook *General Meteorology,* which subsequently went through several editions.

During World War II and the early postwar years, Byers served as a consultant to several government agencies, including the Department of Defense, Atomic Energy Commission Manhattan Project, National Science Foundation, and to the Illinois State Water Survey and University of Arizona.

In 1960 the Departments of Meteorology and Geology at Chicago joined to form the Department of Geophysical Sciences. Professor Sverre Petterssen (from meteorology) and Professor Julian R.Goldsmith (from geology) were designated co-chairmen. This opened the possibility for a new career for Byers, who by now was ready for a change. In 1965 he left the University of Chicago to assume duties as dean of a newly formed College of Geosciences at Texas A&M University, with the added title of distinguished professor of meteorology. In 1968 he was appointed academic vice-president. In 1974 he retired and moved into a retirement center near Santa Barbara, California. In 1975 Byers was a visiting professor at the University of Clermont-Ferrand, where he taught cloud physics, lecturing in French.

BYERS THE ORGANIZER AND COMMUNICATOR FOR METEOROLOGY

The remarkable influence of Horace R.Byers in meteorology came in part from his unusual blend of skills. He was an excellent writer and communicator, possibly a result of his early training in journalism. He had great skill in recognizing promising young investigators and in assisting them to accomplish their goals. He was also skilled in marshaling support and galvanizing action in the meteorological community. As a member of the National Academy of Sciences rather early in his career, he was in a position of influence beyond the reach of many others.

Over a period of years, Byers served in leadership roles in several scientific organizations worldwide. He joined the American Meteorological Society in 1929, and was elected to its council (1938–50) and to its presidency (1951–53). He joined the American Geophysical Union, Section on Meteorology, in 1935, and served as section vice-president (1944–47) and president (1947–50). He was elected to the National Academy of Sciences in 1952, and served as chairman of the Section on Geophysics (1966–69). From 1954 to 1960 he served as vice-president of the International Association of Meteorology and Atmospheric Physics, where he contributed to the famed International Geophysical Year. He served as president of the IAMAP from 1960 through 1963. He was a member of the Subcommittee on Meteorological Problems, National Advisory Committee for Aeronautics (now NASA), and the National Research Council's Committee on Meteorology (1956–59).

One of his important contributions was the role he played in the formation and guidance through its early years of the National Center for Atmospheric Research/University Corporation for Atmospheric Research.[3] In early 1956, Detlev W.Bronk, president of the National Academy of Sciences, appointed a committee of the National Research Council to "consider and recommend means by which to increase our understanding and control of the atmosphere…." This Committee on Meteorology, organized in April 1956, consisted of Lloyd V.Berkner and Carl G.Rossby (co-chairmen), Horace R.Byers, Henry G.Booker, Hugh L. Dryden, Carl Eckhart, Paul E.Klopsteg, Thomas F.Malone, John von Neumann, and Edward Teller. Early in the work of the committee, Rossby died, and Jule Charney was appointed to membership. Byers was appointed vice-chairman. The committee was charged with viewing "in broad perspective the present position and future requirements of meteorological research." Byers chaired a working group on education; Charney and Malone co-chaired a working group on research.

A major recommendation from the education group was for the universities to form an inter-university committee to review the needs and problems of meteorological research. This recommendation matched with that of the research group that proposed the establishment of a national institute for atmospheric research organized by a group of universities under a prime contract with the National Science Foundation. In retrospect, the involvement of the NSF turned out to be crucial to the phenomenal progress in meteorology during the past several decades. Byers's distinctive contribution, after the release of the report, was to pick up the telephone and call Henry Houghton at MIT and urge him to take the leadership in acting on the recommendation for a University Committee on Atmospheric Research (UCAR). Byers's telephone call was one of the most important telephone calls on a meteorological matter in the last 50 years. Throughout the early years of UCAR, Byers was involved in the governance of UCAR and the National Center for Atmospheric Research, serving on its Board of Trustees and as board chairman (1962–65).

Less well known, was his role in the initiation of the sequence of international programs in meteorology that ultimately led to the massive World Climate Research Program in the final years of the twentieth century. On an airplane journey to Australia for a conference to review E.G.Bowen's precipitation enhancement program in the Snowy Mountains of Australia, Malone (who had just come from a meeting at the White House to discuss the possibility that President Kennedy might include a proposal for a global initiative in an address to the United Nations) and Byers had a long conversation concerning the scientific merits of such an initiative. His strong endorsement of the initiative and his insistence that it have firm roots in the broad, non-governmental, scientific community carried great weight with Malone. A year after President Kennedy made that proposal, the United Nations invited the non-governmental International Council of Scientific Unions (ICSU) to participate in drawing up this program. Again in the summer of 1963, Byers and Malone traveled together by plane (in the Travelers corporate aircraft) to Toronto to urge Warren Godson (secretary general of the International Association of Meteorology and Atmospheric Physics) to involve all of ICSU in planning the proposed program. The mission was not successful, but at an international conference in Los Angeles in September, Byers's views became a highly successful, joint activity of the governmental and non-governmental sectors and established a kind of partnership that has served the world well—thanks in no small part to the wisdom of Horace Byers.

Byers also played an important role in the formation of the Institute of Atmospheric Sciences (later a department) at the University of Arizona. This came about in an interesting way. In 1953 Lew Douglas, a prominent citizen of Arizona, proposed that the University of Arizona set up a cloud-seeding research group, using funds contributed by local ranchers. The head of an eminent private sector cloud-seeding company was identified to direct the effort. Douglas came to Byers for advice. Professor Byers thought that it would be tragic for the University of Arizona to set up the group under those conditions. Instead, he negotiated an arrangement whereby a research colleague, Roscoe R. Braham, Jr., became the founding director of the institute in Tucson, under a joint appointment between the two universities. Byers continued to serve as an advisor to the Arizona group after Braham returned full time to Chicago.

BYERS THE SCIENTIST

During his senior year at the University of California, Professor Leighly persuaded Byers to write a paper on the summer sea fogs of the California coast. This paper, published as a bulletin of the University of California, Berkeley, was his first published scientific paper. The scientific publications of Horace Robert Byers are mainly in three areas: general meteorology, thunderstorms and severe weather, and cloud physics. Using his skill as a communicator, he wrote many of his papers to acquaint non-meteorologists with some of the latest findings in the field of meteorology.

While at the University of Chicago, Byers organized and directed three pioneering research programs: the Thunderstorm Project, the Artificial Cloud Nucleation Project, and the Cloud Physics Project. Arguably, the pinnacle of his career as a scientist came with the Thunderstorm Project. In later correspondence with one of the authors (R.R.B.), Byers stated that he first became interested in thunderstorms in 1929 as he rode a train from California to MIT. He crossed the Great Plains at night; a night of major thunderstorms along the route. The incessant lightning seemed to challenge understanding. While with the Weather Bureau he began a study of thunderstorm rainfall using data from a Soil Conversation Service network of rain gages in Ohio. This study then was published after he arrived at Chicago.

By the end World War II, thunderstorms were regarded as the most serious weather obstacle to the rapidly expanding aviation industry. In 1946, under pressure from the commercial air lines, the National Advisory Committee for Aeronautics (predecessor of NASA) and the U.S. military departments, Congress passed P.L. 647, which directed the chief of the U.S. Weather Bureau to conduct research on the internal structure of thunderstorms. Weather Bureau Chief Reichelderfer named Byers director of the Thunderstorm Project.[4] It operated in Florida and Ohio during the summers of 1946 and 1947. The final report of the Thunderstorm Project was widely acclaimed as the first definitive study of the interior structure and air motions inside thunderstorms. Well over half the citations to Byers's publications are to this report. This project demonstrated the value of weather-sensitive radar to the safety of airplanes flying through and around thunderstorm conditions and did much to prompt industry to develop radar suitable for routine use on airplanes. While analyzing data from this project, a graduate student (R.Braham) discovered that intense downdrafts develop adjacent to strong updrafts in thunderstorms to form a coupled pair that undergo a regular life cycle.[5] These he called thunderstorm cells. The important role played by strong downdrafts in the structure of thunderstorms was a major new finding of the Thunderstorm Project. The thunderstorm cell model was the centerpiece of the project's final report, and has served as the foundation for much of subsequent research on thunderstorms.

Byers's concern for thunderstorms and severe weather continued beyond publication of the results of the Thunderstorm Project. About 1951 he arranged for the Japanese scientist Ted Fujita to come to Chicago, thus beginning a new chapter in severe storm research for which Professor Byers was justifiably very proud. His last publication was coauthored with Fujita in 1977: "Spearhead Echo and Downburst in the Crash of an Airliner." This paper provided a fitting closure to a career heavily concerned with aircraft safety.

While the Thunderstorm Project was in progress, Irving Langmuir and Vincent Schaefer, of General Electric Laboratories, discovered that silver-iodide smokes were effective in initiating ice crystals in all-liquid supercooled clouds. Experiments in thin supercooled stratus clearly demonstrated that such clouds could be turned to ice crystals if natural ice nuclei were insufficient. This offered a scientific possibility for useful anthropogenic influence on clouds and weather, a possibility that captured the imagination of many persons and led to unwarranted claims of what might be achieved through cloud seeding. Cloud seeding came on like a steamroller. Byers could not escape. The possibility that significant weather changes might be induced through cloud seeding made it imperative that the U.S. military agencies conduct research to assess the probable tactical value of cloud seeding. A high level governmental advisory group recommended that the military conduct research into the physics of precipitation and artificial weather control. About 1951 the U.S. Air Force Cambridge Research Laboratories contracted with the University of Chicago to study the physics of cumulus clouds and their response to seeding. This was part of a multi-agency effort called the Artificial Cloud Nucleation Project. Professor Byers was designated director of the University of Chicago portion. Quickly he engaged several persons from the Thunderstorm Project. The final report, published as an American Meteorological Society Monograph,[6] contained many new findings about the physics of clouds and their response to seeding, but little encouragement for cloud seeding. There were followon contracts and grants that enabled the University of Chicago Cloud Physics Lab, under Byers's leadership, to achieve worldwide distinction in the study of the physics of clouds and their response to cloud seeding. Byers was deeply involved in two very carefully designed and executed scientific experiments to test the efficacy of cloud seeding: the Arizona Seeding Experiment and Project Whitetop. Both experiments went to great lengths to minimize experimenter biases and to cope with the well-known fact that no two clouds are alike nor are they completely independent of nearby clouds or those on nearby days. He firmly believed that statistics and statisticians were essential in the design and evaluation of these experiments. Although the results of these experiments were controversial, they offered little encouragement for cloud seeding.

It was in his views about cloud seeding that Byers came into conflict with the eminent academician Irving Langmuir. Byers was one of many meteorologists who thought that Langmiur's claims for substantial changes in convective clouds and large weather systems, as a result of weather modification, were extravagant and mainly a result of a lack of appreciation for the complexity and variability of natural weather phenomenon. Whereas laboratory experiments can be carefully controlled and replicated, in the atmosphere no two clouds are identical or are completely independent. In the strictest sense, no weather modification experiment can be replicated, and careful statistical controls are required for interpretation of weather modification experiments.

Byers was a constructive critic of weather modification. He advocated basic research in cloud physics. His background in atmospheric thermodynamics and energetics of atmospheric systems made him cautious about the possibility of significant weather changes through seeding. His first scientific paper on this subject, in 1953, called for study of the physical processes of natural rain formation, the physics of artificial intervention (as it was perceived at that time), and the need for carefully designed experiments. In 1965 he published a textbook *Elements of Cloud Physics* based upon class lecture notes at the University of Chicago. His 1974 chapter in the book *Weather and Climate Modification,* edited by W.N.Hess, gives a definitive review of scientific research in weather modification up to about 1971.

BYERS THE INDIVIDUAL

In 1927 Horace R.Byers married Frances Isabel Clark in Berkeley. They had one daughter, Henrietta Byers, who married Thomas W.Bilhorn.

Some who knew him only casually found Professor Byers somewhat formal and reserved, but those who really knew him recognized him as a friend and supporter who worked hard to advance meteorology. He might be called a vigorous go-getter, one who did not like to come off second best. He was a statesman among meteorologists. He also had a lighter side. His humor as a banquet speaker is mentioned in several places. He loved to ride horses. He obtained a private pilot's license in 1941. He was a gourmet cook and connoisseur of fine wines. Over a period of many years he was given the task of selecting "just the right wine" whenever he gathered with colleagues for dining.

AWARDS

1941	Robert M.Losey Award, American Institute of Aeronautics and Astronautics
1952	Elected to the National Academy of Sciences
1959	Award of Merit, Chicago Technical Societies Council
1960	Charles F.Brooks Award, American Meteorological Society
1978	Cleveland Abbe Award, American Meteorological Society

SCIENTIFIC SOCIETIES

Fellow, American Meteorological Society (president, 1952–53; honorary member, 1975)

American Geophysical Union (section president, 1947–48)

International Association of Meteorology and Atmospheric Physics (president, 1960–63)

National Academy of Sciences (chair, Geophysics Section, 1966–69)

Royal Meteorological Society

American Geography Society

American Association for the Advancement of Science

Sigma Xi (president, Chicago chapter, 1958–60)

Phi Kappa Phi

NOTES

1. An account of Professor Carl-Gustaf Rossby's coming to the United States and his association with the Guggenheim Foundation can be found in Byers (1959,2 [pp. 56–59]).

2. H.R.Byers. The founding of the institute of Meteorology at the University of Chicago. *Bull Am. Meteorol Soc.* 57(1976):1343–45.

3. E.L.Hallgren. *The University Corporation for Atmospheric Research and the National Center for Atmospheric Research: An Institutional History.* Boulder, Colo.: 1974.

4. A brief history of the Thunderstorm Project can be found in R.R.Braham, Jr. The Thunderstorm Project. *Bull. Am. Meteorol. Soc.* 77(1966):1835–45.

5. See H.R.Byers. Probing the thunderstorm. *Weatherwise* 1(1948):47–50. Structure and dynamics of the thunderstorm. *Science* 110(1949):291–94.

6. R.Braham, Jr., L.J.Battan, and H.R.Byers. Artificial nucleation of cumulus clouds. *Am. Meteorol. Soc. Meteorol Monogr.* 2(1957):47–85.

SELECTED BIBLIOGRAPHY

1930 Summer sea fogs of the central California coast. *Univ. Calif. Publ. Geogr.* 3(5):291–338.

1931 Characteristic weather phenomena of California. *Mass. Inst. Tech. Meteorol. Pap.* 1(2):1–54.

1937 *Synoptic and Aeronautical Meteorology.* New York: McGraw-Hill.

1941 With V.Starr. The circulation of the atmosphere in high latitudes during winter. *Mon. Wea. Rev.* 47(suppl.).

1942 *Non-frontal Thunderstorms.* University of Chicago Institute of Meteorology Miscellaneous Report No. 3.

1944 *General Meteorology.* New York: McGraw-Hill.

1946 With B.G.Holzman and R.H.Maynard. A project on thunderstorm microstructure. *Bull. Am. Meteorol. Soc.* 27:143–46.

1948 With H.R.Rodebush. Causes of thunderstorms over the Florida peninsula. *J. Meteorol.* 5:275–80.

With R.R.Braham, Jr. Thunderstorm structure and circulation. *J. Meteorol.* 5:71–86.

1949 With R.R.Braham, Jr. *The Thunderstorm: Final Report of the Thunderstorm Project.* Washington, D.C.: U.S. Government Printing Office.

Thunderstorms. In *Compendium of Meteorology,* ed. T.F.Malone, pp. 681–93. Boston: American Meteorological Society.

1953 With R.R.Braham, Jr. Thunderstorm structure and dynamics. In *Thunderstorm Electricity,* ed. H.R.Byers, pp. 46–65. Chicago: University of Chicago Press.

1954 The atmosphere up to 30 kilometers. In *The Earth as a Planet,* vol. 2, ed. G.P.Kuiper, pp. 299–370. Chicago: University of Chicago Press.

1955 With R.K.Hall. A census of cumulus-cloud height versus precipitation in the vicinity of Puerto Rico during the winter and spring of 1953–1954. *J. Meteorol.* 12:176–78.

1957 With J.B.Sievers and B.J.Tufts. Distribution in the atmosphere of certain particles capable of serving as condensation nuclei. In *Artificial Stimulation of Rain,* eds. H.Weickmann and W.Smith, pp. 47–72. New York: Pergamon.

With R.R.Braham and L.J.Battan. Artificial nucleation of cumulus clouds. In *Cloud and Weather Modification. Am. Meteorol. Soc. Meteorol. Monogr.* 2:47–85

1959 Carl-Gustaf Arvid Rossby. In *Biographical Memoirs,* vol. 34, pp. 249–70. Washington, D.C.: National Academy of Sciences.

Carl-Gustaf Arvid Rossby, the Organizer. In *The Atmosphere and Sea in Motion* (Rossby Memorial), ed. B.Bolin, pp. 56–59. New York: Rockefeller Institute.

1962 With T.Fujita. Model of a hail storm as revealed by photogrammetric analysis. *Nubila* 5:85–105.

1965 *Elements of Cloud Physics.* Chicago: University of Chicago Press.

1974 History of weather modification. In *Weather and Climate Modification,* ed. W.N.Hess, pp. 3–44. New York: Wiley.

1976 The founding of the Institute of Meteorology at the University of Chicago. *Bull. Am. Meteorol. Soc.* 57:1343–45.

1977 With T.Fujita. Spearhead echo and downburst in the crash of an airliner. *Mon. Wea. Rev.* 105:129–46.

GERALD MAURICE CLEMENCE

August 16, 1908–November 22, 1974

BY RAYNOR L. DUNCOMBE

Gerald maurice clemence was born near Greenville, Rhode Island, on August 16, 1908, the first child of Richard R. and Lora E. (Oatley) Clemence. He died in Providence, Rhode Island, on November 22, 1974, after an illness of several months. He was one of a small group of dynamical astronomers in this country before the dawn of the space age, and his scientific career spanned the entire period from the lead pencil era of hand computing to the use of the most powerful electronic calculators. Influenced by the career of Simon Newcomb, whose accomplishments he greatly admired, Clemence brought the U.S. Nautical Almanac Office back to the preeminent position in dynamical astronomy it had enjoyed in the later part of the nineteenth century.

YOUTH AND EDUCATION

As a child Gerald lived on an 80-acre farm in northern Rhode Island with a younger sister and three younger brothers, his mother, and an older friend of hers, who was much like a grandmother to them. The farm was mostly woods, with about 10 acres under cultivation. They kept a cow or two, a horse, and hens, and his chief duties were looking after the barn, mowing the lawn, and shoveling snow. His father ran a dairy farm about 10 miles distant, on which lived his father's parents and two maiden sisters, and was often absent from his own family for days at a time. According to Gerald's own recollections, he attended elementary school only in the third, fifth, and seventh grades. Beyond this, his education was provided at home by his mother, herself a schoolteacher and a most imposing woman both in stature and character. When Gerald completed the eighth grade at the age of 12, his mother thought him too young to enter high school, so he kept the house for one winter while his mother taught school. It was during this early period that he developed his love for good music and literature. His mother had a phonograph with a hundred of the best records of that time and an assorted library of nearly two thousand books. He taught himself to play the piano and violin, and throughout his life he found relaxation in reading and in performing or listening to music. Among his favorite authors was Ambrose Bierce, because of his incisive style and mode of expression, traits that Gerald himself mastered and used. His first acquaintance with astronomy, according to his own recollections, was through a newspaper column "Planets and Stars," which he began to read at the age of eight. An aunt taught him the constellations and how to identify the planets, but he stated later that most of what he learned of astronomy came from reading books and articles.

It has been said that some people are born great, some achieve greatness, and others have greatness thrust upon them. Gerald was of the middle variety and he well exemplified Abraham Lincoln's early motto: "I shall study and prepare myself, and some day my chance will come." After graduation from high school he entered Brown University. Assuming his chief interest to be mathematics, he majored in that subject with an additional year of graduate study and earned the degree of Ph.B. in 1930. "As a recreation," he said later, he took a civil service examination for astronomer and upon passing with a high grade (he was first in a field of 50), he accepted an appointment to the U.S. Naval Observatory in Washington, D.C., "attracted by the seemingly high salary of $2,000 per annum." Gerald brought with him his new bride, Edith Melvina (Vail) Clemence, a Canadian girl he had met while visiting his mother Lora at Rhode Island Hospital in June 1927. At the time Edith was head nurse of Ward F at the hospital. They were married at the Vail homestead in Brockway, New Brunswick, on August 17, 1929.

EARLY CAREER AT THE U.S. NAVAL OBSERVATORY

Clemence was assigned at first to the Time Service and later to the Nine-Inch Transit Circle Division under the direction of H.R.Morgan. Morgan was a specialist in star catalogues and fundamental meridian circle observations. Such work is multidisciplinary in the sense that it involves the mechanics of the instrument, the psychology of the observers, the mathematics of practical astronomy, the reduction of vast amounts of observational data, and the gift of intuitive judgment and good sense. Morgan was a superb teacher: patient, meticulous, precise, completely dedicated to his work. And Gerald was an excellent student. After he mastered the fundamentals of such work he decided to take on two ambitious projects concerning the planets Mercury and Mars.

The orbits of the major planets of the Solar System, which had been adopted for international use by most major nations, had been computed in the later part of the nineteenth century. G.W.Hill spent seven years of his life computing the orbits of Jupiter and Saturn. The others were computed under the direction of Simon Newcomb, director of the Nautical Almanac Office (1877–97). By the mid-1930s there existed nearly half a century of observations of even better quality than those made previously, which had never been used in establishing the basic elements for each planet.

In addition to his required duties in the Nine-Inch Transit Circle Division Gerald decided to undertake the extra work of comparing all of the observations of Mercury with Newcomb's orbit in order to derive more accurate orbital elements and to render more reliable the predictions and other uses of these elements. This effort evolved into a Works Progress Administration project with three technicians working under his supervision over several years and resulted in a vastly improved set of elements that clearly demarked the excess motion of the perihelion predicted by general relativity. These results appeared in the *Astronomical Papers of the American Ephemeris* (1943), the series of publications started by Simon Newcomb to document his research, which Gerald reactivated and continued.

The situation with respect to Mars was even worse. As Gerald recounted later, "While inspecting a 20-year-old graph showing the discrepancies between the observed positions of Mars and the theory of its motion, I was struck by the systematic character of the deviations and in a flash of insight surmised that the theory was at fault." It became obvious to him from the periodic character of the residuals that the Fourier series that represented the motion were either inadequate or actually contained some errors. Gerald decided to derive an entirely new theory, completely independent of any previous work on Mars and following Hansen's method as Hill had used it. The fortitude of such a decision must be judged in the context of the computing facilities at his disposal at the time. They consisted of a lead pencil, large sheets of computing paper, a hand-operated "Millionaire" desk calculator, and considerable manual dexterity. Eventually this project, which took over 12 years, was completed by means of punched-card machines and then electronic calculators. It proved to be the greatest single accomplishment of Clemence's entire scientific career. The first order theory of Mars was documented in the *Astronomical Papers of the American Ephemeris* (1949).

TRANSFER TO THE NAUTICAL ALMANAC OFFICE

The year 1940 brought some changes that crucially affected the course of Gerald's career. Wallace J.Eckert had just been appointed director of the Nautical Almanac Office, and Dirk Brouwer became the director of the Yale University Observatory. They had been colleagues and collaborators for the previous 10 years at Columbia and Yale, respectively. Eckert's notable forte at that point was the use of punched-card machines for scientific computation, and almost immediately he revolutionized the Nautical Almanac Office and celestial navigation by the automatic production of the new *Air Almanac*. He offered Gerald an appointment in the office only one position below the assistant director, and thus Gerald left the Transit Circle Division (with a wealth of experience that was later to stand him in good stead).

Gerald quickly adapted the punched-card equipment to the problems of the Almanac Office and to his own work on the theory of Mars. In 1942 he was promoted to the position of assistant director, and Paul Herget of the University of Cincinnati joined the staff. The routine work of the Nautical Almanac Office and other war work commanded the highest priorities during these years, and Gerald and Paul cooperated on many projects for the armed forces. They also developed the principle in the construction and use of mathematical tables known as the optimum-interval method (1944). In 1945, at the end of the war, Eckert resigned to become director of IBM's Watson Scientific Computing Laboratory at Columbia University, Herget returned to

Cincinnati as director of the Cincinnati Observatory, and Gerald was promoted to the post of director of the Nautical Almanac Office. This was probably the proudest moment of his life, because he had attained the post once held by Simon Newcomb, whom he greatly admired and respected. He was deeply concerned with the responsibilities of his new position, and his astuteness, good judgment, and administrative skills came to the fore.

THE GOLDEN YEARS FOR CELESTIAL MECHANICS

In 1947 the Office of Naval Research began a sustained period of support for research in celestial mechanics through a contract involving Yale, the Nautical Almanac Office, and the Watson Scientific Computing Laboratory. The Cincinnati Observatory joined in the effort and the congenial and constructive relationships that existed among Clemence, Brouwer, Eckert, and Herget was terminated only by the deaths of Brouwer (in 1966) and then Eckert (in 1971). The preliminary agenda for this research involved (1) a revision of the motions of the principal planets; (2) work on the secular perturbations of Pluto; (3) work on a new mathematical theory of the motions of Saturn and Jupiter; (4) calculations to develop the theory of the motions of the first four minor planets; (5) completion of the development of the theory of the motion of Mars by Hansen's method; and (6) measurement of photographic plates of Saturn's satellites to allow evaluating the mass of the system.

The research output of this coalition was prodigious and in the period between 1949 and 1970 resulted in 22 contributions to the *Papers of the American Ephemeris* and *Nautical Almanac,* as well as many shorter articles in scientific journals. In addition, over 25 Ph.D. dissertations were based on research carried out in this project. Gerald was a prolific contributor, individually and in concert with others. Gerald's paper on the system of astronomical constants (1948) formed the basis for the later introduction of the idea of ephemeris time at the 1950 Paris conference. He played a primary role in the simultaneous numerical integration of the orbits of the five outer planets (1951) and subsequently produced the tables for the computation of the perturbations of the five outer planets by the four inner ones (1954). He also produced tables for the coordinates of the center of mass of the Sun and the five outer planets (1953). By this time, several comparisons of numerical integrations of the orbit of Mars with his first-order theory had indicated that some second- and higher-order terms were of significance. He amended his theory to account for these omissions and produced the theory of Mars completion in 1961. This magnificent piece of work, the most accurate and the only one of its kind that had been done since the turn of the century, stands as a monument to Gerald's perseverance and genius. A geocentric ephemeris based on his theory for 1950–2000 was published in 1960.

In 1958 another turn in his career occurred when he was appointed to the newly created position of scientific director of the U.S. Naval Observatory. In this post the administration of the scientific programs of the whole observatory became his responsibility. He assumed his new duties with the same foresight, good planning, scientific insight, and administrative ability he had exercised as director of the Nautical Almanac Office. The high regard in which he was held by the national and international scientific communities enhanced the standing of the observatory. As his administrative duties increased the volume of his scientific research diminished, although there was still a steady flow of articles on relativity, astronomical constants, and time. It was during this period that he collaborated with Brouwer in the production of the excellent text *Methods of Celestial*

Mechanics (1961) and began his work with Woolard on the equally important text *Spherical Astronomy* (1966).

Dismayed by the lack of time to carry out his ambitious program of research on the motions of the Sun and planets, he retired at the age of 55, hoping to find an academic position that would allow him more time. In 1963 Brouwer offered him the position of senior research associate at Yale, and Gerald was able to continue his work on the general perturbation theory of the motion of Earth. Upon the sudden death of Brouwer in 1966 Gerald was promoted to full professor and was given the scientific and administrative responsibility for the astronomy department until such time as a new director could be found. These new duties impinged on his research, and the work on the theory of the Earth was not finished at the time of his death.

In the area of astronomical navigation Gerald made many contributions. He produced many technical reports on subjects such as bubble sextant errors, refraction, dip, irradiation, and time. Because of the high regard in which he was held internationally and with the full cooperation of D.H. Sadler, superintendent of H.M.Nautical Almanac Office, he was able to convince the naval administration that it was to everyone's benefit to unify the British and American air almanacs. This unification was later extended to all tables for navigation in the United States and the United Kingdom and led to their use in numerous other countries. Ultimately it became possible to unify the astronomical ephemerides, which were then published jointly in both countries.

A farsighted report "The Need for Training Students in Celestial Mechanics" (1947) anticipated the future need for scientists trained in the fundamentals of orbital mechanics. With the onset of the space age and the launch of *Sputnik* in 1957 Gerald cooperated with Brouwer in launching the series of Yale Summer Institutes in Dynamical Astronomy aimed at meeting the burgeoning requirement for scientists trained in this subject. He presented lectures in the early institutes and provided other help to the program. Otherwise his role in the space age was mostly supervisory, although U.S. Naval Observatory personnel were involved in many aspects of the Earth satellite programs.

OFFICES, AWARDS, AND HONORS

Gerald's reputation as a scientist and as an administrator was well recognized in the United States and abroad, and he was drafted to serve in many roles. From 1949 to 1966 he served as associate editor of the *Astronomical Journal* and from 1969 to 1974 as editor. He oversaw the expansion of the journal resulting from the resurgence of interest in classical and fundamental astronomy as large high-speed calculators appeared and the requirements of the space age arose. The American Astronomical Society called upon his talents over the course of his career, and he served as president from 1958 to 1960. In 1952 he was elected to membership in the National Academy of Sciences. He became chairman of the Board of Directors of the B.A.Gould Fund from 1953 to 1969. In 1955 he was elected a fellow of the American Academy of Arts and Sciences. From 1962 to 1965 he was chairman of the Division of Physical Sciences of the National Research Council. In 1946 he was elected a fellow of the Royal Astronomical Society of Great Britain and in 1952 an associate.

Gerald was an active participant in the activities of the International Astronomical Union, serving as president of Commission 7 (Celestial Mechanics) from 1948 to 1955 and of Commission 4 (Ephemerides) from 1964 to 1967. He received the U.S. Navy Award for Distinguished Achievement in 1963 and for Superior Achievement in 1964. He was elected an honorary member of the Royal Astronomical Society of Canada in 1946. In 1965 he was awarded the Gold Medal of the Royal Astronomical Society of Great Britain “in recognition of his application of celestial mechanics to motions in the Solar System and his fundamental contributions to the study of time and the system of astronomical constants.” Sir Richard Woolley, president of the society, noted the many similarities between Gerald’s accomplishments and those of his famous predecessor Simon Newcomb. Gerald greatly appreciated this comparison. Later in 1965 Gerald presented the George Darwin Lecture on “Inertial Frames of Reference.” In 1975 he was posthumously awarded the J.C.Watson Medal of the National Academy of Sciences.

THE SCIENTIST AND THE FAMILY MAN

As a scientist Gerald presented a reserved appearance, was conservatively dressed, and maintained a dignified composure. When speaking, he thoughtfully considered his remarks and gave them with an economy of words. His scientific papers were similarly concise: to the point and without excess verbiage. In speaking and in writing he chose his words carefully and they meant exactly what he intended them to convey. As a person, Gerald was a sincere, forthright individual who was guided by an ethical code absorbed at an early age from his parents. Throughout his life he maintained close contact with his three brothers and his sister. He was a devoted husband and father (of two sons) and took great delight in their accomplishments. His principal hobby was good music: He was self-taught and accomplished on the violin, the piano, and the organ. On occasion he played the organ in several churches, including the Washington Cathedral, and was a member of the Organists Guild. A secondary hobby was watching trains (sometimes in the company of Paul Herget). When time permitted they would go to the famous horseshoe curve on the Pennsylvania Railroad, carefully noting each type of locomotive observed, especially in the age of steam engines. In his travels he went by train whenever feasible.

Gerald was a patient mentor, a kind friend, and a steadfast colleague. He has given his students and associates a target to strive for in their own careers. In his final illness he was taken to a Providence nursing home near Brown University, while Edith took an apartment nearby in the area where they had lived as newlyweds 45 years before. After an illness of several months he died in Roger Williams Hospital.

He was survived by his widow, Edith, and two married sons, Gerald Vail Clemence and Theodore Grinell Clemence.

THIS MEMOIR was derived from Gerald Clemence's published papers; his autobiographical sketch on file at the National Academy of Sciences; from data received earlier from Paul Herget and D.H.Sadler; and from the recollection of the writer, who was fortunate enough to be Gerald's student, colleague, and friend for a number of years at the Nautical Almanac Office. Editorial review by Gerald Vail Clemence and his wife, Barbara, and by Donald Osterbrock is gratefully acknowledged.

SELECTED BIBLIOGRAPHY

1937 With P.Sollenberger. Lunar effects on clock corrections. *Astron. J.* 48:78–80.
1943 The motion of Mercury 1765–1937. *Astron. Pap. Am. Ephemeris* no. 11, part 1.
1944 With P.Herget. Optimum-interval punched-card tables. *Math. Table Aids Comp.* 1:173–76.
1947 The relativity effect in planetary motions. *Rev. Mod. Phys.* 19:361–64.
The need for training students in celestial mechanics. *J. Roy. Astron. Soc. Can.* 41:290–94.
1948 On the system of astronomical constants. *Astron. J.* 53:169–79.
1949 Relativity effects in planetary motion. *Proc. Am. Philos. Soc.* 93:532–34.
First-order theory of Mars. *Astron. Pap. Am. Ephemeris* no. 11, part 2.
1950 With P.Herget and H.G.Hertz. Rectangular coordinates of Ceres, Pallas, Juno, Vesta, 1920–1960. *Astron. Pap. Am. Ephemeris* no. 11, part 4.
1951 With D.Brouwer and W.J.Eckert. Coordinates of the five outer planets, 1653–2060. *Astron. Pap. Am. Ephemeris* no. 12.
1953 Coordinates of the center of mass of the Sun and the five outer planets, 1800–2060. *Astron. Pap. Am. Ephemeris* no. 13, part 4.

1954 Perturbations of the five outer planets by the four inner ones. *Astron. Pap. Am. Ephemeris* no. 13, part 5.

1955 With D.Brouwer. The accuracy of the coordinates of the five outer planets and the invariable plane. *Astron. J.* 60:118–26.

1956 Standards of time and frequency. *Science* 123:567–73.

1957 Astronomical time. *Rev. Mod. Phys.* 29:2–8.

1960 With R.L.Duncombe. Provisional ephemeris of Mars 1950–2000. *U.S. Naval Observatory Circular* No. 90.

1961 With D.Brouwer. Orbits and masses of planets and satellites. In *Planets and Satellites,* ed. G.P.Kuiper and B.M.Middlehurst, pp. 31–94. Chicago: University of Chicago Press.

Theory of Mars (completion). *Astron. Pap. Am. Ephemeris* no. 16, part 2.

With D.Brouwer. *Methods of Celestial Mechanics.* New York: Academic Press.

1962 Planetary distances according to general relativity. *Astron. J.* 67:379–81.

1963 Astronomical reference systems. In *Basic Astronomical Data,* ed. K.A. Strand, pp. 1–10. Chicago: University of Chicago Press.

1965 The system of astronomical constants. *Annu. Rev. Astron. Astrophys.* 3:93–112.

1966 The scale of the Solar System. *J. Roy. Astron. Soc. Can*. 60:167–76.
Inertial frames of reference. *Q. J. Roy. Astron. Soc.* 7:10–21.
With E.W.Woolard. *Spherical Astronomy.* New York: Academic Press.

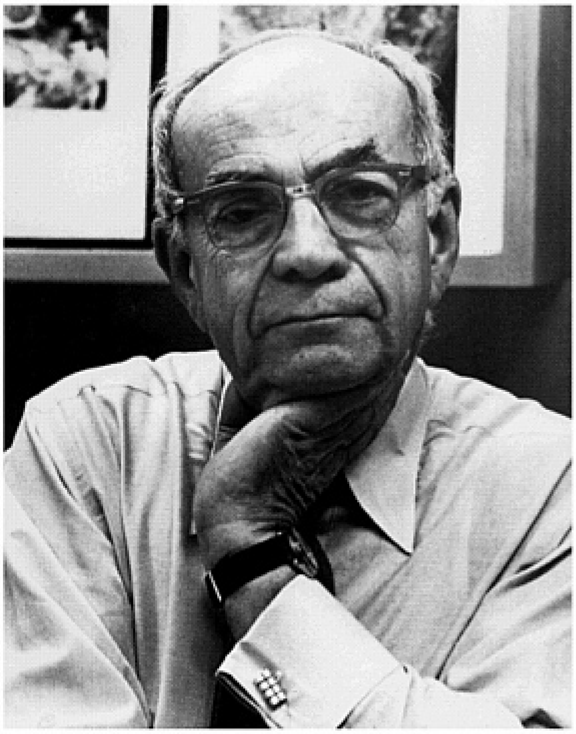


Photo by H. Owens

JULIUS H.COMROE, JR.

March 13, 1911–July 31, 1984

BY SEYMOUR S. KETY AND ROBERT E. FORSTER

JULIUS COMROE WAS AN extraordinary teacher who began his medical career as a surgeon, then became an accomplished investigator and did important original research, but gradually directed his considerable energies into teaching basic biomedical research to graduate physicians and explaining its importance to medical practice and the acquisition of new knowledge. After developing the internationally recognized Cardiovascular Research Institute (CVRI) in San Francisco, he worked tirelessly, in spite of failing health during the last years of his life, to demonstrate to the Congress and the public, that investigator-initiated medical research was essential to improve the nation's health.

Julius H.Comroe, Jr., was born in York, Pennsylvania, on March 13, 1911, the youngest son of the city's preeminent internist. His father as well as his older brother, Bernard, had graduated from the University of Pennsylvania, both the college and the medical school, and were very loyal supporters of the institution. Julius naturally followed them and graduated first in his class from the college in 1931. As an undergraduate he was editor of the college humor magazine and demonstrated his penchant for cartoons by publishing a drawing of top-hatted stage-door

Johnnies outside the dressing room door of Penn's then all-male burlesque frolic, the *Mask and Wig Show*. At Penn Medical School he again graduated first in his class in 1934, and was admitted to the two-year internship program at the Hospital of the University of Pennsylvania. His goal was to become a surgeon, but during an operation on a patient with pelvic inflammatory disease one of Julius's eyes became contaminated. Rather than stay home and have it treated, he went to a surgical meeting in Chicago; the eye became desperately infected and had to be removed. This was the end of his career in surgery, to the benefit of medical science.

In 1936 Julius Comroe married Jeanette Wolfson, a tennis-playing friend and social worker; they had one daughter, Joan. His brother, Bernard, had been the first chief resident of the Hospital of the University of Pennsylvania, later becoming a widely known rheumatologist and author of a classic text. He was warmly regarded at Penn, an inspiration to Julius. Bernard's wife died tragically; he could not face life without her and followed her shortly, leaving his daughter an orphan. Julius and Jeannette moved into Bernard's house to take care of their niece, so that she would not suffer the loss of her home in addition to the loss of both parents.

As a medical student, Comroe had collaborated on a paper on the effects of mecholyl (1933) with Isaac Starr, the professor of clinical therapeutics and a member of the faculty of pharmacology. In 1936 he sought and was given an appointment in the Department of Pharmacology as instructor by Alfred Newton Richards. He began his research there investigating the control of respiration with Carl Schmidt, who was already established in the field. Corneille Heymans in Belgium had reported that lowering the oxygen content of blood flowing to the region of the bifurcation of the common carotid stimulated ventilation in animals, for which finding he won the Nobel Prize in 1938. The precise region in which the change in oxygen was detected and the relative importance of blood O_2 partial pressure (P_{02}) versus O_2 concentration was a matter of dispute. With the help of W.H.F.Addison in anatomy (1937), Comroe and Schmidt (1938) showed that it was the tiny carotid body that was sensitive to a fall in blood Po_2 and to a rise in blood Pco_2. This was an emergency system to protect against a fall in arterial Po_2 as contrasted with O_2 concentration and had little effect on normal respiration. These concepts of the function of the carotid bodies have held up over the years, established Comroe's reputation in the field, and helped him win a travel fellowship to the XVI International Physiological Congress in Zurich in 1938 and a Commonwealth Fellowship to work with Sir Henry Dale in London in 1939.

In 1927, before they reported chemosensitivity in the carotid bifurcation, Heymans and Heymans had also described a chemosensitive mechanism in the aortic arch region, but these results were challenged; so the existence of aortic chemoreceptors was in dispute when Comroe started his investigations. Again in collaboration with Addison (1938,1), Comroe carried out detailed anatomic studies of the aortic chemoreceptor, particularly to determine its blood supply, which was shown to be from the aorta in dogs and from the coronaries in cats. Thus armed, Comroe was able to identify their function by injecting at different sites in the great vessels and by blocking blood flow to the aortic chemoreceptive area (1939). This was the definitive work on the aortic chemoreceptors, showing they caused an increase in ventilation when arterial P_{O2} fell, or known chemical stimulators of the carotid body such as lobeline or NaCN were added to the blood. This stimulation of ventilation was less than that when the carotid body was similarly excited.

Schmidt and Comroe wrote several reviews summarizing their important work on the regulation of ventilation (1939,2; 1940; 1941).

Comroe also investigated the sensitivity of the central respiratory center located somewhere near the dorsal surface of the medulla (the fourth ventricle) (1943,1) to micro injections of solutions containing P_{CO2}, which produced a marked increase in ventilation of cephalad to the obex, restricting the central chemoreceptor to this region. Acids were less effective and lobeline ineffective. This led to the general conclusion that the arterial Pco_2 of blood perfusing the medullary region of the brain stem is the major determinant of normal ventilation, and that the function of the peripheral chemoreceptors was to protect the brain against hypoxia.

Comroe and Schmidt now had evidence for the control of respiration at rest by arterial P_{CO2} and P_{O2} and next tackled the ongoing problem of how ventilation is regulated during exercise, when these blood gases are essentially normal in the face of a massive hyperventilation. They sought the explanation in increased nerve traffic from contracting muscles and did find that stimulating peripheral muscle groups in man and anesthetized animals did increase ventilation, but not enough to account for the total increase seen in exercise (Comroe and Schmidt, 1943,2).

Comroe added on to his natural abilities as a teacher the experience gained in the outstanding pharmacology course of Richards and Schmidt. When he first joined the department he was given charge of the moribund course in materia medicae and made it into a popular offering. As in all his teaching he showed that ingenuity and careful preparation were essential.

In 1944 Comroe and Robert D.Dripps applied the most modern techniques of the time to the measurement in humans of arterial and alveolar P_{O2}, whose difference had been the subject of an intense disagreement between August Krogh in Denmark and J.S.Haldane in Oxford from the 1890s until the 1920s (1944). Krogh believed O_2 diffused passively from alveolar gas to capillary blood. In this case arterial P_{O2} should be less than or possibly equal to alveolar gas P_{O2}. On the other hand, Haldane believed that O_2 could be secreted from alveolar gas into capillary blood against a P_{O2} gradient. In this latter case, arterial P_{O2} should be greater than alveolar. Collection of arterial blood from humans without surgery was first reported in 1912; the measurement of P_{O2} in blood had only recently become possible. Comroe and Dripps equilibrated a small bubble of gas with 500 times its volume of arterial blood and then measured the O_2 in the bubble, finding that at rest at sea level, the arterial P_{O2} was 97.1 mm Hg and alveolar 97.0 mm Hg, not significantly different. This work was the start of a lifelong collaboration.

Dripps eventually moved to anesthesiology within the Department of Surgery, facetiously saying he could not see eating lunch out of a brown bag all his life. His colleagues in pharmacology gave him a going-away party at which Comroe gave him a large wooden mallet with a tag saying “If all else fails, try this.” The two men published many further papers together on clinically applied physiology and pharmacology, particularly related to anesthesiology, until Comroe left Philadelphia in 1957, but their joint productivity continued for the rest of their lives in spite of the 3,000 miles separating them.

From 1944 to 1946 Comroe consulted for the Chemical Warfare Service, with a number of other distinguished pharmacologists and physiologists. This work related to the nerve gases, and he wrote a series of papers on the effects of fluorophosphate compounds on the eye (1946,1; 1946,2), for example.

By 1946 he had been a faculty member of the Department of Pharmacology for 10 years and was still an assistant professor in spite of a growing reputation as an investigator, teacher, and writer. When the possibility of becoming professor and chairman of the Department of Physiology and Pharmacology of the Graduate School of Medicine of the University of Pennsylvania appeared, he took it in spite of advice from Richards. The Graduate School of Medicine (GSM) at Penn was an unusual organization that had been founded in 1912 by the university at the urging of Provost Edward Fahs Smith, partly in response to criticism in the Flexner report about graduate medical education and with the hope of obtaining foundation support. Additionally, two non-university-affiliated medical schools in Philadelphia had their buildings condemned for urban reconstruction and were willing to turn their assets over to the University of Pennsylvania with the stated goal of providing organized didactic training for graduate physicians, particularly in basic science. The university took over these assets and ultimately built a new Graduate Hospital as part of the GSM. The school had extensive clinical and basic science faculty with affiliations to other medical schools in Philadelphia and faculty in each of the basic sciences. The physical facilities for these basic science departments, which were in the buildings of the School of Medicine, were meager. Comroe hoped to expand the student body and the facilities. He was aware of the need for physicians returning from World War II for re-education. He also knew of the accumulated research and instrumentation in government laboratories and the potential benefits to medicine this represented, plus the opportunity it offered for his department to apply it clinically.

Comroe started by assembling a detailed manual describing new instrumentation and classical methods of measuring pulmonary function in health and disease written by individuals who had been developing them during the war. He included comments on each short article from other investigators, so that the little volume entitled *Methods in Medical Research* (1950) presented the opinions of some two dozen individuals in the field. This small volume established his department as a leading center of pulmonary physiology and its application in lung disease.

As chairman of the Department of Physiology and Pharmacology of the Graduate School of Medicine, Comroe directed his efforts in two directions. First, he built a strong research faculty. Seymour Kety joined him from the Department of Pharmacology in the School of Medicine and helped him obtain instruments for the rapid and continuous analysis of respiratory gases at the mouth, including a nitrogen meter developed by John Lilly of the Johnson Foundation at Penn; a breath analysis mass spectrometer, the first practical one of its kind (now in the DeWitt Stetten, Jr., Museum of Medical Research of the National Institutes of Health), which could rapidly analyze any respired gas; and an infrared CO analyzer. He then recruited faculty to use these instruments, first Ward S.Fowler, who dissected the distribution of inspired gas in the lungs with the nitrogen meter (1951). Next, he recruited R.E.Forster, who measured pulmonary diffusing capacity with the mass spectrometer and CO meter and later the rates of reaction of CO and O_2 with red blood cells.

Comroe also wanted to apply Boyle's Law to the measurement of lung volumes, air flow rate, and airway resistance. With Stella Botelho and Robert Nims, Comroe used a surplus bomber nose cone as a body plethysmograph. They then went on to have a more sophisticated body pl ethysmograph designed and constructed (now at the Smithsonian Institution) (1959), which A.B.DuBois instrumented and used to measure airway resistance, lung volume, and instantaneous pulmonary blood flow (1956,1,2,3). As the results of these investigations were reported, physicians from all over the world were attracted to Comroe's department. He also organized a number of short courses offering hands-on experience in pulmonary function studies. With the experience gained in teaching these courses, as well as the slides, illustrations, and diagrams used, Comroe and his junior colleagues produced a thin book on pulmonary physiology and pulmonary function testing, *The Lung* (1955). An international success, the book was translated into several languages and eventually went through three editions. For the next 30 years Comroe collaborated on a long series of papers dealing with clinical applications of pulmonary physiology.

The second direction of his efforts was to develop new methods of teaching basic medical science to graduate physicians. With colleagues in the several disciplines (Seymour Kety, David Drabkin, William Ehrich, Oscar Batson, and John Flick), he was the prime mover in developing an organized didactic course in the GSM, which presented up-to-date basic science for graduate physicians, most of whom had just returned from years in military service. This new course was structured around the major organ systems rather than around departmental disciplines, with lectures and discussion proceeding logically through the basic sciences pertinent to each organ system: anatomy, histology, physiology, pharmacology, microbiology, and pathology, with frequent clinical correlations. Hence, it was called the Correlated Basic Sciences Course. The course, and concomitantly the graduate school, were very successful, having a class of 300 students at the school's peak.

Comroe organized and presented this correlated basic sciences course at the first teaching institute of the American Association of Medical Colleges (1954). Western Reserve Medical School in Cleveland took up the new system concept in the reorganization of its curriculum for medical students. In recent years, several other leading medical schools have developed similar courses with a flourish. It must be emphasized, however, that this course was designed for graduate physicians who had already received a solid foundation in basic medical sciences and not for college graduates just entering medical school.

Cuthbert Bazett, chairman of physiology at Penn, died en route to an IUPS Congress in England in 1950, and Comroe was obviously a strong candidate to succeed him, however he was told confidentially that some of the senior faculty were opposed to his selection and that he would not be offered it. He had ambitious plans for the GSM, particularly in terms of interesting clinicians in doing research and training them to do it. He developed a plan to merge the Philadelphia General Hospital next door with the GSM and expand graduate medical training. This ran into intense opposition from the School of Medicine. By 1956–57 it was clear that the university was opposed to any expansion of the GSM and even to its continued existence. The flux of World War II veterans had fallen off to be replaced by graduate physicians from abroad seeking advanced training, a service in which the university was even less interested.

At this point Julius Comroe was seeking new opportunities. He was invited to look at the chair in pharmacology at the Medical School of the University of California in San Francisco. At that time the UCSF was a divided school with the clinical departments in San Francisco and the basic science departments in Berkeley across San Francisco Bay, where they had moved after the 1906 earthquake. The university was building a new basic science campus and teaching hospital in San Francisco, and Comroe was shown the shell of the hospital and the vacant thirteenth floor, which could not be used for patients. He was discouraged by the philosophy of the entrenched pharmacology faculty and decided not to accept the position. On the way back to the airport Dr. Ellen Brown of the Department of Medicine, who had shown him around, asked him for the names of possible candidates for director of a new cardiovascular institute that the University of California planned to establish in the empty thirteenth floor of the new hospital. Comroe said “me.” Comroe was a pulmonary physiologist, not a cardiovascular physiologist, but as he said frequently, blood flows through all the organs.

He was offered the directorship and proceeded to develop a world-class research institute in San Francisco, which had an enormous influence on the flowering of the whole medical school. During the 26 years he was in San Francisco, what had been a minor provincial institution became one of the best in the United States, with a national and international reputation in medical research and teaching. As Comroe himself pointed out (1983), it took many individuals to produce this change, and there were also propitious societal changes at the time, such as the burgeoning NIH support for research. A determining factor, however, was his constant demand for the highest scientific standards in recruitment and promotion, for which he fought on all fronts and for which many of his colleagues give him full credit. At the time he arrived in San Francisco the school had been accustomed to take a long time to make a new appointment and then it was generally internal. Comroe sought to have national searches for active, productive investigators wherever they might be. This meant that he ruffled many feathers, further handicapping his administrative advancement.

A generic problem of research institutes in a medical school is the potential competition it represents to the research programs of individual departments. Comroe was sensitive to this and used the CVRI to help departments build strong research programs, providing space and funds, but always insisting on the highest scientific standards. Not every department thanked him for his efforts.

The snail-paced bureaucracy of the University of California System was legendary in academic circles, and Comroe soon ran into it after his arrival. His response was typical. He collected data from other universities to demonstrate how long it took a research proposal to pass through the different levels of their administrations, compared these figures with the much longer delay at the University of California, and presented the results to President Clark Kerr; that particular problem was soon remedied. Kerr on several other occasions was very supportive of the CVRI.

After he moved to San Francisco and took on increased administrative responsibilities, Comroe did less research with his own hands, and in the late 1960s gave up his own laboratory. He did not abandon research, but held weekly meetings with the research trainees and the faculty to keep each one abreast of what the others were doing. What he lacked in the minute details of methodology he made up for with his broad views of how research is accomplished. However, he collaborated in a number of original articles, particularly in his first area of interest, the control of respiration and the chemoreceptor (1971).

His activism—speaking and writing in support of basic medical research—expanded enormously. He wrote a series of articles entitled "Physiology for Physicians" in the *New England Journal of Medicine* from 1963 to 1969. Comroe became increasingly concerned about the micromanagement of research by government and business, which were direct ing the research toward specific societal needs of the moment to the detriment of future unpredictable discoveries, their model being NASA's successful engineering program to put a man on the Moon. While on the National Heart Council, he realized how important it was to convince Congress and the public that supporting scientific study at the basic level was actually very practical. In 1971 his old friend Robert Dripps spent a sabbatical at the CVRI; he and Julius Comroe, using scientific and scholarly methods, began a monumental effort to investigate how many of the important new contributions of clinical medicine since the 1940s had depended on research that had been stimulated with the aim of contributing to medical care and how many had been serendipitous. The resulting publication appeared in 1976 and included a careful analysis of 529 key articles that provided the supporting knowledge for advances in topics chosen by 40 physicians, reviewed in turn by 140 consultants, all in an effort to remove as much bias as possible. Comroe and Dripps found that for cardiovascular and pulmonary advances 41 percent of the crucial research was done without any goal to improve the practice of medicine. This argument for the support of basic non-clinical research still stands today. Comroe presented some of this material as editorials in a witty, pungent vein as views from his "Retrospectroscope" from 1974 until about 1978 in the *American Review of Respiratory Disease*. A collection of these was eventually published in a little volume titled *Retrospectroscope: Insights into Medical Discovery* (1977).

He himself supplied an example of an unexpected bonus to clinical medicine of ungoaled basic research. In 1958 with Elizabeth Carlsen he reported measuring the rate of uptake of NO by human red cells to determine the effect of cell size on ligand gas uptake. In 1980 Furchgott made the startling discovery of an endothelium-derived factor that dilates vascular smooth muscle, which turned out to be NO and is accepted as a central mechanism in the regulation of local blood flow. An important facet of its physiologic function is that it be removed rapidly by practically irreversible combination with hemoglobin in red cells, localizing its action to the site of its secretion. The data of Carlsen and Comroe prove this.

Comroe continued teaching to fellows in the CVRI and on the national scene, He delighted in cartoon slides to illustrate a point. Possibly the most famous is a drawing of a growling and ferocious visage with the legend “Your suggestions are gratefully received.” This probably represented his impression of medical school administrators. He took efforts to present complicated matters simply; his oft repeated dictum was that it is better to make it clear to students that to make it precisely correct. In Philadelphia, and later in San Francisco, he presented courses for physicians in such practical topics as how to lecture and how to write scientific articles, using tape-recorded and later video-recorded lectures for self and group criticism. He had a bag of histrionic tricks to make a point such as dropping a large pile of advertisements from pharmaceutical companies on the floor at the start of his lecture to emphasize their efforts to influence therapeutic decisions. One time he realized that the participants in a journal club were not reading the assigned material ahead of time. At the next meeting he announced there would be an exam that day. The one question was to write down the color of the book containing the article. Most flunked but none forgot.

Julius Comroe published nearly 200 scientific articles in his lifetime and wrote 4 books. He was asked to give many distinguished named lectures, was elected to the National Academy of Sciences, the American Academy of Arts and Sciences, and as a fellow of the Royal Academy of Physicians.

He was instrumental in forming the Institute of Medicine and served on its first Executive Committee. He received honorary degrees from the Karolinska Institute, the University of Chicago, and the University of Pennsylvania. He was also awarded the distinguished Jesse Stevenson Kovalenko Medal for medical science of the National Academy of Sciences.

In the 1960s Julius Comroe developed severe back pain that would not yield to conservative therapy and he would not consider surgery. By the 1970s this pain had become so severe that he could not carry on as director of the CVRI, and in 1973 he retired. In 1976 a symposium was held in his honor, bringing together his fellows and colleagues from around the world. Shortly thereafter he was found to have cancer of the prostate, it was treated surgically but by 1983 it had spread to his spine and he was confined to bed for the remainder of his life. He continued writing, however, and produced a humorous description of the birth pangs of the CVRI and a modest description of his part in the ascent to excellence of the School of Medicine of the University of California, San Francisco. He died in 1984; although he discouraged friends from trying to establish a chair in his name (saying they should choose a rich man as they could then raise more money), there is now a Comroe chair at the School of Medicine of the University of California in San Francisco and a student scholarship at the School of Medicine of the University of Pennsylvania given by the Class of 1948. At and after the twenty-fifth anniversary of the CVRI, Jeannette Comroe received hundreds of letters from all over the world attesting to the love and warmth that his colleagues and students held for him, a fitting tribute to a life spent in science and teaching.

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SELECTED BIBLIOGRAPHY

1933 With I.Starr. Further studies on the pharmacology of acetyl â-methyl choline and the ethyl ether of â-methyl choline. *J. Pharmacol. Exp. Ther.* 49:283–99.

1937 With W.H.F.Addison. Vascular relations of the carotid body in the dog. *Anat. Rec.* 67:2.

1938 With W.H.F.Addison. Vascular relations of the aortic arch body in the dog. *Anat. Rec.* 70:2.

With C.F.Schmidt. The part played by reflexes from the carotid in the chemical regulation of the respiration in the dog. *Am. J. Physiol.* 121:75–97.

1939 The location and function of the aortic chemoreceptor. *Am. J. Physiol.* 17:176–91.

With C.F.Schmidt and R.D.Dripps. Carotid body reflexes in the dog. *Proc. Soc. Exp. Biol. Med.*

1940 With C.F.Schmidt. The role of the carotid and aortic bodies in the defense of the mammalian organism against oxygen lack. *Science,* pp. 510–11.

1941 With C.F.Schmidt. Respiration. *Ann. Rev. Physiol.* 3:151–84.

1943 The effects of direct chemical and electrical stimulation of the respiratory center in the cat. *Am. J. Physiol.* 92:510–11.

With C.F.Schmidt. Reflexes from the limbs as a factor in the hyperpnea of muscular exercise. *Am. J. Physiol.* 138:536–47.

1944 With R.D.Dripps. The oxygen tension of arterial blood and alveolar air in normal human subjects. *Am. J. Physiol.* 142:700–707.

1946 With I.H.Leopold. Use of diisopropyl fluorophosphate (ADFP) in treatment of glaucoma. *Arch. Opthal.* 36:1–16.

With J.Todd and G.B.Koelle. The pharmacology of diisopropyl fluorophosphate (ADFP@) in man. *J. Pharm. Exp. Ther.* 87:281– 90.

1950 With others. Pulmonary function tests. In *Methods in Medical Research,* vol. II. Chicago: Yearbook Publishers.

1951 With W.S.Fowler. Lung function studies. VI. Detection of uneven alveolar ventilation during a single breath of oxygen. *Am. J. Med.* 10:408–13.

1954 The teaching of physiology, biochemistry and pharmacology. Report of the first teaching institute of Association of American Medical Colleges, Oct. 19–23, 1953. *J. Med. Ed.* 29:1–196.

1955 With R.E.Forster, A.B.DuBois, W.A.Briscoe, and E.Carlsen. *The Lung.* Chicago: Yearbook Publishers.

1956 With A.B.DuBois, S.Y.Botelho, G.N.Bedell, and R.Marshall. A rapid plethysmographic method for measuring thoracic gas volume. A comparison with a nitrogen washout method for measuring functional residual capacity in normal subjects. *J. Clin. Invest.* 35:322–26.

With A.B.DuBois and S.Y.Botelho. A new method for measuring airway resistance in man using a body plethysmograph: Value in normal subjects and in patients with respiratory disease. *J. Clin. Invest.* 35:327–35.

With G.N.Bedell, R.Marshall and A.B.DuBois. Plethysmographic determination of the volume of gas trapped in the lungs. *J. Clin. Invest.* 35:664–70.

1958 With E.Carlsen. The rate of uptake of carbon monoxide and of nitric oxide by normal human erythrocytes and experimentally produced spherocytes. *J. Gen. Physiol.* 42:83–107.

1965 *Physiology of Respiration: An Introductory Text.* Chicago: Yearbook Publishers.

1971 With L.Jacobs and S.Sampson. Carotid sinus versus carotid body origin of nicotine and cyanide bradycardia in the dog. *Am. J. Physiol.* 220:472–76.

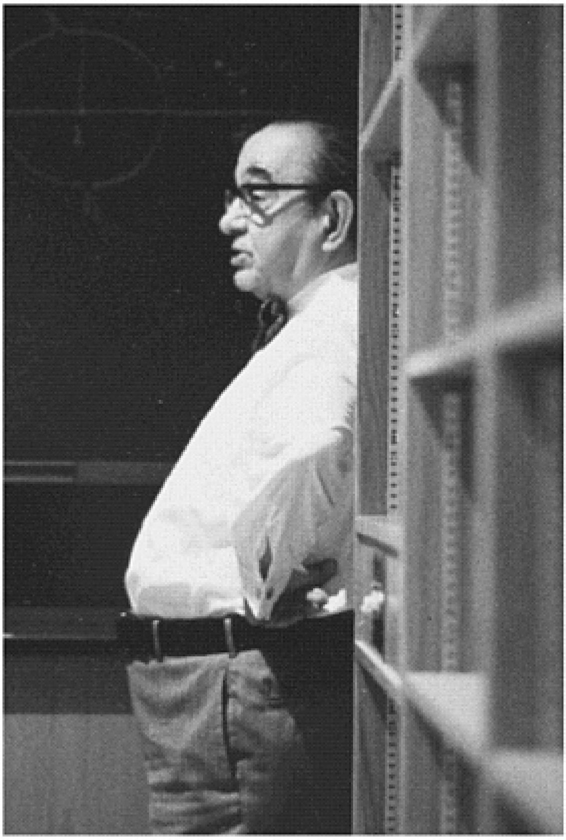
1976 With R.D.Dripps. Scientific basis for the support of biomedical science. *Science* 192:1105–11.

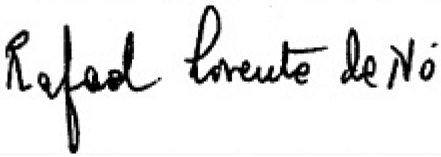
1977 *Retrospectroscope: Insights into Medical Discovery.* Menlo Park, Calif.: Von Gehr Press.

With R.D.Dripps. *The Top Ten Clinical Advances in Cardiovascular-Pulmonary Medicine and Surgery Between 1945 and 1975: How They Came About.* 2 vols. Washington, D.C.: U.S. Government Printing Office.

The First Twenty-Five Years: 1958–1983. San Francisco: University of California.

Exploring the Heart. New York: W.W.Norton.





RAFAEL LORENTE DE NÓ

April 8, 1902-April 2, 1990

BY THOMAS A. WOOLSEY

AT THE BEGINNING OF the twentieth century, studies of the nervous system were still in their infancy. After much difficulty, the principal elements of the nervous system were known to be separate cells—neurons and glia, the components for communication identified as synapses and substrates for simple behaviors understood through electrical stimulation, reflex activity, and careful analysis of brain lesions. The mechanisms by which these elements work were not known. How these elements work together to perform complex behaviors is the question still facing scientists in the new millennium. For most of the twentieth century, Rafael Lorente de Nó was a significant figure in crucial areas of what is now called neuroscience and neurobiology.

When he was elected to the National Academy of Sciences in 1950, Rafael Lorente de Nó was one of the premier neurophysiologists in the United States. While Lorente de Nó pioneered discoveries in many areas, he wished foremost to be remembered for his work in neurophysiology. He contributed to understanding mechanisms of nerve cell communication, potassium channel function, functional organization of the brain stem, neuronal activation through multiple reentrant and parallel pathways, the hippocampus, and modular organization of the cerebral cortex. The breadth of Lorente de Nó's contributions is extraordinary. Today their importance is testified to everywhere; his discoveries are standard textbook information, taken for granted without attribution.

PERSONAL HISTORY

Rafael Lorente de Nó (called Lorente, Dr. Lorente, or Don Rafael by his colleagues, students, and friends, respectively) was born into the well-to-do country family of Francisco Lorente and Maria de Nó (de Lorente) on April 8, 1902, in Zaragoza, Spain. He matriculated in the medical school in Zaragoza at the age of 15. At 18 he transferred to the University of Madrid, where he completed his medical studies in 1923. He was an assistant in the Cajal Institute from 1921 to 1929. Lorente took postdoctoral training in Uppsala from 1924 to 1927 with several months in Berlin in 1925. Beginning in 1927 he trained in otolaryngology in Madrid and several centers in Germany prior to practicing otolaryngology in Santander from 1929 to 1931. In 1931 he returned briefly to Madrid, where he married the vivacious Hede Birfeld, daughter of the professor of German at the University of Madrid.

Shortly thereafter, Lorente and Hede sailed to the United States, where he became the head of the Neuro-Anatomical Laboratory at the Central Institute for the Deaf (CID) in St. Louis. He was appointed lecturer in the Washington University School of Medicine in 1935. Lorente moved to the Rockefeller Institute in 1936 and became a member in 1941. He was naturalized in 1944. When the Rockefeller was re-organized as a university in 1953 Lorente's title was changed to professor. Lorente de Nó retired in 1970, and in 1972 was appointed professor emeritus in the departments of surgery and anatomy and in the Brain Research Institute at the University of California, Los Angeles, where he remained active into the 1980s. Progression of his emphysema and other ailments necessitated a move to Tucson, where his devoted daughter, Edith, as she had in New York and in Los Angeles, supported him until he died from cancer on April 2, 1990.

Lorente de Nó was long an active member of the American Physiological Society and the American Association of Anatomists. In addition to the National Academy of Sciences, he was elected to the American Academy of Arts and Sciences and was awarded honorary degrees by the University of Uppsala, Clark University, and Rockefeller University. Lorente won the Karl Spencer Lushly Award from the American Philosophical Society in 1959. He received the Award of Merit in 1986.

PROFESSIONAL HISTORY

Chronology. Lorente's first paper, a mathematical treatment of thermodynamics, was published when he was 15 (1917). He began his lifelong investigations of the nervous system in Zaragoza, where he undertook independent studies of spinal cord responses to injury with a compression model in tadpoles (1921) under the guidance of Pedro Ramón, professor of obstetrics and gynecology. Ramón had studied the nervous system under the guidance of his illustrious older brother, Santiago Ramón y Cajal. Lorente was a voracious reader and an exceptionally energetic student who was invited to transfer to the University of Madrid to work with Cajal. In 1920 Rafael first met the great Cajal, who was then 68 and far and away the most important and adulated scientist in Spain, having received the Nobel Prize in 1906 (with C.Golgi "in recognition for their work on the structure of the nervous system"). While Cajal continued to work vigorously until his death in 1934, Lorente was his last and arguably most distinguished student. In Madrid, Lorente used silver staining and impregnation methods first to study the cerebral cortex and then the brain stem.

In 1923, his last year of medical school, Lorente returned to Zaragoza expressly to hear Professor Robert Bárány of the University of Uppsala, who served as a visiting professor for several weeks at the medical school. (Bárány won the 1914 Nobel Prize "for his work on the physiology and pathology of the vestibular apparatus.") According to Lorente, Bárány was astounded to find such a knowledgeable young man in Spain. In 1924 Lorente by invitation joined Bárány in Uppsala. In 1925 Lorente briefly interrupted his work in Sweden on the physiology and behavior of the vestibuloocular reflexes to study the architecture of the human cerebral cortex with Oskar and Cécile Vogt at the Berlin Brain Research Institute.

Back in Madrid in 1927, lack of funding forced Lorente to seek clinical training. Based on his research experience, otolaryngology was the natural clinical field for Lorente. He trained first with Professor García Tapia in Madrid and then with leaders at centers in Köningsberg, Frankfurt am Main, and Berlin. When he became chief of otolaryngology in the new Valdecilla Hospital in Santander in 1929, the stage was set for him to become Spain's leader in otolaryngology. He shouldered an enormous clinical load, yet somehow continued his research activities. He was paid by impoverished patients with kittens, which provided the material for studies of the structure of the vestibular and auditory brain stem. A large practice and an insufficient staff lead him to seek opportunities to return to pure research. Lorente had been highly recommended by Bárány and the Vogts to Alan Gregg of the Rockefeller Foundation, who contacted Max Goldstein. Goldstein, founder of the CID in St. Louis, offered Lorente a position as director of the Neuro

Anatomical Research Laboratory. Lorente arrived with his new bride (who was not expected by the CID) in St. Louis in the fall of 1931.[1]

St. Louis in the early 1930s was an exciting place for studies of the nervous system. Pioneering work on the auditory system put the CID in the forefront of hearing research.[1] At the CID Lorente published studies on the structure of the cerebral cortex that he had begun in Berlin. He also fully analyzed materials collected while in Santander. Major works on the VIIIth nerve and the vestibular nuclei were published. A large paper describing the acoustic nuclei of the cat brain stem was accepted by the *Journal of Comparative Neurology,* but it was not published because of the costs of the numerous illustrations. In St. Louis, he instructed James Lee O'Leary in the Golgi methods, which O'Leary used in important studies of the cat visual system.[2,3] Lorente's anatomical papers from the CID are classical (see below), but what really captivated him was the emerging electrophysiology. Discoveries using the cathode ray oscilloscope (termed the "inertia-less smoke drum" by William Landau) in the late 1920s by Joseph Erlanger, Herbert Gasser, and George Bishop, later joined by Peter Heinbecker, O'Leary, and Helen Treadway Graham, were exploding at the Washington University School of Medicine.[1,4]

Funding for science during the Great Depression was especially tight, and Lorente considered the possibility of returning to Spain. Herbert Gasser (1944 Nobel laureate with Erlanger "for their discoveries regarding the highly differentiated function of single nerve fibers") had been appointed chair of physiology at Cornell Medical College in 1931, moving to become the head of the Rockefeller Institute in 1935. Fortunately, just as Lorente's Rockefeller Foundation support at the CID ended, Gasser invited Lorente to join him in New York. Their daily luncheon conversa tions about science, which often crescendoed into vociferous debates, were a prominent feature of the Rockefeller experience for trainees and colleagues for many decades.

As a scientific loner, Lorente never built a large laboratory and was the sole author of most of the work he published. Nevertheless, he was sought after to mentor training in neurophysiology. At the Rockefeller he collaborated with T.P. Feng on the action of barium in rhythmic activity of nerves, A.Gallego on monovalent ions in nerve conduction, Yves Laporte on synaptic function in sympathetic ganglia, and G.A.Condouris on decremental conduction in peripheral nerves. He published a long series of papers with V.Honrubia on experimental observations and theoretical aspects of transmission in nerves. He supervised K.E.Åstrom's anatomical studies on the cranial nerve nuclei in the mouse brain stem.

Neuronal Integration, Synaptic Transmission, and Axonal Conduction. Until 1972, first in St. Louis and then with new oscilloscopes and better amplifiers in New York, Lorente de Nó studied neuronal activation, nerve conduction, and synaptic transmission. Lorente de Nó's conversion to electrophysiology is evident in his April 10, 1934, letter to Cajal. He justified this to Cajal: "…estoy dedicando la mitad de mi tiempo a experimentos fisiologicos" ("just now I dedicate half of my time to physiological experiments"). Further on, he argued for this change in emphasis saying that structure is illuminated by function. Lorente predicted that a mutual colleague would have the same headache in interpreting his experiments "que yo tuve hasta que conseguí montar mi oscilógrafo de rayos catódicos" ("that I had until I made my cathode ray oscilloscope").

Approximately 15 years of work culminated in the publication of the two volume *A Study of Nerve Physiology* (1947). This monograph included detailed mathematical models initiated during a visit in 1940 with Leverett Davis, Jr., at the California Institute of Technology. In the end, Lorente concluded incorrectly that electrical conduction did not depend on the cations sodium and potassium, but he correctly surmised that this process ultimately depended on oxidative metabolism. These two volumes were known to physiology students of the time as the "telephone books," which they resembled in size, color, and readability.[5]

At the CID and the Rockefeller, his early microelectrode studies of the central vestibulo-ocular system extended Sherringtonian principles of synaptic activation to new levels of precision. Lorente developed a profound understanding of the features of spatial and temporal summation and synaptic delay, perhaps because he had an accurate picture of the complexities of the underlying structures. He participated in the debates concerning the nature of synaptic transmission (1940). A number of papers evaluated acetylcholine and other putative neurotransmitters for which he could not establish a specific role. He also could not rule out direct electrical activation of post-synaptic cells. He favored, as did Eccles at the same time, the hypothesis that synaptic transmission was electrical rather than chemical (1953).

Lorente studied impulse conduction in vertebrate peripheral nerves for three decades. As part of this effort, Lorente de Nó first synthesized a series of quaternary ammonium compounds, including tetramethylammonium (TEA), which he substituted for monovalent cations (especially sodium) in his studies of the ionic basis of the nerve impulse (1949). Although not appreciated at the time, TEA is now a crucial standard tool in modern neurobiology as it selectively blocks K^+ channels.[6] Synthesis and application to excitable tissues of this compound were Lorente's great practical contributions to modern neuroscience.

Lorente's attempts to understand the excitability of axons in vertebrate nerves, principally from frogs with and with out coverings ("sheathed" and "desheathed") ultimately lead him into direct contradiction with Alan Hodgkin and Andrew Huxley (who shared the 1963 Nobel Prize with Eccles "for their discoveries concerning the ionic mechanisms involved in the excitation and inhibition in the peripheral and central portions of the nerve cell membrane").[5,7] Their elegant experiments on the squid giant axon and the clean model of how this works are the basis for today's textbook descriptions of axonal conduction. Lorente's quixotic battle against this formulation (which he derisively referred to as "the so-called sodium hypothesis") consumed enormous energy for at least 30 years of his life (1963).[8] These views did not help to keep his earlier significant contributions to neurophysiology in perspective; one imagines, however, that Lorente might have been pleased that, using TEA, K^+ channels in squid and frog axons were shown to differ.[9]

Vestibular Reflexes, VIII^th^ Nerve, and the Vestibular and Auditory Brain Stem. As a medical student in Madrid, Lorente began experiments on the vestibulo-ocular pathways in rabbits (1925). In 1924, when he went to the laboratory of Robert Bárány (perhaps best known for developing the caloric test of vestibular function) and subsequent to his return to Madrid in 1927, he combined functional (reflex), anatomical, and selective lesion studies to understand the vestibulo-ocular reflex arc. Rafael published a number of studies in German (1927), French (1930), and Russian on the VIIth nerve and the vestibular nuclei. After coming to the United States, he published a 56-page paper synthesizing the findings in English (1933). The paper illustrates progress in his thinking on complex circuits in the brain stem. (This work stood for nearly two decades as the authoritative source about the organization and function of brain stem vestibular nuclei.) He observed persistence of vestibular activation of eye movements after midline section of the brain stem to cut inputs from the opposite side. He correctly inferred that there were multiple pathways mediating this response. He also published two long papers on the origins and targets of the VIIIth (vestibulocochlear) nerve suggesting that there was preservation of topography and function from the end organs in the target nuclei (1933).[10] The importance of Lorente's understanding of the role of the brain stem reticular formation was emphasized by Ann Graybiel at a 1978 tribute held at the Rockefeller (see Goodhill's foreword to *The Primary Acoustic Nuclei* [1981]).

With Helen Treadway Graham, he developed electrophysiological skills in studies of cranial motor neurons in the oculomotor, trochlear, and abducent nuclei, which lie just below the floor of the IVth ventricle. The results clearly demonstrated convergent synaptic activity and supported his hypotheses about integration by single neurons. Confirming studies in other neurons were not published by others until nearly 20 years later.

Lorente published a monograph *The Primary Acoustic Nuclei* (1981) with strong support from Victor Goodhill, head of the Department of Otolaryngology at UCLA. This work was originally completed over 50 years earlier and was accepted for publication, but it went unpublished for want of funds during the Great Depression. (Lorente nearly threw the manuscript and exquisite drawings away when he moved from St. Louis to New York in 1936.) This work demonstrates many of Lorente de Nó's best scientific characteristics: a focused approach to an important problem; a clear appreciation of the function and anatomy of his subject; concise, accurate drawings of the material; and a thorough summary of the pertinent literature.

Cerebral Cortex. In 1920 Santiago Ramón y Cajal was approaching the end of his exceptional career. He was the pre-eminent scientist of the Spanish-speaking world. (As a medical student in Zaragoza, Lorente de Nó had read the two-volume *Histologie du Systèm Nerveux de l'Homme et des Vertébrés (Histology of the Nervous System of Man and Animals)* or more likely Cajal's earlier three-tome Spanish original *Textura del Sistema Nervoso del Hombre y de los Vertebrados (Texture of the Nervous System of Man and the Vertebrates)* and the *Recuerdos de Mi Vida (Recollections of My Life)*. Cajal had considered from time to time morphological correlates relevant to the human intellect and advanced the idea, from his comparative work, that these could lie in the greater complexity of cell types in the human cortex. The young Rafael did not accept this proposal and challenged Cajal directly with a vigor that typified his career. To make his point, he chose to investigate the brain of the mouse. In this little animal, the lowliest available creature with a neocortex, Lorente found and described neuronal cell types in the mouse cortex with Golgi's method that were at least as rich as described in Cajal's earlier account of the human cortex. Cajal took Lorente's work for publication in his journal without making any changes. In style and in substance, this paper set a tone for Lorente's subsequent prodigious output. The premise (now termed hypothesis) was clearly stated, the results copiously illustrated and their meaning considered in light of the appropriate literature. The work on the mouse cortex described in "La corteza cerebral del ratón," which appeared in the *Trabajos del Laboratorio de Investigaciones Biológicas de la Universidad de Madrid* (1922), is a classic.[11] Published when Lorente was only 20, it included the first Golgi description of the distinctive region of the somatosensory cortex now known as the "barrel" field.[12]

The great Cajal and the combative young rascal (as Rafael described himself) maintained a cordial yet somewhat argumentative relationship that is rare in the hierarchical struc ture of science, even today. (However, in later life, Rafael Lorente de Nó chose not to accept many offers to reminisce about Cajal.)

During his stay in Berlin in 1925, work with the Vogts acquainted Lorente with the issues surrounding the identification of different architectural (functional) regions of the human brain including its blood vessels (1927). After he got to St. Louis, Lorente de Nó published the cellular architecture and Golgi stained cells of the entorhinal cortex (1933) and the hippocampal formation (1934). From the dates on the drawings, the work was obviously begun just after Lorente's sojourn to Berlin. He applied his good eye and brain to the analyses of cell bodies (cytorarchitecture) and cells as seen with the Golgi stains in several animals from mouse to man. Evidently Cajal kept up with Lorente's work and queried him on specifics. The first line of Lorente's April 10, 1934, letter to Cajal obviously answers a question: "Las figuras a que V. [Cajal] se refiere en su carta (figuras 19, 20 y 21 de mi trabajo sobre el area entorrinal) son esquemáticas…." ("The figures that you refer to in your letter (figures 19, 20 and 21 of my paper on the entorhinal area) are schematics….")

Lorente subdivided the hippocampus proper into regions, which he abbreviated CA1, CA2, etc., (CA=cornu ammonis =Ammon's horn), based on an appreciation of the correlation of different connections with architecture. These designations are now in wide use.[13] It is likely that Lorente's thinking was guided by his work on the brain stem.[14] He ended his second paper (1934) with a model that he described as follows:

> The only possibility for…[a neuron]…using all the impulses seems to be, first, that each synapse sets only a subliminal (chemical or other) change able of summation and, second, that the conduction through the synapses is not followed by a refractory period. The subliminal changes are sum

> mated first in the dendrites then the surrounding of the axon. When the change reaches threshold value, an explosive discharge through the axon takes place. The axon…enters in a refractory state, but the cell body and dendrites do not do so, they continue receiving and adding subliminal changes until the threshold value is reached again and the axon has recovered….
>
> If this conception of the neurone is right, then it becomes easy to understand that impulses arrived at different dendrites or at two points of a dendrite can be summated. As far as I can see this the greatest problem of the physiology of the nerve cell.

His studies of the simpler entorhinal and hippocampal cortices gave him insights about the patterns of neuronal articulation in the cortex. These papers became widely known when his chapter in the cerebral cortex first appeared in Fulton's *Physiology of the Nervous System* (1938). This masterly review of his own and others' works is a remarkable synthesis of information: accurate, broad, insightful, crisply written, and clearly illustrated. It is significant that he actually looked at all of the material again as indicated in Fulton's footnote

> The first three sections (pp. 291–325) of this chapter have been written by Rafael Lorente de Nó. The extent of my debt to him will be obvious to those who peruse it. Dr. Lorente de Nó states in a letter: "One of the reasons why writing it has been so laborious is that I have verified in my collection of brain sections the truthfulness of every statement in the text and of every line in the drawings."[15]

Lorente used his experience with the vestibulo-ocular system to put functional meaning to the cortical neurons he saw. Perhaps the key that he had, and his mentor Cajal lacked, was direct experience with the physiology of the brain. He clearly articulated the idea that the cells of the cerebral cortex are arranged in vertical modules that include interneurons and parallel and reentrant pathways. The organi zation of cortex into functional columns that Mountcastle demonstrated in 1957 has been extended widely and is one of the central tenets of neurobiology. The importance of Lorente's synthesis was summarized by Mountcastle in the last paragraph of his landmark paper

> The hypothesis that such a vertically linked group of cells is the elementary unit for cortical function is not new. Such a conclusion was reached by Lorente de Nó from his extensive studies on synaptic linkages of cortical neurons.[16]

Raphael Lorente de Nó: The Person. Lorente de Nó's scientific career spanned seven decades. His contributions were profound and diverse. With the passage of time it is easier to step back and view his whole corpus of work, to sort through it and glean the significant essentials free from the heat of argument. Lorente de Nó was independent and energetic. His early successes surely made him confident. A quick mind and voracious, intelligent reading pointed him in new and tractable directions. His energy drove him through an enormously productive professional life. He trained and collaborated with the best scientists of his time: three Nobel laureates, in three distinctively different areas of "neuroscience," in three different lands. His impressions on them and his capacity for hard work opened doors with each of them and they in turn opened doors for Don Rafael. He was a neurobiologist long before the word was coined.

I first came across Lorente's work in the summer of 1966 as I was reading the literature on the architectonics of the mouse brain.[17] Lorente's paper figured prominently in the discussion of M.Rose's study of the cytoarchitecture of the mouse cortex,[18] a copy of which I had at the University of Wisconsin. The library in Madison did not have the *Trabajos,* so in innocent desperation I wrote Lorente at the Rockefeller to request a reprint of the 1922 article. I promptly got back a note, in a hand I would later recognize well, thanking me for the request but politely indicating that the reprint supply had been exhausted many years before. One month later, back at Johns Hopkins, I read the elegant paper in the library of the Phipps Clinic. What wonderful illustrations!

It is thanks to Lawrence Kruger at UCLA that I actually got to meet Lorente in Los Angeles nearly nine years later. Short in stature, Lorente was an urbane, charming, and inquisitive man excited about science and life. His faculty for language was obvious; his English was perfect. It was difficult to reconcile the man with the reputation for pugnacious polemics that consumed so much of his later career. At this and subsequent meetings he shared what questions drove his choices for investigation and the conditions that surrounded the answering of those questions. This was fascinating stuff.

Lorente traveled to New York in May 1978 for Rockefeller University's celebration of Lorente and David P.C.Lloyd's contributions and the conferring of honorary degrees. I invited him to stop in St. Louis on his way to present the work on the acoustic nuclei that I knew he was preparing for publication. He would be pleased to come and discuss that subject, he said, but only if he could give three lectures concerning the neural sheath and the sodium hypothesis first. We made the deal and he came. The lectures on the sheath and sodium were fascinating on several levels, but cellular physiologists in the audience reacted strongly with their feet to the speaker's data and his interpretations of them. The last lecture, given in the traditional Saturday neuroscience series, concerned the acoustic system. A large, rapt audience was convinced by the speaker's data and his interpretations of them. Throughout his visit Lorente listened to and engaged many different colleagues at Washington

University whose work in some way or another related to areas he had touched.

There was another and possibly more astounding aspect to this visit. In our earlier discussions I had learned from Lorente that, when he was at the CID, he had introduced Nancy Blair to his colleague and pupil O'Leary, and they were subsequently married. The O'Learys were mentors and friends to my wife and me. Although O'Leary died in 1975, it occurred to us that there might be others in St. Louis who were Lorente's friends from the 1930s. As I drove him in from the airport he responded to my question about them saying that he doubted very much whether his friends were still living. I pressed him, and he finally recalled, "…the most intelligent and interesting woman I ever met." On further interrogation it was clear that he was speaking of our neighbor Natalie Grant (Mrs. Samuel B.) across the street.[19] In short order Lorente was reminiscing with her and Dr. Grant. My wife, Cindy, as she elegantly and so often does, quickly expanded the planned dinner party to include acquaintances from Lorente's St. Louis days and other colleagues of long standing then living in St. Louis. Other than C.C.Hunt, his wife, Marion, and ourselves, all were septuagenarians at the very least. The evening was fascinating, as Lorente was obviously stimulated by and stimulating to all with whom he reminisced in our living room almost to dawn. It was obvious that he and his wife, Hede, had formed an integral part of an exceptional, lively, and ultimately very distinguished "crowd" whose interests ranged widely to most areas of human endeavor.

In summary, Lorente was the last and most acclaimed student of Ramón y Cajal. Lorente de Nó was the first Spaniard to become a neurophysiologist. His lasting contributions were (1) defining the organization of brain stem vestibular and auditory systems; (2) synthesis of TEA, a com pound that is now a standard tool for analysis of potassium channel function; (3) distinction between non-refractory spatio/temporal summation in neuronal dendrites and somata and refractory all-or-none action potential in the axon; (4) provocative involvement in the quest to understand the basis of axonal conduction and synaptic transmission; (5) recognition of and naming the principal divisions of the hippocampal formation; and (6) formulation of the basic idea of the anatomical (and functional) columnar organization of the cerebral cortex.

The list is indeed diverse and impressive. Perhaps it is for this reason that it is so difficult to fully comprehend Rafael Lorente de Nó's extraordinary impact on science.

I THANK Javier de Filipe of the Instituto Cajal in Madrid for a copy of Lorente's letter dated April 10, 1934, to Cajal in response to Cajal's letter of March 26, 1934, to him (items 1135–1139 in the Museo Cajal Madrid). Renee D.Mastrocco kindly provided information from the archives at Rockefeller University and Jenny S.Mun furnished information from the National Academy of Sciences. Much of the information was gathered for a previous article on Lorente de Nó by Lawrence Kruger and me. I thank Larry W.Swanson for his photograph of Lorente during his first lecture on April 26, 1978, during a visit to St. Louis, which is reproduced here with his permission.

NOTES

1. H.S.Lane. *The History of the Central Institute for the Deaf,* pp. 230–31. St. Louis: The Central Institute for the Deaf, 1981.

2. J.L.O'Leary. A structural analysis of the lateral geniculate nucleus of the cat. *J. Comp. Neurol* 73 (1940):405–30.

3. J.L.O'Leary. Structure of the area striata of the cat. *J. Comp. Neurol.* 75(1941):131–64.

4. L.H.Marshall. The fecundity of aggregates: The axonologists of Washington University, 1922–1942. *Perspect. Biol. Med.* 26(1983):613–36.

5. L.Kruger. Lorente de Nó: The electrophysiological experi

ments of the later years. In *The Mammalian Choclear Nuclei: Organization and Function,* eds. M.A.Merchán, J.M.Juiz, D.A.Godfrey, and E.Mugnaini, pp. 503–11. New York: Plenum, 1993.

6. M.J.Zigmond, F.E, Bloom, S.C.Landis, J.L.Roberts, and L. R.Squire. *Fundamental Neuroscience,* p. 136. San Diego: Academic Press, 1999.

7. A.Gallego. Lorente de Nó's scientific life. In *The Mammalian Choclear Nuclei: Organization and Function,* eds. M.A.Merchán, J.M. Juiz, D.A.Godfrey, and E.Mugnaini, pp. 431–35. New York: Plenum, 1993.

8. L.Kruger and T.A.Woolsey. Rafael Lorente de Nó: 1902– 1990. *J. Comp. Neurol.* 300(1990):1–4.

9. C.M.Armstrong and B.Hille. The inner quaternary ammonium ion receptor in potassium channels of the node of Ranvier. *J. Gen. Physiol.* 59(1972):388–400.

10. V.Honrubia, L.F.Hoffman, A.Newman, E.Naito, Y.Naito, and K.Beykrich. Sensoritopic and topologic organization of the vestibular nerve. In *The Mammalian Choclear Nuclei: Organization and Function,* eds. M.A.Merchán, J.M.Juiz, D.A.Godfrey, and E. Mugnaini, pp. 437–49. New York: Plenum, 1993.

11. R.Lorente de Nó. The cerebral cortex of the mouse (A first contribution—the "acoustic" cortex). (Trans. A.Fairén, J.Regidor, L.Kruger) *Somat. Mot. Res.* 9(1992):3–36.

12. T.A.Woolsey and H.Van der Loos. The structural organization of layer IV in the somatosensory region (SI) of mouse cerebral cortex: the description of a cortical field composed of discrete cytoarchitectonic units. *Brain Res.* 17(1970):205–42.

13. M.J.Zigmond, F.E, Bloom, S.C.Landis, J.L.Roberts, and L. R.Squire. *Fundamental Neuroscience,* p. 1426. San Diego: Academic Press, 1999.

14. L.W.Swanson. Lorente de Nó and the hippocampus: Neural modeling in the 1930s. In *The Mammalian Choclear Nuclei: Organization and Function,* eds. M.A.Merchán, J.M.Juiz, D.A.Godfrey, and E.Mugnaini, pp. 451–56. New York: Plenum, 1993.

15. J.F.Fulton. The cerebral cortex: Architecture, intracortical connections and motor projections. In *Physiology of the Nervous System,* ed. J.F.Fulton, p. 291. London: Oxford University Press, 1938.

16. V.B.Mountcastle. Modality and topographic projection of single neurons of cat's sensory cortex. *J. Neurophysiol.* 20(1957):408–34.

17. T.A.Woolsey. Somatosensory, auditory and visual cortical areas in the mouse. *Johns Hopkins Med. J.* 121(1967):91–112.

18. M.Rose. Cytoarchitektonischer Atlas der Grosshirnrinde der Maus. *J. Psychol. Neurol.* 40(1929) 1–51.

19. T.A.Woolsey. Glomérluos, columns and maps in cortex: An homage to Lorente de Nó. In *The Mammalian Choclear Nuclei: Organization and Function,* eds. M.A.Merchán, J.M.Juiz, D.A.Godfrey, and E.Mugnaini, pp. 479–501. New York: Plenum, 1993.

SELECTED BIBLIOGRAPHY

1917 Temperatura. *Revista del Ateneo Científico Escolar* 2 (10):1–14.

1921 La regeneración de la medula espinal en las larvas de batracio. *Trabajos del Laboratorio de Investigaciones Biológicas de la Universidad de Madrid* 19:147–83.

1922 La corteza cerebral del ratón. (Primera contribución. La corteza acústica.) *Trabajos del Laboratorio de Investigaciones Biológicas de la Universidad de Madrid* 20:41–78.

Contribución al conocimiento del nervio trigémino. *Vol. II. Libro en Honor de D. Santiago Ramón y Cajal,* pp. 13–30. Madrid: Jimenez y Molina.

1925 Etudes sur l'anatomie et la physiologie du labyrinthe de l'oreille et du VIII^{e} nerf. Première partie. Les réflexes toniques de l'oeil: Quelques donnés sur le mécanisme des mouvements oculares. *Travaux du Laboratoire de Recherches Biologiques de l'Université de Madrid* 23:259–392.

1926 On the tonic labyrinth reflexes of the eyes. *Acta Otolaryngologica* 9:163–78.

1927 Untersuchungen über die Anatomic und dir Physiologie des Ohrlabyrinthes und des Nervus octavus. *Monatsschrift für Ohrenheilkunde und Laryngo-Rhinologie* 61:857–96, 1066–1130, 1152–90, 1300–57.

Ein Beitrag zur Kenntnis der Gefässverteilung in der Hirnrinde. *Journal für Psychologie und Neurologie* 35:19–27.

1930 Physiologie du labyrinthe. *L'Oto-Rhino-Laryngologie Internationale* 18:317–30.

1933 Anatomy of the eighth nerve. I. and II. The central projection of the nerve endings of the internal ear. *Laryngoscope* 43:1–38.

Anatomy of the eighth nerve. III. General plan of structure of the primary cochlear nuclei. *Laryngoscope* 43:327–50.

Studies on the structure of the cerebral cortex. I. The area entorhinalis. *Journal für Psychologie und Neurologie* 45:381–438.

Vestibulo-ocular reflex arc. *Archives of Neurology and Psychiatry* 30:245– 91.

1934 Studies on the structure of the cerebral cortex. II. Continuation of the study of ammonic system. *Journal für Psychologie und Neurologie* 46:113–77.

1935 The summation of impulses transmitted to the motoneurones through different synapses. *American Journal of Physiology* 113:524–28.

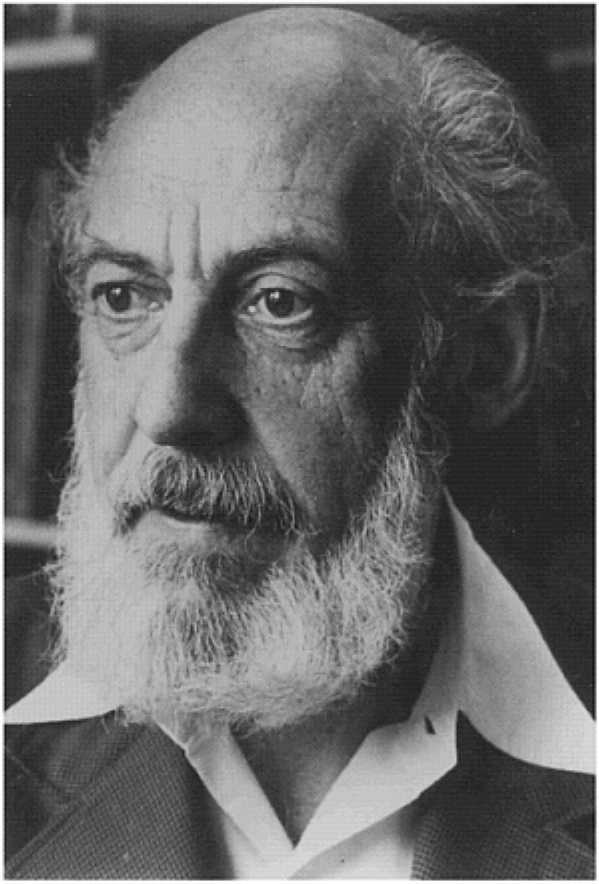
1938 Analysis of the activity of the chains of internuncial neurons. *Journal of Neurophysiology* 1:207–44.

The cerebral cortex: Architecture, intracortical connections and motorprojections. In *Physiology of the Nervous System,* ed. J.F.Fulton, p.291–339. London: Oxford University Press.

1939 Transmission of impulses through cranial motor nuclei. *Journal of Neurophysiology* 2:402–64.

1940 Release of acetylcholine by sympathetic ganglia and synaptic transmission. *Science* 91:501–503.

1946 Correlation of nerve activity with polarization phenomena. *Harvey Lectures* 42:43–105.
1947 A study of nerve physiology. *Studies from the Rockefeller Institute for Medical Research.* Part I, 131:1–496; Part II, 132:1–548.
1949 On the effect of certain quaternary ammonium ions upon frog nerve. *Journal of Cellular and Comparative Physiology* 33(Suppl. 1):3–231.
1953 Conduction of impulses in the neurons of the oculomotor nucleus. In *Ciba Foundation, The Spinal Cord,* ed. J.L.Malcohmer, J.A.B.Gray, G.E.W.Wolstenholme, and J.S.Freeman, pp. 132– 79. Boston: Little, Brown.
1959 With G.A Condouris. Decremental conduction in peripheral nerve. Integration of stimuli in the neuron. *Proceedings of the National Academy of Sciences U. S. A.* 45:592–617.
1963 With V.Honrubia. On the effect of sodium-free solutions upon isolated single frog nerve fibers. *Proceedings of the National Academy of Sciences U. S. A.* 49:40–45.
1981 *The Primary Acoustic Nuclei.* New York: Raven Press.



Courtesy of Columbia University

SAMUEL EILENBERG

September 30, 1913–January 30, 1998

BY HYMAN BASS, HENRI CARTAN, PETER FREYD, ALEX HELLER, AND SAUNDERS MAC LANE

SAMUEL EILENBERG DIED IN New York, January 30, 1998, after a two-year illness brought on by a stroke. He left no surviving family, except for his wide family of friends, students, and colleagues, and the rich legacy of his life's work, in both mathematics and as an art collector.

"Sammy", as he has long been called by all who had the good fortune to know him, was one of the great architects of twentieth-century mathematics and definitively reshaped the ways we think about topology. The ideas that accomplished this were so fundamental and supple that they took on a life of their own, giving birth first to homological algebra and in turn to category theory, structures that now permeate much of contemporary mathematics.

Born in Warsaw, Poland, Sammy studied in the Polish school of topology. At his father's urging, he fled Europe in 1939. On his arrival in Princeton, Oswald Veblen and Solomon Lefschetz helped him (as they had helped other refugees) find a position at the University of Michigan, where Ray Wilder was building up a group in topology. Wilder made Michigan a center of topology, bringing in such figures as

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Norman Steenrod, Raoul Bott, Hans Samelson, and others. Saunders Mac Lane's invited lecture there on group extensions precipitated the long and fruitful Eilenberg-Mac Lane collaboration.

In 1947 Sammy came to the Columbia University mathematics department, which he twice chaired and where he remained till his retirement. In 1982 he was named a University professor, the highest faculty distinction that the university confers.

Sammy traveled and collaborated widely. For fifteen years he was a member of Bourbaki. His collaboration with Steenrod produced the book *Foundations of Algebraic Topology,* that with Henri Cartan the book *Homological Algebra,* both of them epoch-making works. The Eilenberg-Mac Lane collaboration gave birth to category theory, a field that both men nurtured and followed throughout their ensuing careers. Sammy later brought these ideas to bear in a multivolume work on automata theory. A joint work on topology with Eldon Dyer may see posthumous publication soon.

Among his many honors Sammy won the Wolf Prize (shared in 1986 with Atle Selberg), was awarded several honorary degrees (including one from the University of Pennsylvania), and was elected to membership in the National Academy of Sciences of the USA. On the occasion of the honorary degree at the University of Pennsylvania in 1985, he was cited as "our greatest mathematical stylist".

The aesthetic principles that guided Sammy's mathematical work also found expression in his passion for art collecting. Over the years Sammy gathered one of the world's most important collections of Southeast Asian art. His fame among certain art collectors overshadows his mathematical reputation. In a gesture characteristically marked by its generosity and elegance, Sammy in 1987 donated much of his collection to the Metropolitan Museum of Art in New York, which in turn was thus motivated to contribute substantially to the endowment of the Eilenberg Visiting Professorship in Mathematics at Columbia University.

—Hyman Bass

HENRI CARTAN

Samuel Eilenberg died in New York on January 30, 1998, after spending two years in a state of precarious health. I would like to write here of the mathematician and especially of the friend that I gradually discovered in the course of a close collaboration that lasted at least five years and that taught me many things.

I met Sammy for the first time at the end of December 1947: he had come to greet me at LaGuardia Airport in New York, a city buried under snow, where airplanes had been unable either to take off or to land for two days. This was my first visit to the United States; it was to last five months. Of course, Eilenberg was not unknown to me, because since the end of the war I had begun to be interested in algebraic topology. Notably I had studied the article in the 1944 *Annals of Mathematics* in which Eilenberg set forth his theory of *singular homology* (one of those theories which immediately takes on a definitive shape). I had, for my part, reflected on the "Künneth formula", which gives the Betti numbers and the torsion coefficients of the product of two simplicial complexes. In fact, that formula amounts to a calculation of the homology groups of the tensor product of two graded differential groups as a function of the homology groups of each of them. The solution involves

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not only the tensor product of the homology groups of the factors but also a new functor of these groups, the functor Tor. At the time of my first meeting with Sammy, I was quite happy with telling that to him.

This was the point of departure for our collaboration, by means of postal mail at first. Then Sammy came to spend the year 1950–51 in Paris. He took part in my seminar at the École Normale, devoted that year to cohomology of groups, spectral sequences, and sheaf theory. Sammy gave two lectures on spectral sequences. Armand Borel and Jean-Pierre Serre took an active part in this seminar also.

Independently of the seminar, Sammy and I had work sessions with the aim of writing an article that would develop some of the new ideas born out of the Künneth formula. We went from discovery to discovery, Sammy having an extraordinary gift for formulating at each moment the conclusions that would emerge from the discussion. And it was always he who wrote everything up as we went along in precise and concise English. After the notion of *satellites* of a functor came that of *derived functors,* with their axiomatic characterization. Gradually the theory included several existing theories (cohomology of groups, cohomology of Lie algebras, in the sense of Chevalley and Eilenberg, cohomology of associative algebras). Then came the concept of *hyperhomology*.

Of course, this work together took several years. Sammy made several trips to my country houses (in Die and in Dolomieu). Outside of our work hours he participated in our family life.

Sammy knew how to put his friends to work. I think I remember that he persuaded Steenrod to contribute the preface of our book, where the evolution of the ideas is explained perfectly. He arranged also for other colleagues to collaborate in the writing of the chapter devoted to finite groups. Our initial project of a mere article for a journal was transformed; it became a book that we would propose to a publisher and for which it would be necessary to find a title that captured its content. We finally agreed on the term *Homological Algebra*. The text was given to Princeton University Press in 1953. I do not know why the book appeared only in 1956.

For fifteen years Sammy was also an active member of the Bourbaki group. It was, I think, in 1949 that André Weil, who was living in the United States, made contact with him in order to have him collaborate on a draft for use by Bourbaki, entitled "SEAW Report on Homotopy Groups and Fiber Spaces". It is therefore very natural that Eilenberg was invited to the Congress that Bourbaki held in October 1950. He was immediately appreciated and became a member of the group under the name "Sammy". It is necessary to say that he mastered the French language perfectly, which he had learned when he was living in his native Poland.

The collaboration of Sammy with Bourbaki lasted until 1966. He took part in the summer meetings, which lasted two weeks. He knew admirably how to present his point of view, and he often made us agree to it.

The above gives only a faint idea of Samuel Eilenberg's mathematical activity. The list made in 1974 of his publications comprises, besides 4 books, 111 articles; the first 37 articles are before his emigration from Poland to the United States in 1939, and almost all are written in French. He was not yet twenty years old when he began to publish. The celebrated articles written with S.Mac Lane extended from 1942 to 1954. The list of his other collaborators is long: N.E.Steenrod, J.A.Zilber, T.Nakayama, T.Ganea, J.C. Moore, G.M.Kelly, to cite only the main ones. Starting in 1966, Sammy became actively interested in the theory of automata, which led him to write a book entitled *Automata,* *Languages, and Machines,* published in 1974 by Academic Press.

I have not mentioned a magnificent collection of sculptures in bronze, silver, or stone, patiently collected in India, Pakistan, Indonesia, Cambodia,…, some of which dated to the third century B.C. In 1967 he gave a great part of his collection to the Metropolitan Museum in New York.

In 1982 Eilenberg retired from Columbia University, where he had taught since 1947. In 1986 his mathematical work was recognized by the award of the Wolf Prize in Mathematics, which he shared with Atle Selberg.

The last time I saw Sammy was when the Université de Louvain-la-Neuve organized a conference in his honor. Our meeting there was not without emotion. He was for me a friend whose kindness, humor, and faithfulness cannot be forgotten.

SAUNDERS MAC LANE

Samuel Eilenberg, who made decisive contributions to topology and other areas of mathematics, died on Friday, January 30, 1998, in New York City. He had been a leading member of the department of mathematics at Columbia University since 1947. His mathematical books, ideas and papers had a major influence.

Eilenberg was born in Poland in 1913. At the University of Warsaw he was a student of Borsuk in the active school of Polish topology. His thesis, concerned with the topology of the plane, was published in *Fundamenta Mathematica* in 1936. Its results were well received in Poland and in the

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USA. In 1938 he published in the same journal another influential paper on the action of the fundamental group on the higher homotopy groups of a space. Algebra was not foreign to his topology!

Early in 1939 Sammy's father told him, "Sammy, it doesn't look good here in Poland. Get out." He did, arriving in New York on April 23, 1939, and going at once to Princeton. At that university Oswald Veblen and Solomon Lefschetz efficiently welcomed refugee mathematicians and found them suitable positions at American universities. Sammy's work in topology was well known, so a position for him was found at the University of Michigan. There Ray Wilder had an active group of topologists, including Norman Steenrod, then a recent Princeton Ph.D. Sammy immediately fitted in, did collaborative research (for example, with Wilder, O.G.Harrold, and Deane Montgomery). His 1940 paper in the *Annals of Mathematics* formulated and codified the ideas of the "obstructions" recently introduced by Hassler Whitney. He also argued with Lefschetz. Finding the Lefschetz book (1942) obscure in its treatment of singular homology, he provided an elegant and definitive treatment in the *Annals* (1944).

Sammy's idea was to dig deep and deeper till he got to the bottom of each issue. This I learned when I lectured at Ann Arbor about group extensions. I had calculated an example of group extensions for an interesting factor group involving a prime number *p*. When I told Sammy this result, he immediately saw that it answered a question of Steenrod about the regular cycles of the *p*-adic solenoid (inside a solid torus, wrap another one *p* times around, and so on, ad infinitum). So Sammy and I stayed up all night to find out the reason for this unexpected appearance of group extensions. We found out more: it rested on a "universal coefficient theorem" which gave cohomology with any coeffi cient group *G* in terms of homology and an exact sequence involving Ext, the group of group extensions. Thus Sammy insisted on understanding this unexpected connection between algebra and topology. There was more there: the connection involved mapping topology into algebra, so we were forced to invent functors, natural transformations, and categories to describe this. All told, this led to our fifteen joint papers.

They all involved the maxim: Dig deeper and find out. For example, Hurewicz and Heinz Hopf had observed that the fundamental group of a space had effects on the higher homology and cohomology groups. Sammy, with his knowledge of his singular homology theory, had just the needed tools to understand this, which resulted in our discovery of the cohomology of groups. Sammy saw that this idea went further, so he started Gerhard Hochschild on his study of the cohomology of algebras and then went on to write, with Henri Cartan, that very influential book on homological algebra, which caught the interest of many algebraists and provided the first book presentation of the important French technique of spectral sequences.

Sammy applied his maxim in other connections. With Joe Zilber he developed the category of simplicial sets as a new type of space—using his singular simplices with face and degeneration operations. With Calvin Elgot he wrote about recursion, a topic in logic. By himself he wrote two volumes on *Automata, Languages, and Machines*. And with Eldon Dyer he prepared two volumes (not yet published) on *General and Categorical Topology*.

Algebraic topology was decisively influenced by Eilenberg's earlier 1952 work with Norman Steenrod, entitled *Foundations of Algebraic Topology*. At that time there were many different and confusing versions of homology theory, some singular, some cellular. This book used categories to show that they all could be described conceptually as presenting homology functors from the category of pairs of spaces to groups or to rings, satisfying suitable axioms such as "excision". Thanks to Sammy's insight and his enthusiasm, this text drastically changed the teaching of topology.

At Columbia University Sammy took vigorous steps to build up the department. He trained many graduate students. For example, his students and postdocs in category theory included Harry Applegate, Mike Barr, Jonathan Beck, David Buchsbaum, Peter Freyd, Alex Heller, Daniel Kan, Bill Lawvere, Fred Linton, Steve Schanuel, Myles Tierney, and others. He was an inspiring teacher.

Early in 1996 Sammy was felled by a stroke. It became hard for him to talk. In May 1997 I was able to visit him; he was lively and passed on to me a not clearly understood proposal. He was then able to spend some time in his apartment on Riverside Drive. I think his message then to me was the same maxim: Keep on pressing those mathematical ideas. This is well illustrated by his life. His ideas—singular homology, categories, simplicial sets, generic acyclicity, obstructions, automata, and the rest—will live on.

Our fifteen joint research papers have been collected in the volume *Eilenberg/Mac Lane, Collected Works,* Academic Press, Inc., New York, 1988.

Next, I comment on Eilenberg's contributions to the sources of homological algebra. The startling idea that homology theory for topological spaces could be used for algebraic objects first arose with the discovery of the cohomology groups of a group. Hurewicz had considered spaces which are aspherical (any image of a higher-dimensional sphere can be deformed into a point) and had shown that the fundamental group π_1 determines the homotopy type of the space—and hence its homology and cohomology groups. Hopf had then found explicit formulas for the ho mology (Betti) groups of such a space. Then Eilenberg-Mac Lane exhibited the n^{th} cohomology group $H^n(X, A)$ of such a space with coefficients in an abelian group A as a functor of π_1 and A—the n^{th} cohomology $H^n(\pi_1, A)$ of the group π_1 with coefficients in the π_1-module A. In particular H^1 was simply the group of "crossed homomorphisms" $f{:}\pi_1 \rightarrow A$ satisfying

$$f(xy)=xf(y)+f(x)$$

and taken modulo the "principal" such—those f given as $f(x)=xa-a$ for some a in A. The elements of $H^n(\pi_1, A)$ were functions $f(x_1,\ldots, x_n)$ of n elements x_i satisfying a suitable equation, modulo trivial solutions. In other words, the cohomology of π_1 was given as the cohomology of a certain chain complex, the so-called "bar resolution". In the terminology subsequently refined by Cartan-Eilenberg, $H^n(\pi_1, —)$ was the $(n-1)^{st}$ "derived" functor of $H^1(\pi_1, —)$. In other words, old functors lead to new ones.

Eilenberg very quickly saw that such cohomological methods would apply to any algebraic situation. He explained this in the 1949 paper [2]. In 1948 he wrote with Chevalley a paper on the cohomology theory of Lie algebras, and about the same time he encouraged Gerhard Hochschild, then one of Chevalley's Ph.D. students, to introduce cohomology groups for associative algebras. In each of these cases the cohomology groups in question were the derived functors of naturally occurring Hom functors. Classical questions of algebraic topology also entered by way of the Künneth formulas. These formulas originally were stated to give the Betti numbers and torsion coefficients of a product of two spaces X and Y. This really involved the tensor product of homology groups, and in the famous Eilenberg-Steenrod book it appears in the following short exact sequence:

$$0 \to \sum_{m+q=n} H_m(X) \otimes H_q(Y) \to H_n(X \times Y)$$
$$\to \sum_{m+q=n-1} \mathrm{Tor}\Big(H_m(X), H_q(Y)\Big) \to 0.$$

Here "exact" means that at each point the image of the incoming arrow is the kernel of the outgoing arrow. Also, Tor(A,B) is a functor of abelian groups, as is $\otimes$; in fact, Tor turns out to be the first derived functor of $\otimes$! The definitions of these terms do suffice for the topological task in question: elements of finite order in the groups A and B give elements in Tor. I clearly recall an occasion when I tried to explain to Professor Künneth at Erlangen University that this abstract language did indeed produce his original numerical Künneth formulas. As stated, Tor is the first derived functor of $\otimes$; it turns out for modules that there are also higher derived functors $\mathrm{Tor}_n(A, B)$ for each n. The construction of these higher torsion products and their description by generators and relations were examined by Eilenberg-Mac Lane; these products provided new examples of higher derived functors of modules. For abelian groups A and B, $\mathrm{Tor}_n(A, B)=0$ when $n>1$.

Now return to the functor Ext (A, B), the group of abelian group extensions E of B by A, so that E appears in a short exact sequence of abelian groups:

$$0\to B\to E\to A\to 0.$$

It turns our that the functor Ext (A, —) is the first derived functor of Hom (A, —) and thus that there are higher derived functors $\mathrm{Ext}_n(A, —)$. They vanish for abelian groups A, but not generally for modules. The work of the Japanese mathematician Yoneda showed that an element of $\mathrm{Ext}_n(A, B)$

could be represented as a long exact sequence of modules (with n intermediate terms):

$$0 \to B \to E_1 \to E_2 \to \ldots \to E_n \to A \to 0.$$

All these various examples of the construction of new functors as "derived" functors of given ones were at hand for Eilenberg. He saw how they could be used to determine a homological "dimension" for algebraic objects, and he established the connection with the Hilbert notion of a syzygy in a 1956 paper [3]. This provided the background for the influential Cartan-Eilenberg book [1] on homological algebra. This text emphasized how the derived functors for a module M could be calculated from *any* "resolution" of M by free modules, a long exact sequence

$$0 \leftarrow M \leftarrow X_0 \leftarrow X_1 \leftarrow X_2 \ldots$$

with all X_j free. One simply applies the functor to the resolution with the M term dropped and then takes the homology or cohomology of the resulting complex. This effectively generalized the computation from specific "bar resolutions" used to define the cohomology of a group. The ideas of homological algebra were presented in two pioneering books by Cartan-Eilenberg [1] and Mac Lane [4]. The Cartan-Eilenberg treatise had a widespread and decisive influence in algebra. This again illustrates the genius of Eilenberg: If essentially the same idea crops up in different places, follow it out and find out where it lives.

ALEX HELLER

When I met Samuel Eilenberg in 1947, he was introduced as Sammy. He was always referred to as Sammy. It would be wrong to speak of him otherwise. I was then a student; I promptly became *his* student. I would like to record what drew me then to Sammy and continued over the years to do so—namely, what I perceived as his radical insistence on lucidity, order, and understanding as opposed to trophy hunting, and his idea of how that understanding was to be achieved.

Perhaps I should illustrate this by a partial (in both senses) account of his mathematical career. At the end of the 1930s algebraic topology had amassed a stock of problems which its then available tools were unable to attack. Sammy was prominent among a small group of mathematicians—among them, for example, J.H.C.Whitehead, Hassler Whitney, Saunders Mac Lane, and Norman Steenrod—who dedicated themselves to building a more adequate armamentarium. Their success in doing this was attested to by the fact that by the end of the 1960s most of those problems had been solved (inordinately many of them by J.F.Adams).

Sammy's contributions appeared for the most part in a series of collaborations. With Mac Lane he developed the theory of cohomology of groups, thus providing a proper setting for the remarkable theorem of Hopf on the homology of highly connected spaces. This led them to the study of the Eilenberg-Mac Lane spaces and thus to a deeper understanding of the relations between homotopy and homology. Their most fateful invention perhaps was that of category

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theory, responding, no doubt, to the exigencies of algebraic topology but destined to radiate across most of mathematics.

In collaboration with Steenrod, Sammy drained the Pontine Marshes of homology theory, turning an ugly morass of variously motivated constructions into a simple and elegant system of axioms applied, for the first time, to functors. This was a radical innovation. Heretofore homology theories had been procedures for computing; henceforth they would be mathematical objects in their own right. What was especially remarkable was that in order to achieve this, Sammy and Steenrod undertook to raise the logical level of the things that might be so regarded.

The algebraic structures of the new algebraic topology were proving themselves useful in other parts of mathematics: in algebra, representation theory, algebraic geometry, and even in number theory. Together with Henri Cartan, Sammy systematized these structures under the rubric of *Homological Algebra,* once more raising the level of discourse by introducing such notions as derived functors. I am tempted to insert a parenthesis here. This latest innovation brought its authors into conflict with the "establishment" by putting in question the very notion of definition, raising a fundamental question of the relation between category theory and set theory that has yet to be put definitively to rest. Since homological algebra has proved indispensable, the honors lie, I think, with Cartan and Eilenberg. In any case, the field proliferated so rapidly that Grothendieck, only a few years later, was said to have spoken of their book as "le diplodocus", regarding it apparently as palaeontology.

The roots of homological algebra lay nevertheless in algebraic topology, and Sammy, in collaboration with John Moore, returned to these. They introduced such novelties as differential graded homological algebra and relative homological algebra to provide homes for the new techniques intro duced not only by Sammy and his collaborators but also by a new generation including Serre, Grothendieck, and Adams. Notable among them are the so-called Eilenberg-Moore spectral sequences, which deal with pullbacks of fibrations and with associated fiber bundles.

Unfortunately neither Sammy nor his last collaborator, Eldon Dyer, lived to complete their ultimate project of refounding algebraic topology in the correct —which is to say, homotopical—setting. Perhaps this project was too ambitious. I learned from Eldon how much agony accompanied even such choices as that of the correct definition of a topological space. Some part of their book may yet survive, and others are already continuing their project piecemeal.

As I perceived it, then, Sammy considered that the highest value in mathematics was to be found, not in specious depth nor in the overcoming of overwhelming difficulty, but rather in providing the definitive clarity that would illuminate its underlying order. This was to be accomplished by elucidating the true structure of the objects of mathematics. Let me hasten to say that this was in no sense an ontological quest: the true structure was intrinsic to mathematics and was to be discerned only by doing more mathematics. Sammy had no patience for metaphysical argument. He was not a Platonist; equally, he was not a non-Platonist. It might be more to the point to make a different distinction: Sammy's mathematical aesthetic was classical rather than romantic.

Category theory was one of Sammy's principal tools in his search for mathematical reality. Category theory also developed into a mathematical subject with its own honorable history and practitioners, beginning with Mac Lane and including, notably, F.W.Lawvere, Sammy's most remarkable student, who saw it as a foundation for all of mathematics and justified this intuition with such innovations as categorical semantics and topos theory. Sammy did not, I think, want to be reckoned a member of this school. I believe, in fact, that he would have rejected the idea that mathematics needed a foundation. Category theory was for him only a tool—in fact, a powerful one—for expanding our understanding. It was his willingness to search for this understanding at an ever higher level that really set him apart and that made him, in my estimation, the author of a revolution in mathematics as notable as that initiated by Cantor's invention of set theory. Like Cantor, Sammy has changed the way we think about mathematics.

PETER FREYD

Thirty years ago I found myself a neighbor of Arthur Upham Pope, the master of ancient Persian art. He had retired in his nineties to an estate in the center of the city of Shiraz in southern Iran, where I lived, briefly, across the street. I found an excuse for what has to be called an audience, and I mentioned that I was a friend of Samuel Eilenberg.

"I don't know him," he said. "I know *of* him, of course. How do you know him?"

"We work in the same area of mathematics."

"You're talking about a different Eilenberg. I meant the dealer in Indian art."

"Actually, it's the same person. He's both a mathematician and a collector of Indian art."

"Don't be silly, young man. The Eilenberg I mean is not a *collector* of Indian art, he's the *dealer* in Indian art. I know

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him well. He established the historicity of one of the Persian kings. He certainly is not a mathematician."

End of audience.

In later years even Arthur Upham Pope would have known. In the art world, Eilenberg became universally known as "Professor". Indeed, if one walked with him in London or Zürich or even Philadelphia and one heard "Professor!", it was always Eilenberg who was being hailed, and it was always the art world hailing him.

If you heard "Sammy!", you knew it was a mathematician.

It was complicated, explaining that name. For a person who knew him first through his works, it was hard to conceive of him as "Sammy". And upon meeting him for the first time, it was even harder: He was in charge of entire fields of mathematics—indeed, he had created a number of them. Whenever he was in a room, he was in charge of the room, and it did not matter whose room it was. Sammy? The name did not fit.

But he had to have a name like Sammy. I said it was hard to explain. Here was one of the most aggressive people one might ever meet. He would challenge almost anything. If a person mentioned something about the weather, he would challenge it: once in California I heard him insist that it was not weather; it was climate. But somehow it was almost always clear: it was all right to challenge him right back. Aggressive and challenging, but not at all pompous. One cannot be pompous with a name like Sammy.

Sammy kept his two worlds, mathematics and art, at something of a distance. But both worlds seemed to agree on one thing, the very one that Arthur Upham Pope had insisted upon: Sammy was the dealer.

Without question, Sammy loved playing the role of dealer. In the days when mathematicians were in demand and jobs were easy to come by, Sammy loved to tell about the math market he was going to create. The trade would be in mathematician futures: "This one's done only two lemmas and one proposition in the last year; the most recent theorem was two years ago; better sell this one at a loss." With his big cigar (expensive) and his big gold ring (in fact, a valuable Indian artifact), he could enter his dealer mode at a moment's notice. One always wondered just how many young mathematicians' careers were in his hands.

But his two worlds, mathematics and art, perceived this role of dealer quite differently. In mathematics we understood that it was a role he loved playing, but that he was only playing. His being a mathematician was what counted, and he would have been the same mathematician whether or not he played the dealer, indeed, whether or not he played—and he did—high-stakes poker. This was not so clear in his other world.

It was usually frustrating trying to explain to others how Sammy was perceived by his fellow mathematicians. Sammy had an unprintable way of saying that mathematics required both intelligence and aggression. But imagine not knowing how his mathematics—when he had finished—would totally belie that aggression. Imagine not knowing how remarkably well-behaved his mathematics always was. Imagine not knowing how his mathematics, when he had finished, always seemed preordained and how it seemed no more aggressive than, say, the sun rising at its appointed sunrise time.

Forty years ago Sammy hoped to turn the study of Indian bronzes into an equally well-behaved subject. He had already acquired a reputation for being the best detector of fakes in the business, and he believed he could axiomatize the process. He even had a provisional list of axioms, and it was truly an elegant list.

A few years later we found ourselves at a small French-style bistro in La Jolla, California. We had been out of touch:

there had been an argument about mathematical ethics, but somehow we had resolved it; the dinner was something of a celebration of the resolution. I asked him about his book on bronzes.

"The axioms failed."

"What does that mean?"

"It means that I've been taken. I bought a fake."

He had suspected it only after the work had been in his bedroom for a few weeks. He had the pleasure, at least, of investigating until he found out who the master faker was and tracking him down in his studio, not to berate him, but to congratulate him.

After that, Sammy made a point of not building bridges between his two worlds. I recall just one exception. He moved from a conversation about sculpture to one about mathematics. Sculptors, he said, learn early to create from the inside out: what finally is to be seen on the surface is the result of a lot of work in conceptualizing the interior. But there are others for whom the interior is the result of a lot of work on getting the surface right. "And," Sammy asked, "isn't that the case for my mathematics?"

Style is only one part of his mathematics—as, of course, he knew—but there are, indeed, wonderful stories about Sammy, attending only to what seemed the most superficial of stylistic choices, restructuring entire subjects on the spot.

Many have witnessed this triumph of style over substance, particularly with students. But the most dramatic example had a stellar cast. D.C.Spencer gave a colloquium at Columbia in the spring of 1962, and Sammy decided it was time to demonstrate his get-rid-of-subscripts rule: "If you define it right, you won't need a subscript." Spencer, with the greatest of charm—it was for good reason that he was already affectionately known as "Uncle Don" — followed Sammy's orders and proceeded to restructure his subject while standing there at the board. One by one, the subscripts disappeared, each disappearance preceded by a Sammy-dictated redefinition. He had virtually no idea of the intended meanings of any of the symbols. He was operating entirely on the surface, looking only at the shape of the syntax.

The process went on for several minutes, until Sammy took on the one proposition on the board. “So now what does that say?”

“Sammy, I don’t know. You’re the one making all the definitions.”

So Sammy applied his definitions, and one by one the subscripts continued to disappear, until finally the proposition itself disappeared: it became the assertion that a thing was equal—behold—to itself.

“My mother’s father had the town brewery and he had one child, a daughter. He went to the head of the town yeshiva and asked for the best student,” Sammy told me one day. “So my future father became a brewer instead of a rabbi.”

Sammy regarded prewar Poland with some affection. He felt that he had been well nurtured by the Polish community of mathematicians, and he told me of his pleasure on being received by Stefan Banach himself, a process of being welcomed to the holy of holies, the café in which Banach spent his time during the annual Polish mathematical conferences. By the time Sammy came to the U.S. in his mid-twenties he was a well-known topologist.

When I questioned him on his attitude about prewar Poland, he answered that one must “watch the derivative”: Don’t judge just by how good things are, but by how fast they’re becoming better.

Sammy’s view of Poland since the war was more complicated. It was particularly complicated by what he viewed as its treatment of category theory as a fringe subject.

In the late 1950s Sammy began to concentrate his mathematical activities, both research and teaching, on category theory. He and Mac Lane had invented the subject, but to them it was always an applied subject, not an end in itself. Categories were defined in order to define functors, which in turn were defined in order to define natural transformations, which were defined finally in order to prove theorems that could not be proved before. In this view, category theory belonged in the mainstream of mathematics.

There was another view, the “categories-as-fringe” view. It said that categories were defined in order to *state* theorems that could not be stated before, that they were not tools but objects of nature worthy of study in their own right. Sammy believed that this counterview was a direct challenge to his role as the chief dealer for category theory. He had watched many of his inventions become standard mathematics— singular homology, obstruction theory, homological algebra— and he had no intention of leaving the future of category theory to others.

Today the language of category theory has permeated a good part of mathematics and is treated with some respect. It was not ever so. There were years before the words “category” and “functor” could be pronounced unapologetically in diverse mathematical company. One of my fonder memories comes from sitting next to Sammy in the early 1960s when Frank Adarns gave one of his first lectures on how every functor on finite-dimensional vector spaces gives rise to a natural transformation on the *K*-functor. Frank used that construction to obtain what are now called the Adams operations, and he used those to count how many independent vector fields there could be on a sphere. It was not until then that it became permissible to say “functor” without a little snort.

In those years, Sammy was a one-man employment agency for a fresh generation of mathematicians who viewed categories not just as a language but as a potentially central mathematical subject. For the next thirty-five years he went to just about every category theory conference, and, much more important, he used his masterly expository skills to convey categorical ideas to other mathematicians. Sammy's efforts succeeded for the language of category theory, and he never abandoned his efforts for the theory itself. He was confident that the categorical view would eventually be the standard mathematical view, with or without his salesmanship. Its inevitability would be based not on Sammy's skills as a dealer but on the theorems whose proofs required category theory. That was obvious to Sammy. He wanted to make it obvious to everyone else.

HYMAN BASS

Sammy visited the University of Chicago for a topology meeting while he was department chair at Columbia. I was then a graduate student, working with Irving Kaplansky on topics in homological algebra. So I was already familiar with some of Sammy's work when I first met him and we discussed mathematics. Homological algebra was insinuating itself into commutative algebra and algebraic geometry through the pioneering work of Maurice Auslander and David Buchsbaum (Sammy's student) and J.-P.Serre. Kaplansky was introducing many of my cohorts to this work.

When I graduated in 1959, in a now distant time of affluent mathematical opportunity, I contemplated a year at the Institute for Advanced Study. But Sammy, while I accompa

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nied him to an art dealer in downtown Chicago (an errand whose significance I only later appreciated), persuaded me that it would be better first to launch my professional career as a regular faculty member, doing both research and teaching. That might now seem a difficult case to make, but it fit with my own disposition, and, in any case, Sammy had a charismatic charm and warm humor that were hard to resist.

Sammy's mentoring made me virtually his student. Columbia's was a small and intimate department, with such figures as Harish-Chandra, Serge Lang, Paul Smith, Ellis Kolchin, Dick Kadison, Edgar Lorch, Masatake Kuranishi, Lipman Bers, Joan Birman, and, briefly, Heisuke Hironaka, Steve Smale, Wilfried Schmid, and many others. The department featured some strong personalities, but Sammy, along with Lipman Bers when he arrived somewhat later, set the tone and style of the department. Research in topology, algebraic geometry, complex analysis, number theory, and the then budding category theory were quite active there. Though a faculty member, I functioned much like a student, learning about both mathematics and the intellectual culture of our discipline.

Over the years my appreciation deepened for the way Sammy worked and thought about mathematics. Though quite accomplished at compution and geometric reasoning, Sammy was preeminently a formalist. He fit squarely into the tradition of Hilbert, E.Artin, E.Noether, and Bourbaki; he was a champion of the axiomatic unification that so dominated the early postwar mathematics. His philosophy was that the aims of mathematics are to find and articulate with clarity and economy the underlying principles that govern mathematical phenomena. Complexity and opaqueness were, for him, signs of insufficient understanding. He sought not just theorems, but ways to make the truth transparent, natural, inevitable for the "right thinking" person.

It was this “right thinking”, not just facts, that Sammy tried to teach and that, in many domains, he succeeded in teaching to a whole generation of mathematicians.

In some ways Sammy seemed to have a sense of the structure of mathematical thinking that almost transcended specific subject matter. I remember the uncanny sensation of this on more than one occasion when sitting next to him in department colloquia. The speaker was exposing a topic with which I knew that Sammy was not particularly familiar. Yet a half to two thirds of the way through the lecture, Sammy would accurately begin to tell me the kinds of things the speaker was going to say next.

Though his mathematical ideas may seem to have a kind of crystalline austerity, Sammy was a warm, robust, and very animated human being. For him mathematics was a social activity, whence his many collaborations. He liked to do mathematics on his feet, often prancing while he explained his thoughts. When something connected, one could read it in his impish smile and the sparkle in his eyes.

He was engaged with the world in many ways, a sophisticated and wise man who took a refined pleasure in life. His was a most satisfying and inspiring influence on my own professional life. After his stroke, it was painful to see Sammy, frail and gaunt and deprived of speech when his still active mind had so much yet to say. Yet he bravely showed the same good humor and dignity that marked his whole life. He leaves us with much to treasure, even while we miss him.

SOME PH.D. STUDENTS OF SAMUEL EILENBERG

Kuo-Tsai Chen (1950)
Alex Heller (1950)
David Buchsbaum (1954)
Ramaiyengar Sridharan (1954)
Kalathoor Varadarajan (1954)
F.William Lawvere (1963)
Harry Applegate (1965)
Estelle Goldberg (1965)
Myles Tierney (1965)
George A.Hutchinson (1967)
Jonathan M.Beck (1967)
Stephen C.Johnson (1968)
Albert Feuer (1974)
Chang-San Wu (1974)
Martin Golumbic (1975)
Alan Littleford (1979)

REFERENCES

[1] H.CARTAN and S.EILENBERG, *Homological algebra,* Princeton Univ. Press, Princeton, NJ, 1956.
[2] S.EILENBERG, *Topological methods in abstract algebra: Cohomology theory of groups,* Bull. Amer. Math. Soc. 55 (1949), 3–37.
[3] ———, *Homological dimension and syzygies,* Ann. Math. (2) 64 (1956), 328–336.
[4] S.MAC LANE, *Homology,* Springer-Verlag, Berlin, 1963.

SELECTED BIBLIOGRAPHY

Transformations continues en circonference et la topologie du plan, *Fund. Math.* XXVI (1936), 62–112.

On the relation between the fundamental group of a space and the higher homotopy groups, *Fund. Math.* XXXII (1939), 167–175.

With Mac Lane, S., Group extensions and homology, *Ann. Math.* 43 (1942), 758–831.

With Mac Lane, S., Natural isomorphisms in group theory, *Proc. Nat. Acad. Sci. U. S. A.* 28 (1942), 537–543.

With Wilder, R.L., Uniform local connectedness and contractibility, *Amer. J. Math.* 64 (1942), 613–622

With Harrold, O.G., Jr., Continua of finite linear measure I, *Amer. J. Math.* 65 (1943), 137–146.

Singular homology theory, *Ann. Math.* 45 (1944), 407–447.

With Mac Lane, S., General thory of natural equivalences, *Trans. Amer. Math. Soc.* 58 (1945), 231–294.

With Mac Lane, S., Relations between homology and homotopy groups of spaces, *Ann. Math.* 46 (1945), 480–509; 51 (1950), 514–573.

With Montgomery, D., Fixed point theorems for multi-valued transformations, *Amer. J. Math.* 68 (1946), 214–222.

Homology of spaces with operators, *Trans. Amer. Math. Soc.* 61 (1947), 378–417.

With Mac Lane, S., Cohomology theory in abstract groups, I, *Ann. Math.* 48 (1947), 51–78.

With Mac Lane, S., Cohomology and Galois theory, I: Normality of algebras and Teichmüller's cocycle, *Trans. Amer. Math. Soc.* 64 (1948), 1–20.

With Mac Lane, S., Homology of spaces with operators, II, *Trans. Amer. Math. Soc.* 65 (1949), 49–99.

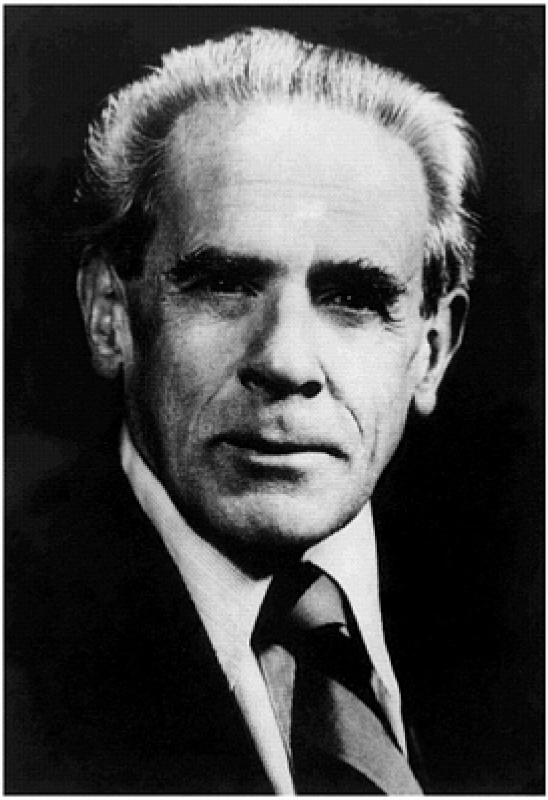
With Zilber, J.A., Semi-simplicial complexes and singular homology, *Ann. Math.* 51 (1950), 499–513.

With Steenrod, N.E., Foundations of Algebraic Topology. Princeton Univ. Press, Princeton, NJ, 1952.

With Mac Lane, S., Acyclic models, *Amer. J. Math.* 75 (1953), 189– 199.

With Mac Lane, S., On the groups $H(\ ,n)$, I, *Ann. Math.* 58 (1953), 55–106, 60 (1954), 49–139 and 513–557.

With Mac Lane, S., On the homology theory of abelian groups, *Canad. J. Math.* 7 (1955), 43–53.
With Cartan, E., Homological Algebra, Princeton, Univ. Press, Princeton, NJ, 1956.
With Ganea, T., On the Lusternik-Schnirelmann category of abstract groups, *Ann. Math.* 65 (1957), 517–518.
With Moore, J., Adjoint functors and triples, *Illinois J. Math.* 9 (1965), 381–398.
With Kelly, G.M., Closed categories. In *Proceedings, Conference on Categorical Algebra, La Jolla, 1965,* pp. 421–562. Springer-Verlag, New York, 1966.
Automata, Languages, and Machines (2 vols.). Academic Press, New York, 1974–76.
With Dyer, E., General and Categorical Topology (Vols. A & B), Cambridge Univ. Press, 2000.



JORDI FOLCH-PI

March 25, 1911-October 3, 1979

BY MARJORIE B.LEES AND ALFRED POPE

JORDI FOLCH-PI[1] WAS A colorful and truly unique personality whose sharp intellect, insight, and willingness to express his opinions were widely appreciated. He was a Catalan physician-scientist and a leader in the emerging field of neurochemistry. Folch made major scientific contributions to the areas of lipid chemistry and structural biochemistry and was widely considered to have inherited the mantle of Johannes Thudichum, the nineteenth-century founder of the field of structural neurochemistry.

Folch's studies at the Rockefeller Institute Hospital Laboratories in New York showed that a brain lipid fraction called cephalin by Thudichum was actually a mixture of several components, which he identified as phosphatidyl ethanolamine, phosphatidyl serine, and inositol-containing lipids. At 33 years of age Folch was called to the McLean Hospital, a psychiatric affiliate of the Massachusetts General Hospital, as director of the new Biological Research Laboratory with the stated mission to characterize the structural components of the nervous system in health and disease. He successfully developed a broad-based, internationally recognized program, which he continued to lead until his retirement in 1977. Folch's initial scientific priority was the quan titative extraction of brain lipids free of non-lipid contaminants. The resulting chloroform-methanol lipid extraction and washing procedure became widely used and was one of the most cited papers in the biochemical literature. His approach led to the identification of new lipid and protein components in the brain and to the recognition of proteolipids, the major protein of central nervous system myelin, as a new class of lipoproteins. Other seminal research included methods for the isolation of water-soluble glycolipids, which are still used for isolation of gangliosides and studies on the chemistry of brain maturation, brain electrolytes, copper- containing proteins, and trypsin-resistant proteins.

THE EARLY YEARS

Jordi Folch-Pi was born in Barcelona on March 25, 1911, the son of Rafel Folch and Maria Pi. It was an intellectual Catalan and Spanish family. His father, trained as a lawyer, was a successful businessman and a dedicated poet. His father participated in a Catalan literary competition (The Floral Games) and was awarded the Golden Violet prize for his poem about the destruction of a Catalan cathedral. Folch's mother, Catalan by birth, was brought up in Toulouse, France, spoke fluent French, and was certified as a high-school teacher in Barcelona. Jordi was the third in a family of four children, with two older brothers and a younger sister. He followed the usual education course of his day, with the important exception that he attended the Lycée Française of Barcelona. He credited that experience to the development of a personal discipline that was particularly valuable for his future career. After receiving a bachelor of science degree in 1927 from the Institute Balmes of Barcelona University, Folch took courses in the Faculty of Medicine and received his M.D. degree cum laude from the University of

Barcelona Medical School in 1932 and his licentiate the following year. The clinical training at the university was first rate and included a period as an intern in the surgical clinic of Dr. Antoni Trias and as the sole physician in Almedret, a small Catalonian village of 800 people, where he substituted for his brother Albert for several months. By contrast, the basic sciences consisted mainly of lectures with little opportunity for hands-on laboratory experience.

Folch was fortunate to have the opportunity to study at the Institute of Physiology in Barcelona, which was founded by his cousin August Pi-Sunyer and Jesus Marie Bellido and was dedicated to carrying out basic research using contemporary methods and ideas. Folch worked as an assistant to another cousin Cesar Pi-Sunyer and by the time he received his M.D. degree, they had jointly published four papers on glycogen synthesis in three different languages (German, French, and Spanish). Folch also studied blood glucose and lactic acid metabolism under the direction of the man he considered his scientific mentor, Professor Rosend Carrasco-Formiguera. He was the person who particularly encouraged the young Folch in his research. It is of interest that many years later, at the age of 80, Carrasco spent several months at the McLean Research Laboratory studying proteolipids (see below) in red blood cells.

Folch's experiences at the Institute of Physiology intensified his interest in physiology and in clinical questions, particularly as they related to metabolic problems. He recognized a need for more formal training in biochemistry in order to pursue an independent scientific career. Thanks to Carrasco's contacts, Francisco Duran-Reynals, a biochemist at the Rockefeller Institute in New York, became interested in Folch and arranged for him to come to that institution as a volunteer. This was made possible in mid-1936 by fellowships from the Barcelona City Hall and the Autonomous

Catalan Government. In a presentation much later Folch stated: "After I arrived in New York, Duran-Reynals exercised an enormous influence over me, not only as a scientific model but also as a definer and interpreter of ethical and social values of North American society."[2]

The primary goal of his visit to the United States was to learn biochemistry as applied to medicine under the direction of Dr. Donald D.Van Slyke, the foremost practitioner of that art at the time. Folch intended to return to Spain, where he very much wanted to fight on the Loyalist side in the Spanish Civil War (1936–39), but his family urged him to remain in the United States. The entire Folch family were active Spanish Loyalists. His oldest brother, Alfred, a physician and surgeon, and his second brother, Frederic, an engineer, both fought for the Loyalists but had to flee to Toulouse at some point during the war. Albert subsequently emigrated to Mexico, as did his sister, Nuria Folch de Sales and her husband, a famous Catalan poet. One day, Folch's father received word that he was on a list of people to be arrested the next day, and he immediately escaped to France by boat and headed for Toulouse. Shortly thereafter, Folch's mother fled north and literally walked through the Pyrenees in a harrowing winter nighttime trip. Jordi acquiesced to his family's wishes, remaining at the Rockefeller Institute for a total of nine years.

THE ROCKEFELLER YEARS

Folch arrived at the Rockefeller in 1936 as a volunteer assistant. The following year he obtained a formal position as an assistant and later as an associate on the scientific staff of the Hospital of the Rockefeller Institute for Medical Research in Van Slyke's department. Folch's first assignment at the Rockefeller Institute was a project with Dr. Irvine Page on pituitary hormone disturbances. Folch's role was to analyze plasma lipids in these disorders. He soon realized that the commonly used extraction of lipids with petroleum ether had problems in that the extraction was not quantitative and the extract contained non-lipid contaminants. These simple observations influenced the direction of Folch's research for many years thereafter. He devised a procedure that involved precipitation of lipids and proteins with colloidal iron and removal of most of the non-lipid components with water.

Concomitantly, he played a role in the development of two other methods.[3] One was a manometric method for carbon analysis of organic materials utilizing a glass apparatus previously developed by Van Slyke. At the time, this apparatus was widely used for gas analysis in clinical and basic research. The other was a quantitative method for measuring potassium in organic samples. Each of these methods was pertinent to Folch's subsequent research activities. To address the need for methods for the analysis of specific lipids the first priority was to obtain purified lipids from bovine brains to be used as standards. Using the newly developed method for carbon analysis, along with other chemical methods, he characterized the isolated cephalin fraction. According to Thudichum, the physician, oenologist, and founder of the field of structural neurochemistry, this was pure phosphatidyl ethanolamine, but Folch showed that the amounts of carbon and of amines were not consistent with the accepted formula. This in turn led to a series of classic papers published in the *Journal of Biological Chemistry* showing that cephalin was not a single lipid but rather was a mixture of at least three lipids. This was shown by elegant studies that culminated in the isolation, purification, and characterization of phosphatidyl ethanolamine and a new amine-containing lipid entity identified as phosphatidyl serine. With D.W.Wooley he showed for the first time that inositol was a component of brain lipids and subsequently isolated and characterized mono-, di- and triphosphoinositides.

During the first half of the twentieth century, the Rockefeller Institute was the premier center for biomedical research in America and generated first-rate science in a stimulating intellectual environment. This environment led to Folch's many long-term friendships with distinguished biomedical scientists. Nobel laureate Herbert Gasser was director of the Institute during Folch's tenure, and other notables with whom he interacted included Rafael Lorente de Nó, Réné Dubos, Lyman Craig, Sanford Moore, and William Stein. Additional active collaborators included Jordi Casals, Howard Schneider, Peter Olitsky, and D.W.Wooley. During Folch's first four years in New York, he lived at International House, where he had an opportunity to interact with people of all disciplines and from many countries. For the following two years he shared an apartment with the microbiologist and scientific philosopher Réné Dubos. In 1940 Jordi met a young Barnard student Willa Babcock, whom he courted for several years and married in June 1945. They had three children: Raphael Charles (1946), Diana Maria (Mrs. Everett Ferguson) (1951), and Frederic Albert Jordi (1958). Willa Babcock Folch-Pi was a scholar in her own right and obtained a Ph.D. in 1968 in Romance languages at Harvard University with a major interest in medieval poetry. She was a Bunting fellow at Radcliffe College, taught both Spanish and French at Tufts University in Medford, Massachusetts, and was an academic dean at the latter institution. Mrs. Folch-Pi currently resides in Center Sandwich, New Hampshire.

THE TRANSITION TO MCLEAN HOSPITAL

McLean Hospital is a psychiatric affiliate of the Massa chusetts General Hospital and already had a distinguished record of research on mental illness dating back to 1888. In 1901 Otto Folin began a program to develop methods to study the urine of psychiatric patients, but the ensuing comprehensive studies showed no significant differences between urinary metabolites in normal and mentally ill people. In 1908 Folin left to head the Department of Biological Chemistry at Harvard Medical School, where he became the first Professor of Biological Chemistry in the United States. The tradition of biochemical research had continued at McLean in accordance with the view stated by E.Stanley Abbot that "in psychiatry we must seek to learn the patient's total reaction (biological and psychological) to his total environment."[4]

Over the years several competent, dedicated biochemists in the McLean Laboratories maintained this commitment with minimal financial support. By the early 1940s, however, the basic sciences were no longer active and a new beginning seemed in order. To the credit of the Board of Trustees of the Massachusetts General Hospital and a prestigious committee of Harvard Medical School professors a decision was made to establish a free-standing research center devoted to fundamental investigations in biomedical sciences pertinent to mental health and disease. This visionary decision was backed by a commitment of funds to construct and equip a new laboratory building and to search for and support a director who would develop a comprehensive program on the biochemistry of the nervous system. A.Baird Hastings, an active member of the committee and at the time chairman of the Department of Biological Chemistry at Harvard Medical School, had been a student of Donald D.Van Slyke. Van Slyke was called upon for advice and recommended his protégé, the 33-year-old Jordi Folch-Pi.

Folch's original findings at Rockefeller had brought him immediate attention as a leader in lipid chemistry, a field particularly appropriate for studying the brain. Folch's creativity, vision, and scintillating personality soon convinced the committee of his potential as a leader. In 1944 he was appointed director of scientific research at McLean and assistant professor of biological chemistry at Harvard Medical School and was given the challenge to establish a broad research program on the biochemistry of the nervous system that would have long-range relevance for the problems of mental disease. Folch enthusiastically threw himself into the task of planning a state-of-the-art building, while simultaneously continuing his research at Rockefeller. In May 1946 the new building was dedicated with a scientific symposium of distinguished speakers. Folch gave a masterful presentation, describing the special attributes of the biochemistry and physiology of the brain and the nature of the problems that had to be solved. It is striking to realize the amazing progress that has been made since his presentation in 1946. Yet, the concepts he discussed remain valid to this day and provide a useful framework for current neuroscientists to consider.

By autumn the laboratories were fully operational with support staff that came with him from New York and additional staff that he recruited. Folch's strategy was to begin the program with two divisions, one representing his own area of interest and expertise in the structural chemistry of the macromolecular components of the brain. He was soon joined in these endeavors by Marjorie Lees, a graduate student and recipient of one of the first predoctoral fellowships in a newly instituted U.S. Public Health Service program. A complementary division was set up to study the microchemical anatomy and pathology of the brain. Dr. Alfred Pope, a neuropathologist with training in microchemistry, was appropriately recruited to head this unit.

THE SCIENTIFIC PROGRAM AT THE MCLEAN HOSPITAL RESEARCH LABORATORY (BIOCHEMISTRY)

Folch rapidly demonstrated his ability to get to the heart of a problem, to focus on his scientific goals, and to avoid extraneous questions. He felt strongly that, to understand brain function at the molecular level, new analytical methods had to be developed, and he set about doing so. It should be remembered that much of his work began in an era when methods used routinely today were in their beginning stages or did not exist. Chromatography—including thin-layer chromatography, gas chromatography, and mass spectrometry—was at a primitive stage, tissue culture techniques were only recently introduced, and immunological and molecular approaches were essentially nonexistent. Biochemical reagents often had to be purified in the laboratory or synthesized from scratch. It was even necessary to build one's own equipment. Despite these limitations, or perhaps because of them, Folch was able to make remarkable progress by utilizing his insights for the development of imaginative chemical and physical approaches.

Folch's fundamental philosophy was that, to understand the structural chemistry of the brain and its macromolecular complexes, it was necessary to identify and quantitate all the brain components (i.e., "everything" must be accounted for). He had recognized early the limitations of the then current harsh methods of lipid extraction and had explored several potential new procedures. The initial goal at McLean was to develop mild procedures for the quantitative extraction of brain lipids free of non-lipid contaminants. Recognizing the high lipid-solvating power of chloroform-methanol mixtures, Folch used these solvents for brain tissue extraction. Several years were required before the now "classic" method for removal of non-lipid contaminants in a two-phase system evolved. The final choice was elegantly simple but had widespread impact: A chloroform-methanol tissue extract was mixed with water and a lower chloroform phase and an upper methanol-water phase separated either by gravity or centrifugation. To select the appropriate volumes of water a series of cylinders containing a known volume of solvent were lined up, various amounts of water were added, and the mixture that separated into two phases most rapidly was selected.

This extraction and washing procedure was important because it resulted in the quantitative extraction of tissue lipids in a single step and the subsequent removal of water-soluble contaminants in the upper phase; however, the upper phase contained gangliosides (see below). The method was gentle and was carried out at room temperature or below; boiling solvents that might alter the lipids structurally were not required. The same procedure could be applied to any tissue and in amounts ranging from milligrams to hundreds of grams, the only requirement being that solvent proportions had to be kept constant. The method became one of the most highly cited papers of the 1950s, second only to the Lowry procedure for protein analysis. In more recent years scientists have often failed to cite the original reference and Folch periodically indicated his displeasure about that. This omission may be the ultimate compliment in that the procedure had become so standard and well known that there was no need to cite it. Indeed, in laboratories around the world the name Folch was commonly used as an adjective and referred to as the Folch procedure or as a verb (to Folch the tissue meant to extract the tissue as described by Folch, Lees, and Sloane Stanley [1957]).

First and foremost the procedure literally opened up a new era in the field of lipid structure, metabolism, cell biol ogy, and physiology and allowed scientists worldwide to address new questions concerning lipid structure and function. It also provided the foundation for a major part of Folch's subsequent scientific contributions. He used it to examine the changes in brain lipids and proteins during development and in brain pathology, particularly in lysosomal storage diseases. It provided the starting point for experiments that ultimately identified the myelin proteolipid protein as an encephalitogenic agent in an animal model for multiple sclerosis. His pioneering studies in these areas provided insights into the structure and function of myelin.

The procedure was used to address the question of the differences between the composition of brain gray and white matter. Because purified myelin could not be isolated in that era, the best that could be done was to scrape off gray matter and scoop out white matter from the remaining brain to produce gray- and white matter-enriched fractions. Large amounts of sample were required for the subsequent chemical analysis and there were periods when staff members went to the local slaughterhouse almost daily to obtain bovine brains. Everyone —students, technicians, postdoctoral fellows, and scientific staff—spent the day scraping gray matter from the brains using wooden tongue depressors. As one technician commented: "For this I had to go to college?" But, it was worthwhile, because as an outgrowth of these monotonous activities, two classes of components were identified: proteolipids in white matter and water-soluble glycolipids in gray matter. Both were identified as a consequence of Folch's insights and insistence on accounting for everything. Conceptually, his most important finding and the one that had the greatest impact on the understanding of myelin and other membrane proteins was the presence of a new class of ubiquitous "lipoproteins" that he designated proteolipids.

After washed total lipid extracts of bovine white matter were dried and redissolved in chloroform-methanol, a reproducible amount of solids remained insoluble. Most investigators would have viewed this as junk and would have discarded it. The combination of Folch's curiosity and his determination to account for "everything" led him to pursue the observation further. The solids were found to contain a marked excess of nitrogen, and an amino acid analysis indicated a hydrophobic protein with a high content of sulfur-containing amino acids. It became evident that the lipid extracts contained proteins with lipid-like properties (i.e., they could be extracted from the tissue with organic solvents). They were lipoproteins with the reverse solubility properties of the blood lipoproteins and were therefore named proteolipids and affectionately called PLP.

The characterization of proteolipids became a major focus of Jordi Folch's research program. Brain white matter PLP was identified as the major protein of central nervous system myelin, and much effort went into its chemical and physical characterization. Progress was slow because of the tendency of proteolipid proteins to precipitate irreversibly and because of their resistance to proteolytic digestion. Initially it was assumed that the solubility in organic solvents derived from a lipid shell surrounding the protein, but he later showed that all of the free lipid could be removed with retention of chloroform-methanol solubility. The apoprotein, however, still contained 2–3 percent covalently bound, esterified, long-chain fatty acids. Although acylated bacterial and viral proteins had been described previously and shown to have diverse structural and metabolic functions, to the best of our knowledge, PLP was the first acylated protein identified. The relatively rapid turnover of the fatty acid moiety[5] compared to the slow turnover of the protein moiety suggests an important physiological function for the fatty acid. Under appropriate conditions, the protein devoid of lipid was converted from a chloroform-methanol-soluble form to a water-soluble form. This conformational flexibility was associated with a relative decrease in alpha helical structure and an increase in beta structure, properties postulated to have functional significance. The existence of a molecule with these properties was initially greeted with skepticism, but subsequent studies showed it to be the structural prototype for a widely distributed family of membrane proteins referred to as tetraspan proteins and to have properties similar to certain ion-channel proteins.

Chloroform-methanol extracts of gray matter revealed the presence of water-soluble glycolipids. These were identified in the upper phase of gray matter extracts as gangliosides on the basis of the excess amino nitrogen in the upper phase of the washed extracts. Gangliosides had been described previously by the German chemist Ernst Klenk. The gangliosides isolated by Folch were high-molecular-weight, water-soluble glycolipids that crystallized as long strands. Careful chemical analysis showed the presence of fatty acids, sphingosine, carbohydrate, a primary amine, and a chromogenic group later identified as neuraminic acid. Folch realized that he was dealing with either an aggregate or a mixture of closely related compounds, but analytical procedures to differentiate between the alternative possibilities were limited. It was much later that the diverse structures and functions of gangliosides were recognized. Nevertheless, Folch's isolation procedures provided the basis for these later studies and are still widely used for the study of gangliosides. With Folch, one of the authors (M.B.L.) of this memoir, carried out early analyses of tissues from patients with infantile and juvenile Tay-Sachs disease, which not only confirmed the ganglioside accumulation in these diseases but also demonstrated additional lipid abnormalities.

Although Folch is best known for his studies on lipids and proteolipids, his scientific contribution to biochemistry and neurochemistry were remarkably broad and included proteins and disease processes. He was interested in neurokeratin, a protein component obtained by early chemists after subjecting the brain to brutal chemical procedures. To attempt to prepare neurokeratin by mild procedures, he isolated from a chloroform-methanol-insoluble fraction a trypsin-resistant protein fraction (TRPR), which contained phosphopeptides and phosphoinositides chemically bound to protein. Further studies on brain proteins were directed to determining optimal conditions for aqueous extraction. These led to an in-depth study of copper-containing proteins in Wilson's disease that showed the excess protein in Wilson's disease occurred in a different form from the protein in the normal brain.

At the dedication of the new McLean Research Building Folch emphasized the importance of electrolytes in the nervous system. An anion deficit had been reported in the brain, but a role for acidic lipids had not been considered. Folch discovered phosphatidyl serine and polyphosphoinositides, isolated gangliosides, and devoted much time to characterizing sulfatides. These acidic lipids are all in myelin, and he proposed that they could compensate for the low anion levels reported. This hypothesis was supported later when the three major central nervous system myelin proteins were each shown to have high isoelectric points. Thus, in addition to hydrophobic interactions, ionic interactions between these basic myelin proteins and acidic lipids may help to maintain the multilamellar myelin structure. More focused studies were carried out on the effects of specific cations on sulfatides and gangliosides.

Despite these diverse projects, Folch's bibliography is not very extensive by current standards. Each publication was significant, however, and presented new insights and concepts. Data he considered trivial or incomplete were simply filed away. It was well known that Folch had the largest collection of unpublished material of any scientist. His memory was phenomenal, and he never forgot an experiment. Much of the unpublished material survives in the McLean Hospital archives.

A STATESMAN OF SCIENCE

Jordi Folch-Pi is recognized universally as one of the founders of the field of structural chemistry of complex lipids and as a leader in the development of neurochemistry as a distinct discipline within the neurosciences. Folch's arrival at Harvard and McLean corresponded with a time of renewed interest in neurochemistry in the United States and Europe, but it was not as yet viewed as an organized field of study. Over the next two decades, in major part through his leadership, the International Society of Neurochemistry (ISN) and the American Society of Neurochemistry (ASN) were formed. Folch's contributions to these activities have been amply documented in *Journal of Neurochemistry* articles by Herman Bachelard[6] and Donald Tower.[7] The immediate roots of the ISN were traced by Bachelard to a series of biennial International Neurochemical Symposia beginning in the 1950s. Folch presented his landmark studies on the chemical maturation of the brain at the first of these Symposia and served as editor for two of the subsequent symposia. Discussions in the course of these Symposia identified the need for a permanent international forum for neurochemistry, and a provisional organizing committee was formed with Folch taking a lead role in what culminated in the formation of the ISN. He subsequently served as ISN secretary, chairman, program committee chairman (three times), historian, and president of the fifth ISN meeting held in Barcelona, the city of his birth. Concomitant with the beginnings of the ISN, Folch became a founding member of the Committee on Neurochemistry of the World Federation of Neurology and had a leading role in the organization of the ASN. He served as secretary of the organizing committee and subsequently as ASN secretary, president, and councilor. His contributions to that organization can best be summarized by a quote from Tower's history of the ASN: "If any one person were to be credited with having conceived, created, and nurtured the ASN, it would be Jordi Folch-Pi."[7] Other leading scientists were, of course, actively involved and supportive of Folch's efforts, but it was he who sparked others to action and made things happen. The fruits of his role in neurochemistry are perhaps shown by five major neurochemical societies that are now listed on the World Wide Web, along with many smaller local neurochemistry societies.

During Folch's years as Director of Scientific Research at McLean Hospital he built the laboratory rapidly into a world-class research center within the hospital, Harvard, and the greater Boston community. At the McLean Hospital Research Laboratories, Folch not only provided intellectual leadership but also presided over all aspects of its functioning—from recruiting staff to ensuring the correct temperature of the cold room. The force of his personality along with his scientific abilities attracted students, collaborators, and visiting scientists from throughout the world. Folch thoroughly enjoyed working on experiments at the laboratory bench and took every opportunity to work directly with students in the tradition of the old European master-apprentice relationship. This provided an invaluable opportunity for trainees to learn to think about scientific questions, design experiments, and write manuscripts. It is thus not surprising that among the 30 or more trainees who passed through the Biochemical Research Laboratory and were exposed to his influence are scientists who became professors, medical school deans, departmental chairmen, and entrepreneurs.

As a consequence of Folch's able management and personal example of scientific achievements, the resources of the laboratory quadrupled within a decade of its founding, with a ten-fold increase in the professional staff. The next decade brought physical and intellectual expansion with the addition of two new units, along with suitable laboratory space and staff. One, headed by Dr. George Hauser, was established to study dynamic aspects of brain structure and a second unit headed by Dr. J.David Robertson introduced biophysical methods to the study of brain structure. This essentially completed the incorporation of aspects of neurochemistry envisioned at the time of the dedication of the McLean Research Laboratory in 1946.

In addition to building the scientific image of McLean Hospital, Folch's wise counsel was consistently sought in crucial changes at McLean and at Massachusetts General Hospital, of which McLean was a part. He brought to any deliberations in which he participated a clarity of thought and a willingness to articulate an unpopular opinion that was invaluable for decision making. Folch also played an important role at Harvard Medical School, where in 1956 he became the first Professor of Neurochemistry in the Department of Biological Chemistry. Folch was particularly proud of his service at Harvard on the Beecher committee, which had been charged with developing a formal definition of death. He will mostly be remembered by members of the Harvard Medical School faculty for his marvelous blend of integrity, candor, wit, irreverence, and good sense embodied in his comments on key faculty issues—all delivered in idiosyncratically literate, heavily accented, passionate language.

During his illustrious career Folch received many honors. He was elected to the American Academy of Arts and Sciences in 1956 and to the National Academy of Sciences in 1978. He was an honorary professor in the Faculty of Medicine at the University of Barcelona, Spain. He was awarded honorary degrees by the University of Montpelier, France, and by the University of Chile, Santiago. He was one of Spain's most prestigious scientists and the king of Spain, Juan Carlos, presented him with a medal as honorary councilor of the Supreme National Council for Scientific Research.

One cannot conclude a memoir of Jordi Folch without commenting on his personality and his interests outside the scientific domain. Everyone who knew him, be it well or casually, will recall the amazing breadth of his knowledge, his sharp intellect, and the intensity of his opinions. He loved nature, mountain climbing, and skiing, all of which he indulged in passionately. He cultivated the art of conversation and could discuss his views on literature, history, food, or politics with equal knowledge and fervor. After his retirement in 1977 he was Professor of Neurochemistry Emeritus and continued to be active as honorary biochemist at McLean Hospital until his death. On October 3, 1979, after a day of spirited discussions in the laboratory, Folch drove through a thunderstorm and arrived at his Back Bay Boston home. Shortly afterward he was found dead of a heart attack in his chair. It was a loss of a gifted scientist, friend, and mentor, known not only for his contributions to neurochemistry but also loved for his wisdom, humanity, and joie de vivre.

ACKNOWLEDGMENTS

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NOTES

1. We have used Folch-Pi, the Spanish version of the family name, and Folch, the paternal version of the name, interchangeably. Mostly, he used only the latter. During the later part of his life, however, he reverted to the hyphenated name, according to the Spanish convention.

2. Translated by Willa Folch-Pi from an article by J.Folch-Pi: La formacié d'un home de ciencié. *Ann. Med.* 62(1976):623–39, a publication of the Academy of Medical Sciences of Catalonia and the Balearic Islands.

3. D.D.Van Slyke and J.Folch. Manometric carbon determination. *J. Biol. Chem.* 136(1940):509–41. J.Folch and M.Lauren. Estimation of potassium in biological materials as potassium phosphotungstate. *J. Biol. Chem.* 169(1947):539–49.

4. S.E.Abbot. The biological point of view in psychology and psychiatry. *Psychol. Rev.* 23 (1916):117–28.

5. O.A.Bizzozero and L.K.Good. Rapid metabolism of fatty acids covalently bound to myelin proteolipid protein. *J. Biol. Chem.* 266(1991):17092–98.

6. H.Bachelard. 25 years of the International Society for Neurochemistry. *J. Neurochem.* 61 (1993) (suppl.): S287–S307.

7. D.B.Tower. The American Society for Neurochemistry (ASN): Antecedents, founding, and early years. *J. Neurochem.* 48(1987):313– 26.

SELECTED BIBLIOGRAPHY

1941 With H.A.Schneider. An amino acid constituent of ox brain cephalin. *J. Biol. Chem.* 137:51–62.

1942 With D.W.Woolley. Inositol, a constituent of a brain phosphatide. *J. Biol. Chem.* 142:963–64.

Brain cephalin, a mixture of phospatides. Separation from it of phosphatidyl serine, phospatidyl ethanolamine and a fraction containing an inositol phosphatide. *J. Biol. Chem.* 146:35–44.

1948 The chemical structure of phosphatidyl serine. *J. Biol. Chem.* 174:439– 50.

1949 Brain diphosphoinositide, a new phosphatide having inositol metadiphosphate as a constituent. *J. Biol. Chem.* 177:505–19.

1951 With M.Lees. Proteolipids, a new type of tissue lipoproteins. Their isolation from brain. *J. Biol. Chem.* 191:807–17.

With S.Arsove and J.A.Meath. Isolation of brain strandin, a new type of large molecule tissue component. *J. Biol. Chem.* 191:819– 31.

With I.Ascoli, M.Lees, J.A.Meath, and F.N.LeBaron. Preparation of lipide extracts from brain tissue. *J. Biol. Chem.* 191:833–41.

1954 With B.H.Waksman, H.Porter, M.B.Lees, and R.D.Adams. A study of the chemical nature of components of bovine white matter effective in producing allergic encephalomyelitis in rabbits. *J. Exp. Med.* 100:451–71.

1955 Composition of the brain in relation to maturation. In *Biochemis* *try of the Developing Nervous System,* ed. H.Waelsch, pp. 121–36. New York: Academic Press.

1956 With F.N.LeBaron. The isolation from brain tissue of a trypsin-resistant protein fraction containing combined inositol, and its relation to neurokeratin. *J. Neurochem.* 1:101–108.

1957 With H.Porter. Cerebrocuprein I, a copper-containing protein isolated from the brain. *J. Neurochem.* 1:260–71.

With M.Lees and G.H.Sloane Stanley. A simple method for the isolation and purification of total lipids from animal tissues. *J. Biol. Chem.* 226:497–509.

With M.Lees and G.H.Sloane Stanley. The role of acidic lipides in the electrolyte balance of the nervous system of mammals. In *Metabolism of the Nervous System,* ed. D.Richter, pp. 174–99. London: Pergamon Press.

1959 With M.Lees. Studies on the brain ganglioside strandin in normal brain and in Tay-Sachs disease. *AMA J. Dis. Child.* 97(part II):730– 38.

With J.Casals, A.Pope, J.A.Meath, F.N.LeBaron, and M.Lees. The chemistry of myelin development. In *Biology of Myelin.* ed. S.Korey, pp. 122–37. New York: P.B.Hoeber Press.

1961 With M.B.Lees. A study of some human brains with pathological changes. In *Chemical Pathology of the Nervous System,* ed. J. Folch-Pi, pp. 75–82. Oxford: Pergamon Press.

With G.R.Webster. Some studies on the properties of proteolipids. *Biochim. Biophys. Acta.* 49:399–401.

1964 With M.B.Lees and S.Carr. Purification of bovine brain white matter proteolipids by dialysis in organic solvents. *Biochim. Biophys. Acta.* 84:464–66.

With M.Matsumoto and R.Matsumoto. The chromatographic frac tionation of brain white matter proteolipids. *J. Neurochem.* 11:829– 38.

1965 With R.Quarles. Some effects of physiological cations on the behavior of gangliosides in a chloroform:methanol:water biphasic system. *J. Neurochem.* 12:543–53.

1966 With D.Tenenbaum. The preparation and characterization of water soluble proteolipid protein from bovine brain white matter. *Biochim. Biophys. Acta.* 115:141–47.

1970 With G.Sherman. Rotatory dispersion and circular dichroism of brain proteolipid protein. *J. Neurochem.* 17:597–605.

1971 With P.Stoffyn. On the type of linkage binding fatty acids present in brain white matter proteolipid apoprotein. *Biochem. Biophys. Res. Commun.* 44:157–61.

1972 With P.J.Stoffyn. Proteolipids from membrane systems. *Ann. N. Y. Acad. Sci.* 195:86–107.

1976 With J.D.Sakura. Preparation of the proteolipid apoprotein from bovine heart, liver and kidney. *Biochim. Biophys. Acta.* 427:410– 27.

ROBERT HOFSTADTER

February 5, 1915–November 17, 1990

BY JEROME I.FRIEDMAN AND WILLIAM A.LITTLE

ROBERT HOFSTADTER WAS BORN in New York City, educated on the East Coast, but spent most of his academic career at Stanford University. He is best known for his work on determining the distribution of charge and magnetic moment in the nuclei of atoms and of the nucleons themselves, for which he was awarded a Nobel Prize in 1961. He extended the work done in the early part of the twentieth century by Ernest Rutherford, who had shown that atoms were composite, containing electrons and a nucleus many thousands of times smaller than the atom. Rutherford discovered this by scattering alpha particles from thin metal foils of the elements and measuring the number of particles scattered as a function of the angle. The surprisingly large number of particles that were scattered through large angles could only be explained by collisions with a heavy, very small, perhaps point-like, positively charged object, which he called the nucleus.

Some 40 years later Hofstadter determined the internal structure of such nuclei by scattering high-energy electrons from thin targets and measuring the distribution of the number of these electrons as a function of angle. In these experiments he built on earlier work by others on electron-

electron scattering from atoms and electron-nuclear scattering by Hanson, Lyman, and Scott at Illinois done at lower energies in 1951. Hofstadter showed that the nuclei had internal structure extending over a small but measurable distance and that the heavier nuclei had a relatively uniform density within a thin surface skin. The Nobel committee considered this to be the first “reasonably consistent” picture of the structure of the nucleus.

Hofstadter fully appreciated the significance of his work on nuclear structure, but nevertheless said on a number of occasions that he felt his major contribution to science was not this but rather his discovery of the photofluorescence of NaI crystals, activated by thallium, which could be used to measure the energy of X rays and gamma rays. This discovery, which he made in his early thirties, became the pre-eminent way to detect and measure the presence and concentration of radioactive elements for studies in biology and medicine, and such detectors have also been used extensively in particle physics, gamma-ray astronomy, geology and many other areas of science.

Bob was born on February 5, 1915, in Manhattan to Louis Hofstadter, a cigar-store owner and salesman, and Henrietta Koenigsberg and attended public school there before entering City College of New York. He showed exceptional ability in mathematics and physics and was particularly stimulated by the clarity and precision of the teaching of Irving Lowen and Mark Zemansky at City College. Bob graduated with a B.S. degree magna cum laude in 1935 at the age of 20, and was awarded the coveted Kenyon Prize in Mathematics and Physics. He also received a Charles A.Coffin Foundation Fellowship from the General Electric Company, which enabled him to attend graduate school. He chose Princeton University, where he began graduate work in physics. A stipulation of the fellowship was that the recipient should be involved in research even in the first year of graduate study. As a result, Bob was exposed to a number of different projects early in his graduate career. These included experimental work on a Wilson cloud chamber, the study of the infrared spectra of organic molecules, and theoretical work on the development of a new type of mass spectrometer. This research left him little time for his course work, and he felt it interfered with his study of quantum mechanics, which he took from Eugene Wigner, and with his goal of becoming a theorist.

These pressures were eased in his second year, when Bob became an assistant to E.U.Condon, who at that time was writing with George Shortley *The Theory of Atomic Spectra,* a text that was to become a classic in the field. Condon's elegance of thought and expression, his blackboard manner, and his humor made a long-lasting impression upon Bob. But after a brief stint as a theorist calculating energy levels for Condon, he joined R.Bowling Barnes's experimental group in the infrared laboratory. Shortly after this, both Barnes and Condon left the university, and Bob was without an advisor. He completed his master's and Ph. D. degrees the following year, very much on his own, at age 23. His thesis included the determination of the oxygen-hydrogen spacing in light and deuterated formic and acetic acids. This work helped elucidate the nature of the hydrogen bond and earned a footnote in Linus Pauling's book *The Nature of the Chemical Bond.*

Through his association with Barnes and Condon, Bob got to know Frederick Seitz, who had been a student of Wigner's and was a frequent visitor to Princeton. Seitz, who much later became the president of the National Academy of Sciences, invited Bob to spend the summer of 1938 at the General Electric Laboratory to study the photoconductivity of willemite (zinc silicate), a fluorescent compound used in television screens. He accepted this invitation and upon his return to Princeton, with a prestigious Proctor postdoctoral fellowship for the 1938–39 academic year, he worked with Robert Herman, also from the infrared laboratory. Together they discovered crystal warm-up currents in willemite, which established the theory of deep traps in crystals. This work provided the background in solid-state physics that was to become important in Bob's later work on NaI(Tl) scintillation counters and other nuclear detectors.

In 1939 Seitz, who had taken a faculty position at the University of Pennsylvania, invited Bob as a Harrison fellow. Bob took him up on the offer, but joined Louis Ridenour's Van de Graaff group in nuclear physics rather than the solid-state group Seitz had expected him to join. It was not a particularly fruitful time for his research, and in 1941 he moved for one semester to City College of New York. While at the University of Pennsylvania he had established a lasting friendship with Leonard Schiff, who was later to become the chairman of the Physics Department at Stanford and a colleague with whom Bob collaborated extensively in his later work on nuclear structure.

With the entry of the United States into the war in 1941, Bob applied to and was accepted by the National Bureau of Standards in Washington, D.C., for work on the optical proximity fuse. There he worked with Joseph Henderson and Seth Neddermeyer. The optical fuse proved less effective than the radio proximity fuse developed at the Harry Diamond Laboratory. This led Bob to resign from the NBS in the middle of the war and join the Norden Company, which was noted for its success in developing the famous Norden bombsight. There Bob worked on a radar altimeter until the war's end.

Bob's interests went well beyond physics and included among other things an appreciation and enjoyment of classical jazz. It was the sound of this music from his apartment in Philadelphia that first brought him to the attention of neighbor Nancy Givan, who also was a music devotee. Together they enjoyed the jazz scene of New York and Philadelphia, the Apollo Theatre in Harlem, and music and dancing at the Savoy Ballroom. They married in Washington, D.C., on May 9, 1942.

In 1946 Bob joined the Department of Physics and Astronomy at Princeton University as an assistant professor. He began research on means for detecting gamma rays, which he hoped would be useful for work on the Princeton cyclotron. After learning of a scintillation counter using naphthalene developed by Hartmut Kallmann in Germany, Bob used his knowledge of solid-state physics, acquired during his studies at the General Electric Laboratory before the war, to develop a detector using activated alkali halides instead of organic crystals. He found that NaI(Tl) sodium iodide, with a few hundredths of a percent of a thallium compound added, was far more effective in detecting gamma rays than was naphthalene or anthracene. The improvement was due to three factors: the high transparency of the material to its own fluorescent emission; the high density of the NaI relative to the organic materials; and the presence of the high atomic weight element, iodine, which made the compound much more effective in stopping gamma rays. He filed a patent on this for the detection of ionizing radiation in 1948. Two years later Bob and his second graduate student, Jack McIntyre, discovered that sharp gamma ray lines could be seen with this detector, making possible gamma ray spectroscopy with a relatively simple apparatus.

The potential of the new detector attracted the attention of physicists at Berkeley, where Bob and McIntyre had worked during the summer of 1949. Princeton did not of fer Bob a promotion to associate professor; instead, he received two offers from the West Coast, one from Berkeley and another from Stanford, where Leonard Schiff was the chairman of the Physics Department. Bob accepted the Stanford offer of an associate professorship and with his family left Princeton in August 1950 to drive across the country to California. En route to Stanford, he and his wife, Nancy, visited Hilda and Eugene Feenberg at Washington University in St. Louis. There Bob discussed his plans for work at Stanford using his NaI(Tl) crystals for the detection of high-energy electrons and gamma rays, and for studies of electromagnetic showers. In the course of this conversation, Eugene is said to have remarked, “Why not do electron diffraction (on nuclei) like the earlier work on atoms?” This was the stimulus that led Bob to his Nobel Prize work and set his mind working on the design of the spectrometer needed to do it. He learned later that Leonard Schiff, in a Stanford Microwave Laboratory Technical Report, had already proposed in 1949 just such studies of nuclei, including that of hydrogen, by electron scattering.

In his first three years at Stanford, Bob worked closely with Jack McIntyre, who had followed him to Stanford as a postdoctoral fellow, and together they extended the application of scintillation counters to the study of X rays, neutrons, alpha particles, and muons. They also applied these counters to the study of electron showers.

This period was an exciting time at Stanford, for it coincided with the development and the successful completion of the world’s first high-energy electron linear accelerator. This was the result of work initiated by W.Hansen and E. L.Chu on disk-loaded waveguide accelerating structures and by W.Hansen, J.R.Woodyard, and E.L.Ginzton on the linear acceleration of electrons using high-power microwave sources. These high power sources, multimegawatt relativistic klystrons, were developed at the same time by M. Chodorow and other members of the Stanford Microwave Laboratory staff.

Initially the Stanford Mark III accelerator had achieved an operating energy of 180 MeV, and in November of 1953 the energy was raised to 400 MeV. Within a couple of years the accelerator achieved reliable operation at 600 MeV. The availability of this machine at this time gave Bob the unique opportunity to undertake his pioneering work on the structure of the nucleus.

The concept of using high-energy electrons to study the structure of nuclei was simple in principle, but its realization was not. The new accelerator had to be nursed into stable operation with many hours of conditioning prior to each run. The duty cycle of the accelerator was very low, with the particles bunched into short bursts that were well separated from one another. These bursts, with many electrons arriving at the same time, made it impossible to detect the individual particles using NaI(Tl) crystals. Bob realized that he needed a very good double-focusing magnetic spectrometer to separate the elastically scattered particles from those that were scattered inelastically, and to measure their angle of scattering. He adopted the design of a magnet developed earlier by the nuclear physics group at the California Institute of Technology and built one with the help of a $5,000 grant from the Research Corporation and support from the Office of Naval Research. The magnet weighed 2.5 tons, had a radius of curvature of 16", and could focus electrons of energies up to 180 MeV, the maximum energy the Stanford Mark III accelerator could deliver at that time.

The target to be studied was centered in a 20" vacuum chamber through which a filtered and narrowly defined beam of electrons was passed. The filtered beam was pro duced by transporting the primary beam from the accelerator through a two-magnet, double-deflection energy filter that defined the energy to about 3 percent, and separated it from the gamma-ray background. This beam filter had been designed and built earlier by J.MacIntyre and Pief Panofsky.

The scattered electrons exited the chamber through an aluminum foil window, passed through air, and then entered the vacuum chamber of the magnetic spectrometer through another thin foil window. The heavy magnet had to be positioned with great precision. This was done by using a twin 40-mm anti-aircraft gun mount as a base for the magnet; this gun mount was obtained from the Mare Island Shipyard and was lent to him by the U.S. Navy. The very first experiments on gold, the same element Rutherford used to reveal the existence of the nucleus, showed strong deviations from the distribution expected for electrons scattered from a point-like nucleus and indicated that the nucleus had a finite and measurable radius. Measurements on hydrogen nuclei in polyethylene were also made and they, too, showed that even the proton was not a point-like object but had a finite structure. Later studies, made at 188 MeV on a target of hydrogen gas, gave a radius for the proton of about 7×10^{-14} cm.

The structure seen in the distribution of scattered electrons results from the diffraction of the incident electron waves by the charge and magnetic moment of the nucleus. To reveal the nucleus in greater detail, shorter wavelengths were needed, which in turn required higher electron energies. In characteristic fashion, undaunted by the technical details, Bob designed a magnet more than double the linear dimensions of the first, now weighing 30 tons, to accommodate electron trajectories with a radius of curvature of 36". This was built by Bethlehem Steel and, together with a 10-ton shield, was mounted on a larger, double 5" anti-aircraft gun mount, which again was provided by the Navy. This magnet could focus electrons of energy up to 510 MeV. At this time, in late 1955, the Mark III accelerator had been upgraded and operation at 600 MeV had been achieved. Bob and his postdocs and graduate students completed the next series of studies with this spectrometer, and these revealed the structure of various nuclei and of the nucleons in greater detail.

In the next two years, the length of the Mark III accelerator was increased another 90 feet, and with the addition of more klystrons, the accelerator achieved an energy of 1 GeV in 1960. Bob designed yet another double-focusing spectrometer, this one 200 tons in weight with a radius of curvature of 72", which could focus and analyze 1-GeV electrons.

It was during the late 1950s that we first met Bob, and we remember being deeply impressed by the bold manner in which he made the transition from the first 16", almost tabletop spectrometer to this 200-ton behemoth. It was in a similar manner that he made a suggestion in 1954, while sitting in the Schiffs' living room with Felix Bloch, Ed Ginzton, and Leonard Schiff, to build a multi-BeV (GeV) linear accelerator at Stanford. This he wanted in order to provide electrons of shorter wavelength to probe still deeper into the nucleon. He believed that the transition to these energies was simply a matter of engineering. To him the need was clear. His suggestion was followed up shortly thereafter by the formation of a study group that ultimately led to the establishment of the Stanford Linear Accelerator Center (SLAC) and the construction of the two-mile accelerator under the direction of Professor Wolfgang "Pief" Panofsky, which achieved a beam energy of 20 GeV in January of 1967.

The award of the 1961 Nobel Prize in physics to Hofstadter, which he shared with Rudolf Mössbauer, recognized Hofstadter's work that had revealed the structure of nuclei and nucleons and the manner in which he had done the crucial experiments. His citation recognized "the precision [that Hofstadter attained] that has scarcely been attained before in high-energy physics…. You have achieved this precision by improving unrelentingly your methods and equipment in the course of time." The saga of the development of the magnetic spectrometer described above was but one of these items; in addition, beam position control, beam intensity, extraction of an essentially mono-energetic beam from the accelerator, and control of the spectrometer magnetic-field strength all played a critical role in achieving this precision.

As Bob acknowledged some years later, this period in the 1950s was an extraordinary one, one in which he and his small group, with excellent support from the Office of Naval Research, had a virtual monopoly of the field of nucleon and nuclear structure. Further, it provided the basis for his belief, which he defended strongly in subsequent years, that high-energy and elementary-particle physics could be done effectively by small groups, not necessarily by the huge collaborative kinds of teams that we see today. In this he was bucking the trend towards "big science." However, much later he is said to have conceded that this trend towards big science was inevitable and that the halcyon days of the 1950s were unlikely to be seen again in this field.

Early in the 1960s I (W.A.L.) had the good fortune of seeing for myself the way Bob approached obstacles. Stanislav Safrata, Bob, and I were collaborating on an experiment to measure directly the shape of the heavily deformed Ho^{165} nucleus by electron scattering. A large magnetic field had to be applied to a single crystal target of holmium metal to switch it from the antiferromagnetic to the ferromagnetic state. This would align the internal field of the 4f electrons with the applied field, which at low temperatures would align the nucleus itself. The target needed to be held at a few tenths of a Kelvin in the beam of the accelerator. We considered adiabatic demagnetization of a paramagnetic salt as a means to produce these temperatures, but Stan and I were discouraged when we realized just how large was the thermal load from the beam. We spoke to Bob about this, and his immediate response was to say, "Why not use 100 kilograms of the salt? That should be enough!" We were bowled over, for neither Stan nor I had ever thought in such terms. Prior to this, samples of 100 grams or less had been used in cryostats familiar to us. On further consideration, we saw that it was indeed entirely feasible to do it in this way. We had just never thought on such a scale! As it turned out, He^3 became available in sufficient quantities a short time later and this enabled us to use instead a simple He^3 cryostat for the experiment, and the large demagnetization cryostat was, in fact, never built. This illustrated the way Bob approached a problem: He thought nothing of proposing a cryostat a thousand times larger than had ever been considered before, just as he had proposed a two-mile accelerator, many times the length of the Mark III accelerator, because higher energies were needed to see the details of the nucleon. The engineering challenges that would have to be overcome to accomplish these aims never discouraged him.

Bob was elected to the National Academy of Sciences in 1958 and named California Scientist of the Year in 1959. He received many other awards, including the Roentgen Medal in 1985, the U.S. National Medal of Science in 1986, and the Prize of the Cultural Foundation of Fiuggi (Italy).

A decade later, experiments at SLAC using much higher energies employed electrons to probe the nucleon as Hofstadter did. Instead of utilizing the elastic process these experiments studied inelastic scattering from the proton and neutron and provided the first direct evidence of the presence of point-like quarks within the nucleons. The award of the 1990 Nobel Prize to Friedman, Kendall, and Taylor[1] recognized this work. Bob was very pleased to learn of this award, only weeks before the end of his life.

During the 1950s changes began to occur in the academic environment that were of great concern to Bob. Government funding of research was increasing, and many universities saw in it the opportunity to expand their faculties by the use of such "soft money" to offset faculty salaries during the academic year. Stanford was among them. Bob and many of his colleagues in the Physics Department were strongly opposed to this, fearing that it would result in an over-expansion of the university, that individuals would be beholden to the government for their jobs, and that it might lead to charges that the university was gouging the government. Also it was feared that it would result in expansion only in areas for which funding was available and a reduction in the support of basic research in other areas. But others within the faculty welcomed it and saw in it the possibility of creating a much larger department with a broader range of offerings. This difference in viewpoint eventually led to a split within the Physics Department, and the creation of a Division of Applied Physics at Stanford that was partially supported by government funds. Many years later, when government support of research diminished, much of what had been feared came to pass. The university was obliged to re-absorb the additional faculty and to re-allocate teaching. Even though agency support had always played a vital role in his research, Bob believed as a matter of principle that the university's role was the support of teaching and the full support of its faculty, and that this was not the business of government.

He was also opposed to a requirement that emerged, as more government funds came to the universities, that all faculty, students, and staff involved in research should assign to the university all rights, title, and interest related to inventions that they might conceive in their research. He felt again, on principle, that this was not something in which the university should be involved and that it was an interference in the rights of an individual. Eventually, this requirement did become mandatory, and the few who had objected to it ultimately conceded that the fight had been lost.

The coming of SLAC to Stanford raised a number of problems for the university. It was recognized early that a two-mile accelerator was too large to be accommodated within the Physics Department and that an independent university entity would have to be established for it. This was to become the Stanford Linear Accelerator Center (SLAC), a high-energy laboratory funded by the Atomic Energy Commission and later by the Department of Energy.

The presence of SLAC raised the concern that the availability of funds to support the appointment of high-energy physicists at SLAC would result in the university creating fewer positions for appointments in other areas of physics. Bob, although a high-energy physicist, thought that these funds should not be permitted to distort the offerings of the department.

Another issue revolved around the proposed use of the professorial title for SLAC appointments. Bob and others thought that such titles were inappropriate, for they would imply a teaching responsibility, something that was considered to be entirely within the jurisdiction of the Physics Department. On the other hand, Wolfgang Panofsky and

Sidney Drell, who had resigned from the department to become director and head of the Theory Group at SLAC, respectively, thought that, in order to be able to hire the best, such titles were essential.

Related to this was the concern that the existence of a large number of persons of professorial rank at SLAC would result in an inordinately large demand for graduate students. This could result in the Physics Department becoming a service department that would only provide undergraduate teaching and the first two years of graduate teaching for students, the bulk of whom would go on to work at SLAC. Bob worried about this and argued for limits on the number of SLAC faculty, as well as for departmental control of graduate admissions and all aspects of the teaching of physics.

These were some of the difficulties that arose as the transition was made between the regime of the individual investigator in high-energy physics, characterized by Bob's earlier work, and today's big science, which requires large facilities in which hundreds of individuals participate in research projects. The effect of these repercussions was that Bob played a much smaller role in SLAC than might have been expected, considering his interests, his original proposal, and that the accelerator was at his own backdoor. As a consequence, Bob's interests turned to other areas of physics, to which he made several other significant contributions. This was exemplified by his development of a new class of high-energy detectors, detectors for gamma-ray astronomy, and the application of high-energy physics techniques to medicine.

Bob's belief that the study of elementary particles would require the precise measurement of high-energy gamma rays led him to consider the use of large crystal detectors for this purpose. It became apparent to him that there was virtually no limit to the highest energies that these devices could detect. The reason is that high-energy electrons, positrons, or gamma rays produce a shower of charged particles and gamma rays, all of which can be absorbed in a crystal of quite modest size, irrespective of the initial energy. The intensity of the resultant pulse of light emitted by the crystal from all these shower particles is then directly proportional to the energy of the incident particle. The resolution attainable in the GeV range is of the order of 1 percent, providing precision spectroscopy in this energy range. The size of a crystal necessary to absorb 95 percent of the incident energy for such a total absorption shower cascade (TASC) detector can be shown to increase only logarithmically with the incident particle energy. The significance of this can be appreciated when compared with the magnetic spectrometer used by Bob in his earlier studies of the nucleons. There the linear dimensions of the magnet scaled with the energy of the scattered electrons. This, as we saw earlier, led to the requirement that the weight of the magnet scaled with the cube of the energy! Therein lies the advantage of the TASC detector. These TASC and related TANC (total absorption nuclear cascade) detectors for strongly interacting particles have made possible precision spectroscopy in the 100-GeV energy range. As with Bob's work on electron scattering, the concept here was simple, in that the size of the detector scaled logarithmically with energy, but the reduction to practice was not simple. It required, in particular, the development of a new technology for the fabrication of very large crystals of high clarity and the means for preparing these crystals in complicated, space-filling forms to make this happen. Bob described, in a fascinating personal account (1975), the development of these counters and the impressive role that scintillation counters of all types have played in high-energy physics.

One such detector, the "Crystal Ball," developed at Stanford and SLAC was built of a large number (672) of tapered prisms of NaI(Tl) assembled in the form of a 42-inch-diameter hollow sphere. This was used at the Stanford positron-electron accelerator ring (SPEAR) to measure the energy of the gamma rays resulting from the decay of charmonium, which is a meson consisting of a charm quark and antiquark.

Another detector based on the same total absorption principle was incorporated in the Energetic Gamma-Ray Experiment Telescope (EGRET), a NASA project for which Bob was one of the principal investigators and in which Barrie Hughes, a long-time associate and friend, also played a major role. Bob had a long-standing interest in spacebased gamma-ray astronomy. He realized that much of the nuclear physics of stellar objects, details of element synthesis, the formation of nebulae, and theoretical models of supernovae could be studied by gamma-ray spectroscopy from an orbiting satellite. Gamma rays suffer very little absorption and scattering in space and, as Bob pointed out, they travel in straight lines and thus reveal their sources, in contrast to cosmic rays, which, being charged particles, are deflected by magnetic fields or scattered by interstellar dust. EGRET was launched on the Compton Gamma Ray Observatory on April 5, 1991, only a few months after Bob's death. It has provided an unprecedented view of the gamma-ray sky and data on enormously energetic gamma-ray bursts. EGRET has now become a NASA observatory class facility accessible to the entire international astrophysics community.

Bob took a strong interest in the application of high-energy physics techniques to medicine. Extensive use had been made of NaI(Tl) detectors in this field, but in collaboration with Edward Rubenstein of Stanford's Medical School and Barrie Hughes, Bob developed a minimally invasive angiography using synchrotron radiation. The method uses the peripheral venous injection of a minute amount of iodine contrast agent that works its way to the heart. By selecting radiation with an energy on either side of the iodine K-edge and digitally subtracting the two images, they were able to image the arterial system of the heart without interference from absorption by bone or tissue. The exceptionally intense beams of X rays that are available from electron storage rings made this dichromatic subtraction technique practical. In recognition of his many contributions to medical science, Hofstadter was elected to the Institute of Medicine in 1984.

Over the years Bob participated in numerous studies for the government on technological problems of importance to the military. He also testified before the House of Representatives Committee on Science and Astrophysics and the House Science and Technology Committee. He also consulted for KMS Fusion, Inc., on laser fusion, and has described in a simple and elegant manner the progress in this field (1976).

In the early 1950s Hofstadter and Panofsky participated in what is now known as the Screwdriver Report. This study was so named because J.Robert Oppenheimer, when asked in congressional testimony how to detect a nuclear weapon smuggled in a box across a U.S. border, answered, "With a screwdriver!" Bob and Pief were asked by the Atomic Energy Commission to analyze general methods for determining what was inside a crate or suitcase either by passive radiation measurements or by measuring any induced emission resulting from the irradiation of the container with an accelerator or radioactive source.

Bob taught many of the large freshman classes at Stanford, and his students still recall with joy his many demonstrations and his meticulous presentations of the principles of physics. He enjoyed the interaction with his students, both undergraduate and graduate, and with his research colleagues. He felt strongly about the importance of teaching, education, academic freedom, the rights of the individual, and the broader aspects of government. His views on these and other subjects can perhaps best be described in words that Hanoch Gutfreund originally used[2] to depict Albert Einstein's opinions on a variety of public, political, and moral issues, which were "bluntly expressed, controversial, often considered simpleminded and naive, [but] his positions nevertheless had a significant impact." This was very much the way it was with Bob. You always knew where he stood on such issues, and he had little taste for those promoting expediency or compromise.

The Hofstadters had three children: a son, Douglas, and two daughters, Laura and Mary. Douglas obtained his Ph.D. in physics in 1975 from the University of Oregon with a thesis describing the behavior of electrons in crystals in high magnetic fields, effects that are closely related to the quantum Hall effect. Doug, a professor of cognitive science at Indiana University, won the Pulitzer Prize for non-fiction in 1980 for *Gödel, Escher Bach: An Eternal Golden Braid,* an enormously stimulating book linking concepts of mathematics, art, and music, and he is also well known for his contributions to *Scientific American*. Laura, too, is a writer and has written extensively on the medical field.

My wife and I (W.A.L.) have fond memories of occasions spent with Nancy, Bob, and their family celebrating some of the high points of our lives over the past 35 years, and sharing some of the low. I remember their angst over the war in Vietnam but also the sparkle in Bob's eye on acquiring some critical equipment for his laboratory.

Early in the 1960s Nancy and Bob bought a 700-acre ranch in northern California, off Highway 5 near Red Bluff in the foothills of the coast range. There they kept horses and cattle and later raised pedigreed cattle and managed 40 acres of olive trees. This they did in such a seamless fashion that many of Bob's colleagues had no idea that on many a weekend he lived a different life away from the laboratory, a farmer at home on the ranch!

The Hofstadters had a long and happy marriage, punctuated with periods of great joy, but also, especially in the early years, with periods of worry and financial difficulty. They enjoyed living on Stanford's campus. They were strong supporters of the Stanford basketball and football teams and seldom missed a game. Theirs was a beautiful home enriched with flowers, music, art, and memorabilia of their travels. We, and many of the Stanford community, enjoyed the hospitality of their home and the pleasure of conversation with them, their family, and their guests from around the world.

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NOTES

1. Jerome I.Friedman and Henry W.Kendall, Massachusetts Institute of Technology, and Richard E.Taylor, Stanford Linear Accelerator Center, Stanford University, "for their pioneering investigations concerning deep inelastic scattering of electrons on protons and bound neutrons, which have been of essential importance for the development of the quark model in particle physics."

2. Remarks by H.Gutfreund in *Einstein's 1912 Manuscript on the Special Theory of Relativity*. Jerusalem: Israel Museum, 1996.

SELECTED BIBLIOGRAPHY

1938 Vibration spectra and molecular structure. VI. Infrared absorption spectrum of heavy formic acid. *J. Chem. Phys.* 6(9):540–43.

1941 With R.C.Herman. Photoconductivity of a natural willemite crystal. *Phys. Rev.* 59:79–84.

1949 The detection of gamma rays with thallium activated sodium iodide crystals. *Phys. Rev.* 75:796–810.

1950 With J.A.McIntyre. Measurement of gamma-ray energies with one crystal. *Phys. Rev.* 78:617–19

With J.A.McIntyre. Measurement of gamma-ray energies with crystals of NaI(Tl). *Phys. Rev.* 80:131.

1952 Means for detecting ionizing radiation. U.S. Patent 2,585,551.

1953 With A.Kantz. Electron-induced showers in copper. *Phys. Rev.* 89:607–17.

With H.R.Fechter and J.A.McIntyre. High energy electron scattering and nuclear structure determinations. *Phys. Rev.* 92:978–87.

1954 With A.Kantz. Large scintillators, Cerenkov counters for high energies. *Nucleonics* 12(3):36–43.

1955 With R.W.McAllister. Electron scattering from the proton. *Phys. Rev.* 98:217–18.

With J.H.Fregeau. High energy scattering and nuclear structure determinations. III. Carbon-12 nucleus. *Phys. Rev.* 99:1503–1509.

1956 The atomic nucleus. *Sci. Am.* 195:55–68.

Electron scattering and nuclear structure. *Rev. Mod. Phys.* 28:214– 54.

1958 With F.Bumiller and M.R.Yearian. Electromagnetic structure of the proton and neutron. *Rev. Mod. Phys.* 30:482–97.

1961 Shower detectors. In *Methods of Experimental Physics in Nuclear Physics,* eds. L.Yuan and C.S.Wu, pp. 652–68. New York: Academic Press.

With others. Electromagnetic form factors of the proton. *Phys. Rev.* 124:1623–31.

1963 *Electron Scattering and Nuclear and Nucleon Structure. A Collection of Reprints with an Introduction.* New York: W.A.Benjamin.

1967 With others. Scattering of fast electrons by oriented Ho^{165} nuclei. *Phys. Rev. Lett.* 18:667–70.

1968 With E.B.Dally. A high-energy gamma-ray detector with good resolution. *Rev. Sci. Instrum.* 39:658–59.

1969 New detectors for high-energy physics. *Science* 164:1471–82.

1975 Twenty-five years of scintillation counting. *IEEE Trans. Nucl. Sci.* 22:13–25.

With others. Large NaI(Tl) crystals as high resolution spectrometers in high energy physics and gamma-ray astronomy. *IEEE Trans. Nucl. Sci.* 22:286–91.

1976 Laser fusion. *IEEE Trans. Nucl Sci.* NS-24:33–47.

With others. Performance of large, modularized NaI(Tl) detectors. *IEEE Trans. Nucl. Sci.* NS-24:264–69.

1983 The application of synchrotron radiation to non-invasive angiography. *Nucl. Instrum. Methods* 208:665–75.

MARY ELLEN JONES

December 25, 1922–August 23, 1996

BY THOMAS W. TRAUT

FOR ALMOST 50 YEARS Mary Ellen Jones was actively engaged in research related to amino acid metabolism and pyrimidine nucleotide metabolism. In collaboration with Leonard Spector she was a codiscoverer of carbamoyl phosphate, a compound essential for the biosynthesis of arginine and urea, and also for the biosynthesis of pyrimidine nucleotides. The discovery of carbamoyl phosphate was truly significant, as it rapidly influenced research in many other laboratories. An indicator of its importance is that within a few years it became commercially available. By the early 1970s she was among the first to define the new area of multifunctional proteins with her studies of dihydroorotate synthase (also called CAD) and UMP synthase. Jones continued to demonstrate talent for devising new analytical procedures, for cleverly designing experimental approaches, and for insightful analyses of the emerging information.

Jones was the first woman scientist to hold an endowed chair at the University of North Carolina and the first woman to become a department chair at the medical school. Jones was widely recognized for her scientific accomplishments and for her leadership roles. Among her awards were the Wilbur Lucius Cross Medal from Yale University (1982), the North Carolina American Chemical Society Distinguished Chemist (1986), the Thomas Jefferson Award from the University of North Carolina (1990), and the Award in Science awarded by the state of North Carolina (1991). She was elected to the Institute of Medicine (1981), the National Academy of Sciences (1984), the American Association of Arts and Sciences (1991), and the American Philosophical Society (1994). She was very active in the affairs of the Biochemistry Division of the American Chemical Society. She was frequently elected to preside over national organizations: president of the Association of Medical School Departments of Biochemistry in 1985, president of the American Society for Biochemistry and Molecular Biology in 1986, and president of the American Association of University Professors in 1988. Her final honor was to have an 11-story research center dedicated with her name at the University of North Carolina.

Mary Ellen Jones was born on December 25, 1922, in La Grange, Illinois, one of four children of Elmer and Laura Klein Jones. She received an undergraduate degree at the University of Chicago in 1944, having majored in biochemistry. Lacking financial support, she delayed her graduate school career for four years while working full time and saving for her future. She entered Yale University in 1948 and soon began to see enzymology as most intriguing. She completed her dissertation studies in 1951, under the direction of Joseph Fruton.

Her earliest scientific training began at Armour and Company, where she worked half time during her undergraduate school years. After graduation from the University of Chicago, she remained at Armour until 1948. Initially she worked as a bacteriologist in quality control before becoming a research chemist.

At Armour she met Paul Munson, who then was director of the research laboratory. With Munson she would do her first research on androsterone and monopalmitin, leading to two publications in the *Journal of Biological Chemistry*. Jones and Munson were married in 1948, and had two children: Ethan V.Munson (born 1956), currently an associate professor of computer science at the University of Wisconsin-Milwaukee, and Catherine Munson (born 1960), currently a psychiatrist in Charlotte, North Carolina. Jones would later reminisce about how she and Munson had agreed to maintain a dual-career family. To make this possible they would dedicate one salary to obtain help for household work and childcare, enabling Jones to be a parent while continuing as a productive scientist.

When Paul Munson became an assistant professor of pharmacology at Yale, Jones was able to begin graduate studies at that university in 1948. She did her dissertation research under the supervision of Joseph Fruton, completing her studies in only three years while characterizing the catalytic properties of cathepsin C.Fruton was a very helpful mentor and instilled in her the paradigms for good experimental design.

When Munson moved to Boston in 1951, Jones was able to find a postdoctoral position at the Massachusetts General Hospital, with Fritz Lipmann with whom she worked until 1957. By 1957 Jones had two papers published while she was a technician, two more from her graduate studies at Yale, plus another nine papers from her work in the Lipmann laboratory. This productivity enabled her to become an assistant professor in the newly established graduate Department of Biochemistry at Brandeis University in 1957, where she became an associate professor by 1960. When Paul Munson was offered the chair of pharmacology at the University of North Carolina at Chapel Hill in 1966, Jones relocated to that campus in the Department of Biochemistry, where she became professor in 1968.

The move to North Carolina was not easy. By 1965 she had developed a very active laboratory at Brandeis and had become well established in her field. The biochemistry department in Chapel Hill had not been seeking a new faculty member because of a lack of space. Jones therefore found herself located in the basement of a building in the zoology department, a space that was not designed for laboratory research and was also isolated from her new home department. Reminiscing about this time in later years, Jones would note a few unhappy elements of her new situation, but she would normally follow this with a chuckle while emphasizing how she and her new laboratory associates found ways to triumph over their circumstances.

After divorce from Paul Munson a few years later, Jones moved to Los Angeles in 1971, where she worked at the University of Southern California School of Medicine for seven years. In 1978 she returned to the Department of Biochemistry at the University of North Carolina as chair. She led the department until 1989, and she continued active research until the spring of 1995. Unfortunately, her retirement—planned almost two years earlier—came only a few months after she was diagnosed with cancer of the esophagus. She was barely able to initiate her retirement plans for moving to New Mexico, occupying a newly built house and resuming her love for painting. After less than two months she abandoned her new retirement to return to Boston, where she spent her last year as a recipient of vigorous chemotherapy. She died in Waltham, Massachusetts, on August 23, 1996.

Mary Ellen Jones was an energetic and almost tireless worker, highly flexible, and yet very focused. These qualities are important for maintaining an active, independent scientific laboratory, especially while being a department chair who continued very much to be concerned with the current well-being and future development of her department. Given her special circumstances as a developing scientist, these personal traits were essential. She was an ardent supporter of all her students and postdocs, and she continued to be a lifelong advocate for women in science and for minorities in general.

THE EARLY YEARS WITH LIPMANN

Jones's productive three years as a graduate student at Yale had prepared her for enzymology, and she always maintained that each enzyme "develops a character uniquely its own." She had been absolutely delighted to start in the Lipmann laboratory, as she had seen Lipmann's recent work on the importance of high-energy phosphate bonds as truly exciting. This assessment of Fritz Lipmann would be shared two years later by the committee awarding him the Nobel Prize for medicine and physiology in 1953. In the Lipmann laboratory she would study how coenzyme A became activated and would become familiar with the use of ATP to activate biosynthetic molecules. Her initial triumph in this period was the unexpected demonstration that pyrophosphate, rather than orthophosphate, was the direct product in the action of acetyl-CoA synthetase (1953). This was a novel demonstration of ATP being involved in a reaction other than the well-known phospho-transfer reaction. Jones and Lipmann correctly hypothesized that the reaction mechanism involved an enzyme-adenylate intermediate. When some years later DNA polymerase was first being characterized by Arthur Kornberg and his colleagues, they would observe a similar reaction with a pyrophosphoryl cleavage of the nucleotide precursors, thereby helping to establish the general nature of the mechanism described by Jones and Lipmann.

Lipmann proved to be a good mentor, and Jones often mentioned how he coached his postdocs and students to look at all possibilities and to ever be flexible.

Jones's major scientific direction was determined in 1955, when she and Leonard Spector deduced that carbamoyl phosphate should be the most likely agent involved in the synthesis of citrulline from ornithine (see Figure 1). She sometimes spoke of those early exciting days when she and Spector discussed and explored the most plausible structure for the mysterious compound that had to be an intermediary in joining with ornithine to form citrulline. The difficulty then was to actually synthesize carbamoyl phosphate so as to test its possible function. Jones has recounted how Spector was at an early concert of Debussy's *Afternoon of a Fawn*. While the music was compelling, and his date was very attractive, his mind returned to the synthesis of carbamoyl phosphate. A simple strategy for using cyanate with lithium phosphate occurred to him and he dashed back to the laboratory right after the concert. Before mid-night he would have crystals of carbamoyl phosphate.

Then Jones demonstrated that liver cell extracts converted it to citrulline (1955). The cellular biosynthesis of carbamoyl phosphate and its subsequent utilization were rapidly pursued by a number of laboratories. The central position of this compound is depicted in Figure 1, as are the many enzymes involved in the formation or utilization of this metabolite that were subsequently investigated by Jones. Jones and Lipmann then demonstrated that carbamate was first formed from bicarbonate and required ATP (1960). By including the enzyme carbonic anhydrase, they were able to demonstrate that bicarbonate was the immediate substrate for the carboxy phosphate step in the synthesis of carbamoyl phosphate.

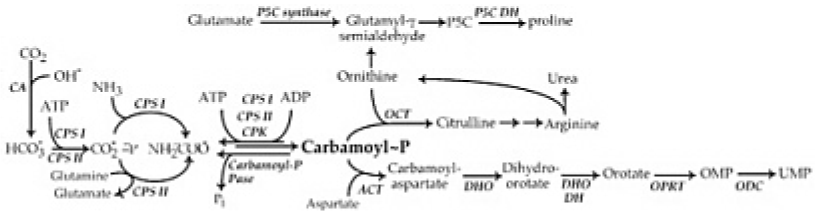


FIGURE 1 Metabolic pathways studied by Mary Ellen Jones. All the enzymes identified were studied by her group: ACT, aspartate carbamoyltransferase; carbamoyl-P pase, carbamoyl phosphate phosphatase; CA, carbonic anhydrase; CPK, carboxyphosphate kinase; CPS, carbamoyl phosphate synthetase; DHO, dihydroorotase; DHO DH, dihydroorotate dehydrogenase; OCT, ornithine carbamoyltransferase; ODC, OMP decarboxylase; OPRT, orotate phosphoribosyltransferase; P5C synthase, pyrroline-5-carboxylate synthase; P5C DH, pyrroline-5-carboxylate dehydrogenase.

As depicted in Figure 1, carbamoyl phosphate is directly involved in joining with aspartate for the synthesis of the pyrimidine base orotate, or in linking with ornithine to form citrulline. This latter reaction was the original focus of research during her years with Fritz Lipmann. Because ornithine is also utilized in the synthesis of proline, defining this pathway also became a challenge for Jones. Her first studies on pyrimidine biosynthesis began shortly thereafter.

Today we know that at least three enzymes can synthesize carbamoyl phosphate. In 1955 it was completely unclear as to whether the synthesis began with the formation of carboxyphosphate and whether this came from bicarbonate or from a carboxyl group on an amino acid, because it was already established that N-acetyl-glutamate was a necessary factor in the synthesis of citrulline. Furthermore, with bacterial extracts it appeared that either ammonia or glutamine could serve as a nitrogen donor. Jones appreciated that the utilization of ammonia in bacterial cell extracts might not be physiologically relevant. Earlier studies with liver extracts had clearly demonstrated that incorporation of ammonia into urea was an important function, and this pathway presumably required the same carbamoyl phosphate synthetase. For almost 10 years there would be uncertainty and confusion about why two ATP molecules were needed for the synthesis of carbamoyl phosphate, what the true nitrogen source was, and whether there was more than one carbamoyl phosphate-synthesizing enzyme in any specific cell or tissue. By 1967 this was largely settled, and Mary Ellen Jones had been pivotal in clarifying the most important details in Figure 1.

In her subsequent career she would pursue both the amino acid metabolism shown in Figure 1 and all the enzymes in the pyrimidine pathway. She would thus become an authority in these two areas of metabolism, publishing a major review on amino acids (1965) and then on pyrimidine biosynthesis (1980). Instead of looking at her career chronologically, it will be more understandable to explore her separate research areas.

A YOUNG INDEPENDENT INVESTIGATOR STUDYING PYRIMIDINE BIOSYNTHESIS IN EUKARYOTES

Having established the existence and function of carbamoyl phosphate while in the Lipmann laboratory (1955), Jones and Spector (now at Brandeis) established that carbon dioxide or bicarbonate was the direct source for the initial activation step leading to carboxy-phosphate (1960). The focus in these early years was completely on the synthesis of citrulline and arginine, and the assay being used always measured the incorporation of bicarbonate plus ammonia as the cosubstrate. The product being measured was citrulline, detected by the only method then available, a colorimetric assay that was convenient but not very sensitive. To assure that formation of citrulline was not limited by the lack of a cellular ornithine carbamoyl transferase (OCT), this enzyme, purified from *S. faecalis,* was always added to the assay.

The Jones group then observed that, of 18 rat tissues, only the liver contained abundant carbamoyl phosphate synthetase activity, while it was barely detectable in kidney and intestine (1961). Equally important was their finding that this activity was localized in the mitochondrial fraction. This result caused some concern as to how most cells were able to synthesize pyrimidines, since carbamoyl phosphate was clearly implicated in that pathway, and since all cells were expected to synthesize nucleotides. In reviewing this subject (1963), Jones for the first time speculated about the existence of two carbamoyl phosphate synthetases: one enzyme in liver using ammonia and a second enzyme dependent on glutamine.

The significant breakthrough came with the next four papers reporting work done with Sally Hager. The incorporation of ^{14}C-bicarbonate by whole cells into possible products was a much more sensitive assay. For the first time they could infer a glutamine-dependent carbamoyl phosphate synthetase activity in mouse tumor cells by readily measuring ^{14}C-bicarbonate incorporation into carbon 2 of uracil (1965). This experimental design was excellent, as it combined a tissue source likely to have higher enzyme levels (tumors consume nucleotides more steadily) with a more sensitive enzyme activity assay. Her laboratory had already established that carbamoyl phosphate is not detectable in fresh blood from rabbits, thereby excluding the liver as the unique source for this compound to be used by other tissues. Therefore Jones now proposed the likelihood that there were two separate carbamoyl phosphate synthetase isozymes, one requiring ammonia for the synthesis of arginine or urea and a second enzyme requiring glutamine for the synthesis of orotate. It simply remained for her group to prove this.

In the following year Jones and Hager reported the first isolation of the glutamine- dependent carbamoyl phosphate synthetase from cytoplasmic extracts of Ehrlich ascites cells and from rat liver (1966). The critical factor impeding earlier efforts was now apparent with their demonstration that the enzyme was extremely unstable. With customary resourcefulness, they had developed an improved purification strategy in which they used a substrate, ATP, to stabilize the enzyme, and this now allowed them to characterize the enzyme. Thereby, they now could explain the fact that this enzyme had never been detected in mammalian cells previously. Their paper was the first to actually demonstrate the existence of carbamoyl phosphate synthetase II. This important achievement was followed with a detailed presentation of the new isolation procedure devised to maintain the enzyme in a more stable form (1967,1). The addition of ATP to the homogenization buffer had a dramatic effect on maintaining the enzyme activity during several purification steps. They showed that the enzyme has a high affinity for glutamine as the nitrogen donor, but shows a modest and unphysiological activity with ammonia. This paper helped to clarify some of the earlier confusion between the two separate sources for nitrogen.

The subsequent paper in the same year again showed a keen sense for experimental design. Jones and Hager used fetal rat liver as a source for the enzymes, since it was clearly evident that liver should have the ammonia-dependent CPS, but could well have the glutamine-dependent CPS in addition. They therefore used their new isotope assay to measure activity with either ammonia or with glutamine as the nitrogen source. In addition, they carefully fractionated the fetal liver extracts by centrifugation to prepare a mitochondrial fraction and a cytoplasmic supernatant fraction (1967,2). The results produced one of those occasions where the light goes on and all becomes clear. Fetal liver had two carbamoyl phosphate synthetase activities, now designated as CPS I and CPS II. CPS I is only in the mitochondrion and preferentially utilizes ammonia in the formation of citrulline by the enzyme ornithine carbamoyltransferase (OCT). CPS II is in the cytoplasm and only uses glutamine for the formation of carbamoyl-aspartate by the enzyme aspartate carbamoyl transferase (ACT).

These results truly helped to resolve the existing confusion in this field. It was becoming evident that bacteria had but a single CPS enzyme, whose product —carbamoyl phosphate—was used for either arginine or for pyrimidine synthesis. In contrast, rats (and presumably other higher eukaryotes) had evolved two CPS enzymes and had physically separated the synthesis of urea (only in mitochondria, and mostly in liver) and the synthesis of orotate or UMP (only in the cytoplasm, and presumably in all cells). The significance of this was that mammals could now have separate control of the initial metabolic step for either of the two pathways by having the respective enzymes in separate subcellular compartments. The work in these last three papers, largely completed at Brandeis, must have been a real boost for Jones, as they were published just as she was reestablishing her laboratory in Chapel Hill.

ASPARTATE CARBAMOYLTRANSFERASES IN BACTERIA

By the mid-1960s the Jones group had devised a procedure to synthesize ^{14}C-carbamoyl phosphate. This increased the sensitivity by twenty-fold for measuring the activity of aspartate carbamoyltransferase with carbamoyl phosphate as the varied substrate. Initially working with the *E. coli*

ACT, an enzyme already well characterized by several laboratories, Jones and her colleagues were the first to demonstrate positive cooperativity by the enzyme for this substrate (1968). Expanding these studies to eight bacterial species, they showed that the sizes of the ACT enzymes, measured by column chromatography, suggested that there were three major classes for this enzyme in the different types of bacteria (1969). Using the same methodology for cell extracts from the eight bacterial species, they now characterized the three types of ACT. Class A enzymes from *P. aeruginosa* and *P. fluorescens* were the largest and were subject to inhibition by pyrimidine nucleotides or ATP. They did not appear to have a separate regulatory sub-unit. Class B enzymes from *E. coli* or *C. freundii* were of intermediate size. They were sensitive to the same regulatory nucleotides, but these appeared to act at a separate regulatory sub-unit. Class C enzymes from *C. freundii* or *S. faecalis* were the smallest enzymes. These showed no regulatory features.

Her postdoc Mary Sue Coleman showed that aspartate carbamoyltransferase from *C. freundii* included both classes B and C enzymes (1971). The larger species could dissociate to form the smaller species, presumably by loss of a regulatory sub-unit, as could be done with the same enzyme from *E. coli.* The combined efforts of her associates Lansing Prescott, T.-Y. Chang, and Linda Adair led to purification of ACT from several bacterial species and characterization of ACTs in each of the three classes above.

MULTIFUNCTIONAL PROTEINS

By the early 1970s Jones had become quite interested in the possibility that in mammals the fusion of genes for enzymes that are consecutive in a pathway could produce much larger proteins containing two or more catalytic activities. Such work in her laboratory was initiated by Tom Shoaf, who demonstrated that Ehrlich ascites cells probably had two such "enzyme complexes," as they were initially called (1973). Shoaf and Jones showed that the enzyme activities for CPS II, ACT, and DHO (see Figure 1) always appeared to be joined, as were the activities for OPRT and ODC.

Although UMP synthase had not yet been purified, my own studies with Jones established that the two activities had to be joined with experiments showing that both activities underwent changes in sub-unit association in tandem, as the enzyme was progressively converted from the monomer to the dimer form (1979). This conversion to the active dimer form could be titrated with various nucleotides, or analogs. Comparing the effectiveness of such ligands in these molecular-size experiments to their K_i in kinetic studies led to the awareness that such effector ligands could produce a conformational response at two binding sites on the UMP synthase protein.

Postdoc Richard Christopherson then worked with the dihyroorotate synthase multifunctional protein (1980,1,2). In some very well-designed experiments, they achieved the first really detailed examination of the mechanism of the dihydroorotase (DHO) reaction. The possibility of channeling had always appeared intriguing, and Christopherson, by doing appropriate kinetic studies with two isotopes for the initial bicarbonate or an exogenous carbamoyl phosphate, was able to quantitate partial channeling of carbamoyl phosphate between the domain where it was formed (CPS II) and the domain where it was utilized (ACT).

The purification of UMP synthase from human tissue by her student Laura Livingstone was extended with her postdoc B.D.Han to produce an expression system for the human protein (1995). This was also an achievement, since years of work by Jones and colleagues on UMP synthase had established that this protein is not very stable. Because one of her initial triumphs came from the search for an optimum buffer system to stabilize carbamoyl phosphate synthetase in the 1960s, this last paper by Jones and her colleagues now defined the conditions for maintaining both catalytic domains of UMP synthase at their optimum.

A genetic disease, orotic aciduria, results from mutations in either catalytic domain of UMP synthase, leading to loss of enzyme activity. A standard expectation is that such mutations are most likely to be harmful if they affect the catalytic site of the enzyme. Jones explored this with her student Mary Perry, who used fibroblasts from a human patient to demonstrate that the mutant enzyme was actually highly unstable to heat denaturation or to proteolysis. A clever strategy involved culturing cells in the presence of azauridine, a nucleoside easily absorbed by cells, and then converted to azaUMP, a very strong inhibitor of OMP decarboxylase. It was anticipated that the nucleotide would bind to the enzyme in the cells and thereby stabilize it during purification experiments. Perry was successful in isolating the mutant protein and established that the mutant enzyme had the same apparent molecular weight and immunoactivity. The defect in the mutant enzyme was therefore one that affected the structural integrity of this bifunctional protein.

PROLINE SYNTHESIS

Studies in the early years with Lipmann had focused on amino acid metabolism. In later years, Jones would continue the effort to demonstrate that mammals could synthesize the amino acid proline, with ornithine as the likely precursor. The scheme that Jones deduced for this synthesis involved the initial formation of glutamyl-semialdehyde, either from ornithine or from glutamate in tissues where ornithine is not abundant. The intermediate glutamylsemialdehyde spontaneously converts to pyrroline-5-carboxy late (P5C), which can then be reduced to proline. Wakabayashi and Jones published the first demonstration of the enzyme P5C synthase in mammals (1983). Because bacteria were known to have this pathway, they used germ-free rats to demonstrate the activity in the animal tissue. Later, her student Curtis Small accomplished the difficult purification of P5C dehydrogenase (1990). This required new assay procedures to increase sensitivity and permitted them to define the kinetics for this enzyme.

MECHANISM OF OMP DECARBOXYLASE

The mechanism for this reaction is not immediately evident, and at least four schemes had been proposed over the years. Now that Jones had a source of pure protein from yeast, and the cDNA coding for it, she began to pursue this question. Jones and her student Jeff Smiley and postdoc Juliette Bell, working in collaboration with Marion O'Leary, made a strong case for a mechanism where cleavage of the scissile C-C bond was the rate-determining step (1990). Using kinetic isotope effects with ^{13}C-OMP as a function of pH, they now proposed that a proton from the enzyme was needed in the transition state to stabilize a nitrogen ylide, thereby facilitating the elimination of the CO_2. These studies were extended as Smiley performed systematic mutagenesis at a key residue, lysine 93. All mutants had no detectable activity, even though binding studies showed that the affinity for OMP was largely unchanged (1992). This implied the importance of lysine 93 directly in catalysis. One mutant, Lys93Cys could be "rescued." This protein was covalently modified at the new cysteine residue with bromoethylamine to yield an enzyme with a cysteine-ethylamine at residue 93, to mimic the normal lysine. This modified mutant protein had recovered much of the enzymatic activity, confirming the most likely role for lysine 93.

Although the above studies were done as Mary Ellen Jones was in her late sixties, she continued to show a spirit for pursuing new directions and new technologies. Jeff Smiley has spoken of how open she was to his using molecular biology for mutation studies—a procedure completely new to her laboratory. She was equally quick to explore using the kinetic isotope effect as an approach to evaluating the mechanism of the enzyme.

The last scientific effort of Mary Ellen Jones was a review paper that we wrote together (1996). The plan for this review had been initiated late in 1994: I would cover the enzymes uridine kinase and β-alanine synthase, while she would focus on UMP synthase. Though her illness became an important factor by early 1995, she still had enough strength and determination to supervise her laboratory for those last few months, while also attempting to put her normal effort into this final manuscript. In our frequent interactions to discuss the progress of this review article a decline in her normal energy, resulting from chemotherapy, became apparent. Although I quickly volunteered to absolve her of all responsibility for the completion of this manuscript, she did not relinquish her commitment. It was still early enough in the progress of her cancer that she projected an outward optimism to continue for many years her enjoyment of science, the arts, and all the colleagues to whom she felt close. By all these people she will always be remembered with great affection.

SELECTED BIBLIOGRAPHY

1953 With S.Black, R.M.Flynn, and F.Lipmann. Acetyl-coenzyme A synthesis through a pyrophosphoryl split of ATP. *Biochim. Biophys. Acta* 12:141–49.

1955 With L.Spector and F.Lipmann. Carbamyl phosphate, the carbamyl donor in enzymatic citrulline synthesis. *J. Am. Chem. Soc.* 77:819–20.

1960 With L.Spector. The pathway of carbonate in the biosynthesis of carbamyl phosphate. *J. Biol. Chem.* 235:2897–901.

With F.Lipmann. Chemical and enzymatic synthesis of carbamyl phosphate. *Proc. Natl. Acad. Sci. U. S. A*. 46:1194–205.

1961 With A.D.Anderson, C.Anderson, and D.Hodes. Citrulline synthesis in rat tissues. *Arch. Biochem. Biophys.* 95:499–507.

1963 Carbamyl phosphate. *Science* 140:1373–79.

1965 Amino acid metabolism. *Annu. Rev. Biochem.* 34:381–418.

1966 With S.E.Hager. Source of carbamyl phosphate for pyrimidine biosynthesis in mouse Ehrlich ascites cells and rat liver. *Science* 154:422.

1967 With S.E.Hager. Initial steps in pyrimidine synthesis in Ehrlich ascites carcinoma in vitro. II. The synthesis of carbamyl phosphate by a soluble, glutamine-dependent carbamyl phosphate synthetase. *J. Biol. Chem.* 242:5667–73.

With S.E.Hager. A glutamine-dependent enzyme for the synthesis of carbamyl phosphate for pyrimidine biosynthesis in fetal rat liver. *J. Biol. Chem.* 242:5674–80.

1968 With M.R.Bethell, K.E.Smith, and J.S.White. Carbamyl phosphate: An allosteric substrate for aspartate transcarbamylase of *Escherichia coli. Proc. Natl. Acad. Sci. U. S. A.* 60:1442–49.

1971 With M.S.Coleman. Aspartate transcarbamylases of *Citrobacter freundii*. *Biochemistry* 10:3390–96

1973 With W.T.Shoaf. Uridylic acid synthesis in Ehrlich ascites carcinoma. Properties, subcellular distribution, and nature of enzyme complexes of the six biosynthetic enzymes. *Biochemistry* 12:4039– 51 .

1979 With T.W.Traut. Interconversion of different molecular weight forms of the orotate phosphoribosyltransferase:orotidine-5'-phosphate decarboxylase enzyme complex from mouse Ehrlich ascites cells. *J. Biol. Chem.* 254:1143–50.

1980 Pyrimidine nucleotide biosynthesis in animals: Genes, enzymes, and regulation of UMP biosynthesis. *Annu. Rev. Biochem.* 49:253–79.

With R.I.Christopherson. The effects of pH and inhibitors upon the catalytic activity of the dihydroorotase of multienzymatic protein *pyr1–3* from mouse Ehrlich ascites carcinoma. *J. Biol. Chem.* 255:3358–70.

With R.I.Christopherson. The overall synthesis of L-5,6-dihydroorotate by multienzymatic protein *pyr1–3* from hamster cells. Kinetic studies, substrate channeling, and the effects of inhibitors. *J. Biol. Chem.* 255:11381–95.

1983 With Y.Wakabayashi. Pyrroline-5-carboxylate synthesis from glutamate by rat intestinal mucosa. *J. Biol. Chem.* 258:3865–72.

1989 With M.E.Perry. Orotic aciduria fibroblasts express a labile form of UMP synthase. *J. Biol. Chem.* 264:15522–28.

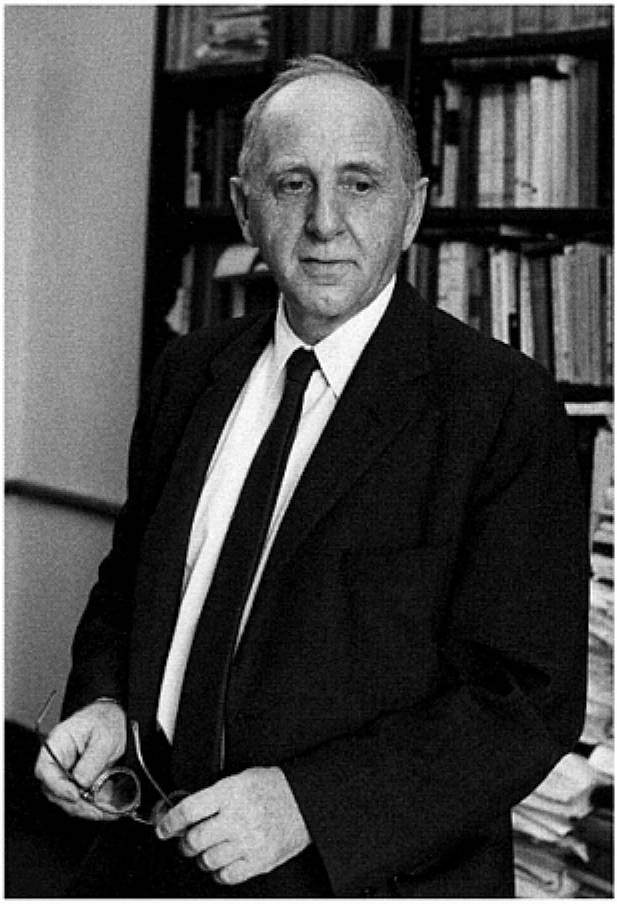
1990 With W.C.Small. Pyrroline-5-carboxylate dehydrogenase of the mitochondrial matrix of rat liver. Purification, physical and kinetic characteristics. *J. Biol. Chem.* 265:18668–72.

1991 With J.A.Smiley, P.Paneth, M.H.O'Leary, and J.B.Bell. Investigation of the enzymatic mechanism of yeast orotidine-5'-monophosphate decarboxylase using ^{13}C kinetic isotope effects. *Biochemistry* 30:6216–23.

1992 With J.A.Smiley. A unique catalytic and inhibitor-binding role for Lys93 of yeast orotidylate decarboxylase. *Biochemistry* 31:12162– 68.

1995 With B.D.Han, L.R.Livingstone, D.A.Pasek, and M.J.Yablonski. Human uridine monophosphate synthase: Baculovirus expression, immunoaffinity column purification and characterization of the acetylated amino terminus. *Biochemistry* 34:10835–43.

1996 With T.W.Traut. Uracil metabolism—UMP synthesis from orotic acid or uridine and conversion of uracil to beta-alanine: Enzymes and cDNAs. *Prog. Nucleic Acid Res. Mol. Biol.* 53:1–78.



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SIMON S. KUZNETS

April 30, 1901–July 9, 1985

BY ROBERT W. FOGEL

THIS MEMOIR PRESENTS AN account of the scholarly career of Simon S.Kuznets. Among the issues considered are his contribution to the development of the empirical tradition in economics; his transformation of the field of national income accounting; his use of national income accounting during World War II to set production targets for both the military and civilian sectors of the economy and to guide the implementation of those targets; his development of a theory of economic growth; his investigation of the interrelationship between economic growth and population growth; his contribution to methods of measurement in economics; and his legacy to the economics profession.

Simon S.Kuznets, recipient of the third Nobel Prize in economics, was a pivotal figure in the transformation of economics from a speculative and ideologically driven discipline into an empirically based social science. Born in Pinsk, Russia, on April 30, 1901, he received his education in primary school and *gymnasium* in Kharkov. He served briefly as a section head in the bureau of labor statistics of the Ukraine before emigrating to the United States in 1922. He entered Columbia University where he received his B.A. in 1923, his M.A. in 1924, and his Ph.D. in 1926. His princi pal teacher at Columbia and his lifelong mentor was Wesley Clair Mitchell, a founder of the National Bureau of Economic Research (NBER) and its director and codirector of research from 1920 to 1946.

Kuznets was a member of the research staff of the NBER from 1927 to 1961. It is there that he met Edith Handler. They were married in 1929 and had two children, Paul and Judith. Kuznets also held professional appointments in economics and statistics at the University of Pennsylvania (1930– 54) and in economics at Johns Hopkins (1954–60) and Harvard (1961–71). During 1932–34 he served in the Department of Commerce, where he constructed the first official estimates of U.S. national income and laid the basis for the National Income Section. During World War II he served as the associate director of the Bureau of Planning and Statistics of the War Production Board. Kuznets was instrumental in establishing in 1936 the Conference on Research in Income and Wealth (which brought together government officials and academic economists engaged in the development of the U.S. national income and product accounts) and in 1947 helped to establish its international counterpart, the International Association for Research in Income and Wealth. He served as advisor to the governments of China, Japan, India, Korea, Taiwan, and Israel in the establishment of their national systems of economic information.

Despite his extensive activities in the design of government programs of economic intelligence and his work in consulting with such private agencies as the Growth Center of Yale University and the Social Science Research Council, Kuznets was a prolific analyst of economic processes and institutions. During the course of his career he produced 31 books and over 200 papers, many of which set off major new streams of research. Among the fields in which he pio neered, in addition to national income accounting, were the study of seasonal, cyclical, and secular fluctuations in economic activity; the impact of population change on economic activity; the study of the nature and causes of modern economic growth based on the measurement of national aggregate statistics; the household distribution of income and its trends in the United States and other countries; the measurement and analysis of the role of capital in economic growth; the impact of ideology and other institutional factors on economic growth; changing patterns in consumption and in the use of time; and methods of economic and statistical analysis. Kuznets's intellectual contributions were acknowledged by his colleagues in many ways, including his election as president of the American Statistical Association in 1949 and of the American Economic Association in 1954.

THE CONTEXT OF KUZNETS'S WORK

To appreciate the magnitude of Kuznets's contributions to the empirical tradition in economics it is necessary to understand the intellectual currents in the American social sciences when he first encountered them in the early 1920s, and the social and political movements that promoted the social sciences during the last quarter of the nineteenth and the early decades of the twentieth century. Social sciences were just beginning to emerge as disciplines before the Civil War. Even though economics was the most articulated of the nascent social sciences, it was treated not as an independent subject but as a segment of a year-long required course in "moral philosophy," which was usually taught to seniors by an ordained minister who surveyed revealed knowledge about the operation of the temporal world. The textbook in the economics portion of this course most widely used in American universities during the 1840s and 1850s was written by Reverend Francis Wayland, president of Brown University and a principal leader of the Northern Baptist Church. The objective of his textbook, he wrote, was to set forth God's laws, so far discovered, regarding the production and distribution of those products that constitute the material wealth of a nation.

The primacy of religious crusaders in economics and the other principal social sciences continued down to the beginning of the twentieth century. About 40 percent of those who founded the American Economic Association (AEA) in 1885 were either ordained ministers or lay activists in evangelical churches. The platform adopted at that meeting called for the united effort of churches, the state, and science to promote Christian social reform. The influence of Richard T.Ely, an economist at the University of Wisconsin, and other academic leaders of the Social Gospel movement (the name given by historians to a religious/political movement that was influential between 1880 and 1930) in the AEA remained strong down to World War I. That influence was made conspicuous by the organizational identification of the AEA with issues that were at the time as highly controversial as the limitation of female participation in industry, the promotion of state and local taxes to fund entitlements, and the promotion of severe restrictions on immigration. This crusading posture was challenged by more secular economists, by those with affiliations to nonevangelical churches, and by those whose economic analysis was orthodox. Although the more orthodox economists gradually became ascendant, it took decades for the AEA to free itself from a lingering commitment to Social Gospel ideology and to become dedicated to objective presentation of evidence and rival theories regarding the functioning of the economy.

There was an important but smaller group of empirically oriented economists. Some of them were associated with the Bureau of the Census, which included a survey of economic activity in the decennial census of 1840. As the economy became transformed by accelerating technological change, the subsequent censuses collected increasingly detailed information on the agricultural, manufacturing, and transportation sectors. The economists associated with these efforts also produced illuminating analyses of the structure and development of such pivotal industries as iron and steel, cotton textiles, and meatpacking.

After the Civil War, a number of states set up bureaus that inquired into the conditions of labor and the standard of living of industrial workers. Led by Massachusetts, these agencies, beginning about 1875, began collecting samples on the income, expenditures, and housing of industrial workers. Toward the turn of the century, a similar program was established at the federal level with Carroll D.Wright, the economist who pioneered such studies in Massachusetts, serving as the first commissioner of labor. Between 1880 and World War I, a number of factors provoked alarm about the deterioration in the conditions of industrial labor. These included technological changes that promoted large-scale enterprises at the expense of small ones, huge waves of immigration that depressed wages, pitched battles between workers and factory owners that required federal troops to quell them (with large losses of life and property), and the increasing severity in business cycles, culminating with the depression of 1893–98, when one out of every six workers was unemployed. The belief that (despite many remarkable technological advances and the obvious affluence of the upper classes) conditions of life had deteriorated for urban workers and for farmers persisted down to the outbreak of World War I.

A number of economists who served on the War Production Board and in other agencies involved in mobilization of the economy during World War I were appalled at the lack of relevant economic information. Several of them concluded that this problem was unlikely to be solved within the federal government and in 1920 established a private, nonprofit, nonpartisan agency called the National Bureau of Economic Research (NBER) to construct national income accounts, collect information on business cycles, and to study the distributions of the national income among households, with the aim of making such information available to both public and private agencies that could use them in the formulation of their policies.

The leader of the NBER from its inception to 1946 was Wesley C.Mitchell, professor of economics at Columbia University. Mitchell was critical of orthodox theory because its generalizations pertained to a nonexistent world, based on speculations about how individuals who adhered strictly to the logic of profit and utility maximization would behave. He sought a comprehensive study of the economic institutions that had actually shaped production and distribution, and the forces that caused such institutions to vary over time and place. He emphasized that the study of aggregate economic behavior under diverse and changing institutional circumstance had to be rooted in the collection and analysis of quantitative information. While he rejected what he called Ricardian and neo-Ricardian theories (hypothetico-deductive models of economic behavior) because he believed they were based on naive assumptions of human motivations, he did not reject theory per se. His objective was the formulation of an economic theory that used postulates based on statistical analysis of existing institutions and of the historical forces that caused them to change over time. Keenly aware of the imperfections of the available data on economic life, he sought to develop procedures that could increase the reliability of the statistics derived from them and establish the range of probable error.

While Kuznets shared Mitchell's skepticism of neo-Ricardian theory, his thrust toward theoretical generalization was much stronger than Mitchell's. Throughout his career Kuznets was influenced by the work of such leading theorists as Joseph A.Schumpeter (who probed the relationship between technological change and business cycles), A.C.Pigou (who identified circumstances under which markets failed to maximize economic welfare), and Vilfredo Parato (who propounded a law governing the distribution of income among households). Kuznets's theoretical inclination is revealed in his second book, *Secular Movements in Production and Prices* (1930), which set forth a prescient theory of steady long-term modern economic growth in Europe and America, beginning toward the end of the eighteenth century. Although growth was steady at highly aggregated levels, at the level of particular industries there was a tendency toward retardation in growth. The logistic curve gave a good fit to the growth pattern of an industry over its life cycle. The main engine of this process, he said, was technological change, although he also acknowledged the role of population growth and changes in demand.

Another important aspect of *Secular Movements* was Kuznets's discovery of "secondary trend," a cyclical movement much longer than a business cycle, which typically ran 3 to 5 years. The periodicity of secondary trend ran between 15 and 25 years. Kuznets probed the links between primary trends, secondary trends, and short-term cyclical fluctuations, considering the correlations between the rapidity of the primary growth rates and the tendency toward both secular and short-term cycles. His analysis was based on examination of evidence for several industries in the United States and several European countries.

Still another notable feature of *Secular Movements* was Kuznets's concern with mathematical functions that could adequately describe the regularities he had uncovered. He argued that mathematical functions were needed for forecasting, which he emphasized was the central purpose of the analysis of time series. In this connection he introduced into economics the logistic curve that had been developed by Raymond Pearl only a few years earlier for the study of the growth of populations of fruit flies in closed containers. He also introduced to economics the curve that Benjamin Gompertz, an English actuary, had published in 1825 to describe the increase in mortality rates with age. Kuznets's discussion ranged not only over issues of the suitability of these and other mathematical functions for forecasting specific processes but also dwelt on the merits of alternative methods of fitting such functions. As notable as the care with which he pursued these issues was the extraordinary breadth and depth of his reading, not only in matters of economics and business, but also in history, demography, biology, statistics, and the physical sciences.

NATIONAL INCOME ACCOUNTING

In 1931, at Mitchell's behest, Kuznets took charge of the NBER's work on U.S. national income accounts that had previously been conducted mainly by Willford I. King. The next 15 years of Kuznets's career was concerned primarily with the construction of U.S. national income accounts. Residual tasks in this line of work, concerned mainly with the measurement of capital formation, continued down to 1961. His first major project was the estimation of U.S. national income for 1929–32, begun at the NBER, but completed in the federal government and published (1934) by the superintendent of documents, as the result of a U.S. Senate resolution requesting such information. Kuznets then extended those accounts backward to 1919 and forward to 1938. The two volumes containing this work (1941) included an extended and thorough discussion of the theoretical foundations for national income accounting and of the practical difficulties of moving from the available sources to the desired measures. Kuznets also evaluated a variety of omissions and other mismeasurements, including estimates of the probable range of error by specific categories and for the annual totals. Kuznets estimated the national income accounts during World War II and compared them with national product during World War I (1945), especially with respect to whether the war effort impinged on the civilian economy or came out of an expansion of total product. In 1946 he published a volume that extended the national income accounts back to 1869.

Kuznets transformed the field of national income accounting by bringing to it a far greater precision than had previously been achieved, by rooting it firmly in welfare theory (which distinguishes between private and social values), and by solving numerous problems related to moving from the imperfect sources containing the raw data to the theoretical conception of "national income." Among the difficult problems that he probed were the impact of monopolistic control of some professions on income; the impact of changes in the distribution of income on the market valuation of particular goods and services; the structure of national product (its distribution across industry) as measured both by income and by employment; the determination of which activities by the government properly belonged in a welfare-theoretic concept of "national income"; the estimation of the contribution to national income of the increase in leisure time; and the identification and estima tion of the bias imparted to national income estimates (especially when used to measure changes in income over time) by the choice of end-period or base-period prices, by the inclusion in income of costs of production (such as the increased cost of controlling crime in large cities), by the omission of home production, and by the difficulties of distinguishing between net and gross capital formation because, among other reasons, capital replacement frequently involved technological improvements.

The depth of Kuznets's theoretical probing was well understood by other specialists in national income accounting. His 1933 article on national income for the *Encyclopaedia of the Social Sciences* served for several decades as a guide on theoretical issues to those constructing national income accounts. His agility at theory became more obvious to others with his critique of a number of issues about the measurement of national income raised by J.R.Hicks (one of the preeminent economic theorists and the co-winner of the fourth Nobel Prize in economic sciences).

One of the most important books that arose from the work on U.S. national income accounts during the 1930s and 1940s was *Income from Independent Professional Practice* (1946), written jointly with Milton Friedman. That book developed age-earnings profiles for specific professions, a device that subsequently became one of the main analytical tools of labor economics. The book also developed and applied the concept of human capital to explain differences in average earnings by professionals. Human capital is today recognized as being far more important than physical capital in the contribution to national income. Its integration into the mainstream of economic theory and measurement has been one of the main advances in economic analysis since World War II, and was an important part of the work of two other Nobel laureates, Theodore W.Schultz and

Gary S.Becker. Thirdly, that book set forth the distinction between transitory and permanent income (expected income over the life cycle), a distinction developed by Friedman, which he subsequently extended to explain anomalies between cross-sectional and longitudinal measures of consumption and savings rates by income, and which was recognized as a seminal contribution in the citation for his Nobel Prize in 1976. Interestingly, these far-reaching contributions were passed over by reviewers of the book at the time of its publication.

SERVICE DURING WORLD WAR II

The power of national income accounting as an instrument of public policy was dramatically demonstrated during the course of World War II. In 1940 Robert Nathan, a former student of Kuznets and subsequently chief of the National Income Section of the Department of Commerce, became the chief of military requirements and industrial studies in the Defense Commission (later called the War Production Board) that President Roosevelt established with the aim of making the United States the “Arsenal of Democracy.” In assessing the capacity to expand military production, Nathan in 1941, and beginning in 1942 in conjunction with Kuznets, used national income accounting together with a rough form of linear programming to measure the potential for increased production and the sources from which it would come and to identify the materials that were binding constraints on expansion. Nathan’s estimates of the potential for military production before Pearl Harbor, which were far greater than the military thought was possible, were adopted by Roosevelt. After Pearl Harbor, the military set forth ambitious new estimates, which Kuznets determined could not be met within the specified time period, pointing out that the effort to do so might result in severe parts shortages and also might place unacceptable pressures on the civilian economy. The Kuznets analysis was adopted as the basis for both civilian and military targets.

In an article written in 1944 Paul A.Samuelson called World War II "an economist's war." This was no idle boast. Economists not only played a vital role on the War Production Board, but also in the Office of Price Administration, which regulated the civilian sector of the economy, and in the Department of the Treasury, which was charged with designing the methods of financing the war (inventing, among other devices, the current withholding system for paying taxes concurrent with the receipt of income). Other agencies in which economists were prominent included the Office of Strategic Services, the predecessor of the Central Intelligence Agency. Economists in that agency planned the daily bombing of Nazi territory on the basis of an analysis of which targets, if destroyed, would most damage war-making capacity. The work of economists during the war so impressed national leaders that Congress passed the Employment Act of 1946, which established the Council of Economic Advisors to the President.

MODERN ECONOMIC GROWTH

Immediately after completing his governmental services during World War II, Kuznets shifted the focus of his research to making use of national aggregate data to analyze international differences in the process of modern economic growth. His analysis focused on 14 nations in Europe and America and on Japan, for which time series went back at least 60 years. There were several aspects to that project. At Kuznets's suggestion in 1948 the Social Science Research Council established a Committee on Economic Growth, with Kuznets as chairman, which recruited leading economists in 11 countries to study the long-term patterns of growth in their respective countries.

At the same time, Kuznets began to study the available aggregate statistics and produced a series of 10 monographs that were published as supplements to the journal *Economic Development and Cultural Change* between 1956 and 1967. These monographs covered such topics as levels and variabilities of growth rates, industrial distribution of national product and labor input, the structure of consumption, trends in capital formation, the distribution of income by households, and the structure of foreign trade. This body of research was subsequently integrated and extended in two books, *Modern Economic Growth* (1966) and *Economic Growth of Nations* (1971).

In these volumes Kuznets set forth a historically based theory of modern economic growth. The modern epoch of growth, which began toward the end of the eighteenth century, was defined as a sustained increase in per capita income accompanied by an increase in total population and sweeping changes in the structure of the economy. The paramount feature that distinguished the modern economic epoch was the systematic application of scientific knowledge to problems of economic production and the development of a science-based technology. By science-based technology he meant that the technology was no longer merely a response to long-standing practical issues, but was often produced by scientific knowledge well in advance of bottlenecks. In the case of electricity, for example, theory preceded the technology for electrical generation and communications by many decades. The development of these technologies induced new demands for a wide range of consumer durables. Moreover, technological applications of science provided a powerful stimulus to the growth of scientific knowledge by providing both new information about previously unknown aspects of nature and by greatly expanding the resource base for the growth of scientific studies.

This complex interaction between scientific knowledge, technological applications, and rapid economic growth, Kuznets argued, required a proper cultural and institutional environment, which in turn required a new set of attitudes. The three key elements of the new *Weltanschauung* were secularism, egalitarianism, and nationalism. By secularism Kuznets meant a concentration on life on Earth with an emphasis on material attainment. By egalitarianism he meant a denial of inborn differences among human beings except as they manifested themselves in achievements: in other words a distribution of rewards according to accomplishments rather than by family connections and social status. By nationalism he referred not only to the capacity of the state to provide the stability needed for the flowering of modern economic growth within a well-defined territory but also to a historically formed community of feeling, with an elite dedicated to modernization.

Kuznets saw no necessary end to the opportunities for continued economic growth. He pointed out that the stock of knowledge was increasing at an accelerating rate without any signs of diminished aggregate returns (although the payoff to particular lines of investment usually eventually declined). He saw no limit to the potential for economic growth because of a petering of the rate of technological change. Although he recognized the pressure of population on depletable resources and the environment, he thought that population would reach a limit well within the carrying capacity of Earth, and he expected technological advances to provide substitutes for depletable resources and to curtail environmental degradation.

Kuznets did, however, envisage a limit to the growth of conventionally defined economic product (those items covered by the national income and product accounts [NIPA]). He recognized that at very high levels of per capita product, preferences for leisure and immaterial products omitted by NIPA might come to predominate in an economy. In a prescient computation published in 1952 he estimated that when the increase in each hour of leisure was valued at the average wage, the per capita income of individuals increased by about 40 percent. Other items omitted from the NIPA accounts included improvements in health and increases in longevity. Of course, there were costs of production that were improperly included in NIPA, such as the increase in expenditures on crime prevention associated with urbanization, but the omitted benefits far exceeded the unexcluded costs.

THE ROLE OF POPULATION GROWTH

Few economists of his era investigated the interrelationships between economic growth and population growth as fully as Kuznets. He was impressed more by the salutary effects of rapid population growth than by its negative effects. The evidence, he noted, indicated no cases in which large increases in population were accompanied by declines in per capita income. Rapid population growth tended to increase per capita income because it increased the number of contributors to useful knowledge. It tended to increase savings both because it increased the ratio of savers to dissavers and increased the amounts saved by upper income groups. Larger populations also promoted economies of scale and the responsiveness to new products (because of changes in the age structure of the population). Despite these generally positive aspects of high rates of population growth, Kuznets recognized that the sharp acceleration in the populations of less developed nations, generally brought about by sharp declines in death rates, sometimes overwhelmed the economies and impeded growth in per capita income.

Kuznets pointed out the economic significance of the fact that accelerated population growth was due primarily to a decline in death rates. The associated decline in morbidity rates served to increase labor productivity, to increase the payoff on investment in the raising and education of children, and to improve the quality of life. Moreover, the more rapid decline of death rates in cities than in rural areas promoted urbanization and speeded industrialization. The tendency of declining death rates to induce lower fertility rates and promote migration also contributed to economic growth by adapting social institutions to new economic opportunities. The reduction in completed family size and the fact that this occurred at differential rates in rural and urban areas led to a removal of younger generations from the influence of the family and exposed them to modern ethics that promoted participation in a rapidly changing economic system. He saw this break between ties of blood and economic rewards as a central factor in the victory of objective tests of economic performance over the more traditional rewards to family connections.

Kuznets's investigations of the synergism between economic and demographic change were so many-faceted they defy a brief summary. I have therefore selected one of his various lines of investigation for further comment. It pertains to the impact of demographic factors on the measured inequality of the distribution of income. Early in his career Kuznets began to struggle with problems of how to measure the degree of inequality in the distribution of income and to identify the factors contributing to the inequality. Such decomposition would point to policies that could relieve the appalling economic conditions of the poor that prevailed in all countries at the beginning of the twentieth century. Kuznets believed that unless the poor shared in the benefits of economic growth at least as fully as the more well to do, the stability of society was at risk. He regarded rapid economic growth and greater distributional equality as desirable and generally consistent goals.

During the 1960s and 1970s when it was apparent that a number of Asian nations had entered onto the paths of both rapid population growth (due to rapidly declining mortality) and rapid growth in per capita income, some of the available evidence seemed to indicate that these developments were increasing the inequality of the income distribution) and hence vitiating the benefits of the modernization of these countries for the poor. Studying the evidence on which this conclusion was based, Kuznets noted that the mechanical application of procedures used for the United States and other developed nations were inappropriate in Asian context, because they failed to take account of the differences in institutions. A key point related to the nature of Asian family cultures, which were different from Western family cultures. As a consequence, the variance in the size of the Asian family (or household) was much larger than in the United States and Western Europe. Not only were the household arrangements of the extended family different but intra-family income flows were different, and these differences were not reflected in standard measures of household income.

When these differences were explicitly acknowledged, a number of important statistical relationships emerged. For example, there was a negative correlation between the number of persons per family and the per capita income of families. Consequently, the very identity of the lower and upper income groups changed, depending on whether the size distribution of income was measured by the total in come per household or by the average income per person in the household. Moreover, the rate of population growth changed the age structure of households. Countries with rapidly growing populations and high fertility rates had a higher proportion of younger household heads and lower shares of heads over age 65 than countries with low population growth. Such demographic variations might increase inequality measured in cross section, even though lifetime income distributions were relatively equal. All these issues could be adequately addressed, Kuznets pointed out, if the sample surveys were designed on the basis of an appropriate theory of the impact of demographic factors on income distributions.

MEASUREMENT IN ECONOMICS

To many colleagues and students Kuznets's most compelling contribution was his mastery of the art of measurement. This art required not merely a thorough grounding in statistical theory. A more difficult achievement was understanding how to apply statistical methods and economic models to the incomplete and biased data with which economists normally work and still produce reliable estimates of key economic variables and parameters. That skill cannot be encapsulated in a simple list of rules, because the circumstances under which a given set of defects in the data is tolerable depends on the issues being addressed, on the statistical and analytical procedures being employed, and on the sensitivity of the results to systematic errors in the data, to the choice of behavioral models, and to the choice of statistical procedures.

Although Kuznets was a quintessential empiricist and a standard bearer for empirical research, his empiricism did not imply hostility to theory. He continually emphasized that a sound theory was needed to identify the variables that had to be measured, and theory had to be invoked in order to determine how the raw data thrown up by normal business or governmental activities should be combined to create the desired measures. Because measurement was dependent on theory, as theory advanced, due to either deeper insights or sounder empirical knowledge, past measures would have to be revised. Thus theoretical and empirical knowledge are at any point in time only asymptotically valid, subject to changing knowledge in both areas as well as to changing social goals, values, and priorities.

Although statistical analysis of quantitative data was a powerful tool in addressing issues of economic policy and in identifying both short- and long-term changes in the economy, it provided no magical solutions. Kuznets repeatedly emphasized that study of quantitative data is filled with pitfalls that have entrapped the most able practitioners of the art at one time or another. Even when the data are relatively good, the procedures appropriate, and the results fairly unambiguous, great care had to be taken in drawing conclusions about the domain to which the findings applied and the predictions that could be reliably based upon them. High on his list of major dangers was the superficial acceptance of primary data without an adequate understanding of the circumstances under which the data are produced. Adequate understanding involved detailed historical knowledge of the changing institutions, conventions, and practices that affected the production of the primary data but were difficult to ascertain and to quantify.

Another point high on Kuznets's list of major dangers was the easy assumption that a good fit of a mathematical model to the data made it an adequate description of significant features of the data. Because of the limitations of data, especially in time series, many different mathematical models, varying in complexity and structure, may give fairly good statistical fits to a given body of data when conventional statistical measures of goodness of fit are invoked. Nor can Occam's razor be glibly invoked to settle such issues, because it is possible that the curve that gives the best fit incorrectly leads to the conclusion that the data were generated a simple process, an elegant "law" of behavior embodied in a single equation, when they were actually generated by complex processes that are badly distorted by the simple function.

Kuznets's choice of estimating procedures was deeply embedded in evaluations of the objectives of a particular investigation. Whether a given body of data was adequate depended not only on inherent limitations of the data set but also on the types of measures that were being constructed from it and the issues to which these measures were addressed. Preliminary analyses of defective data were useful, because they increased the likelihood of upgrading the available data sets or closing gaps in them by demonstrating the social usefulness of such efforts. Indeed, he viewed the preliminary analyses of the available data as an essential part of an asymptotic process of discovery, during which both the underlying data sets and the analytical procedures were perfected and made more suitable to the resolution of the substantive issues.

Like many other statisticians, Kuznets worried about imposing so much structure on the data that the a priori assumptions of the investigation overwhelm whatever information there is in the data. He was skeptical about fitting simple high-order curves to data sets with relatively few observations of questionable quality. Consequently, he tended to work with looser forms of data analysis, often preferring frequency distributions with one-, two-, or three-way classifications to regression analysis. Kuznets objected to the cavalier ways regression analysis was often applied, especially when highly restrictive functional forms were applied to data sets without adequate investigation of the underlying process or institutions under investigation. Too often, functional forms were imposed with inadequate consideration as to whether the data set could bear the weight of the structure imposed on it. Kuznets's evaluation of the validity of substantive findings tended to be cast less as simply right or wrong but more often focused on the reliability of the results and their domain of applicability. He was particularly concerned with the detection and measurement of systematic errors in the data: systematic misreporting, sample selection biases, the impact on results of the underlying behavioral models that circumscribed the collection and analysis of the data, and the impact of the statistical techniques employed in the measurement process.

Although he placed great emphasis on the development of data bases of the highest quality, Kuznets was not a purist who insisted on working only with "perfect" data. Because no data set is ever perfect, his emphasis was on how to exploit the data at hand in order to extract from them whatever useful information they might contain. But then the limitation on the resulting analysis had to be specified, with some results treated as conjectural, and still others treated as illustrative computations.

In assessing the reliability of particular estimates, Kuznets stressed the importance of systematically investigating their relationships to other series and other kinds of information that were logically related to them. He was, in this connection, a master of devising algebraic identities that brought other available data to bear on the estimates at issue in a particularly illuminating way. Such identities were also effective devices for revealing implicit and unsupported assumptions, and thus contributed to the social research agenda.

The most powerful technique that Kuznets employed to evaluate attempts to measure key aspects of economic life was sensitivity analysis. Most measurements in economics are complex combinations of data and a priori assumptions. Much argument about the result of quantitative analysis turns on these a priori assumptions. Moreover, because the arguments used to champion one procedure over another are also a priori, these arguments often produce more heat than light. Kuznets's solution to such problems was sensitivity analysis, by which he meant a careful examination of both the procedures and the data in order to see if plausible ranges of systematic errors in the data, if changes in the a priori assumptions that shaped the analysis, or if the substitution of reasonable alternative estimation procedures make a material difference in the finding. If they do not, the finding is robust; otherwise the data add little to the theoretical considerations that preceded the measurement. The original hypothesis remains an untested hypothesis, despite the gloss provided by the data. Kuznets was persistent in searching for methods of evaluating the sensitivity of measures of economic variables and parameters and ingenious in devising such tests.

KUZNETS'S LEGACY

Kuznets's greatest legacy is his theory of modern economic growth. The proposition that the high growth rate since the eighteenth century in population and per capita income, the sharp changes in the structure of the economy, and the concomitant changes in social institutions and culture are a unique epoch in human history is no longer a theory. It is now a part of the confirmed knowledge of economic science. The research of the past three decades has added important detail to Kuznets's summary of the evidence available in the 1960s and also has modified or corrected some conjectures.

The enhancement of human capital by the environmental controls made possible by modern economic growth may have been more far-reaching than Kuznets realized. Evidence accumulated during the last three decades indicates that the period of modern economic growth was one of major improvements in human physiology induced by accelerating technological change and greater mastery of the environment. This physiological improvement has manifested itself not only in the continuing increase in life expectancy since the 1960s, when it was widely assumed that the century-long increase in life expectancy had come to an end. It is also evident in the steady decline in mortality rates at ages 80 and over, an accelerating decline in the age-specific burden of chronic diseases at older ages, and a 50 percent increase in body size since the eighteenth century, indicative of improvements in the functioning of the principal organ systems.

Recent evidence also indicates that at least in England, modern economic growth may have begun about half a century earlier than Kuznets specified. Rapid increases in agricultural productivity were relatively high from the beginning of the eighteenth century and the shift of labor from agricultural to nonagricultural occupations over the course of the century was substantial. These new findings, mainly for England but also for France, provide a stronger connection between rising productivity and declining mortality rates in the nations that initiated modern economic growth. The high plateau of mortality rates during the middle of the nineteenth century now appears to be a pause in a downward secular trend that was more than a century old when it resumed. The pause appears to be explained by the great difficulty in solving the problems of public sanitation created by the remarkable spurt in urbanization during the nineteenth century.

What is impressive about *Modern Economic Growth* 35 years after its publication is not its faults but how well its major findings have held up. Indeed, some of Kuznets's forecasts, controversial at the time they were made, such as the continuing acceleration of technological change, now seem so obvious it is difficult for those who did not live through the 1950s and 1960s to recognize their path-breaking character. When Kuznets first made this forecast, modern information technology was still in its infancy, organ transplantation and reproductive technology were still largely topics of science fiction, and mapping the human genome, let alone engaging in genetic engineering, was not even encompassed in science fiction. Equally impressive is Kuznets's prescience in recognizing the growing dominance of the nonmarket sectors of the economy. The failure of the official national income accounts to measure the growth of leisure, the value of the increase in life expectancy, and the decline in age-specific chronic disabilities has obscured the continuing acceleration in the secular trend of economic growth. Also obscured is the exceedingly high rate of capital formation due to the remarkable expansion of human capital relative to physical capital. Although physiological capital and knowledge capital are admittedly difficult to measure, the challenge has been accepted by some of the most talented empirical economists today and constitutes one of the most impressive new frontiers of empirical economics.

Another controversial forecast of Kuznets that has held up is the closing of the economic gap between the OECD economies and many Third World economies, particularly in Southeast Asia and Latin America. Kuznets's prediction that food supply would expand more rapidly than popula tion has also been confirmed. Today, the global per capita consumption of food has increased by 15 percent since 1960, despite the doubling of population over the past 4 decades.

Kuznets's approach to the measurement of economic variables is another major facet of his legacy. He did not believe in either economic theory or economic measurement for their own sake. His economic analysis was directly or indirectly shaped by his perception of the major issues of public policy. Kuznets recognized that formal modeling was a useful instrument in the search for theories that could guide economic policy. However, he favored theorizing based on postulates consistent with historical evidence while making use of hypothetico-deductive modeling.

The Kuznetsian approach has grown in strength in recent years, not only at the macro level of analysis but also at the micro level. Historically (evidentially) based analysis has been given a considerable fillip by the reinvigoration of the NBER after Martin Feldstein became its president and chief executive officer in 1978. Although the Kuznetsian blend of theory and historical evidence is evident in all NBER programs, it is particularly marked in those dealing with secular trends in the economy, life-cycle and intergenerational processes in economics, health economics, labor economics, and the economics of aging.

Kuznets's contention that imposing too much structure on data obscures rather than reveals their information content is widely accepted as a guiding principle in empirical economics. In research on many of the most urgent issues of current policy, investigators are increasingly exploiting the properties of frequency distributions and their decomposition. Although regression analysis remains a powerful tool, its limitations and the virtues of less structured forms of data analysis are now widely recognized by empirical economists.

THIS MEMOIR has benefited from comments by Daniel Bell, John S. Chipman, John T.Dunlop, John Kenneth Galbraith, Mark Guglielmo, Katharine J.Hamerton, Max R.Henderson, Susan Jones, Robert E. Lipsey, Mark Perlman, Paul A.Samuelson, Robert M.Solow, Judith K.Stein, David Surdam, and Yasukichi Yasuba.

SELECTED BIBLIOGRAPHY

1930 *Secular Movements in Production and Prices: The Nature and Their Bearing upon Cyclical Fluctuations.* Boston: Houghton Mifflin.

1933 *Seasonal Variations in Industry and Trade.* New York: National Bureau of Economic Research.

National income. In *Encyclopaedia of the Social Sciences.* New York: Macmillan.

1934 National Income 1929–1932. Senate Document No. 124, 73rd Congress, 2nd Session. Washington, D.C.

1941 *National Income and Its Composition 1919–1938.* New York: National Bureau of Economic Research.

1945 With M.Friedman. *Income from Independent Professional Practice.* New York: National Bureau of Economic Research.

National Product in Wartime. New York: National Bureau of Economic Research.

1946 *National Income: A Summary of Findings.* New York: National Bureau of Economic Research.

National Product since 1869. New York: National Bureau of Economic Research.

1948 On the valuation of social income. Reflections on Professor Hicks' article. *Economica* 15(pt. 1):1–16; 15(pt. 2):116–31.

1952 Long-term changes in the national income of the United States of America. In *Income and Wealth,* ser. 2. International Association for Research in Income and Wealth. Cambridge: Bowes & Bowes.

1953 *Shares of Upper Income Groups in Income and Savings.* New York: National Bureau of Economic Research.

1955 Toward a theory of economic growth. In *National Policy for Economic Welfare at Home and Abroad,* ed., R.Lekachman. Garden City, N.Y.: Doubleday.

1961 *Capital in the American Economy: Its Formation and Financing.* For NBER. Princeton, N.J.: Princeton University Press.

1966 *Modern Economic Growth: Rate, Structure, and Spread.* New Haven, Conn.: Yale University Press.

1971 *Economic Growth of Nations: Total Output and Production Structure.* Cambridge, Mass.: Harvard University Press.

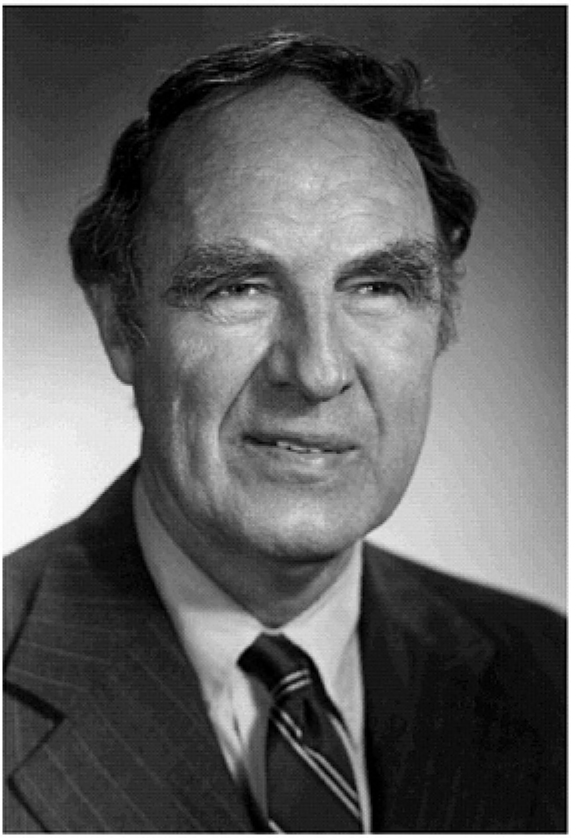
1972 *Quantitative Economic Research: Trends and Problems.* New York: National Bureau of Economic Research.

1973 Modern economic growth: Findings and reflections (Nobel address). *Am. Econ. Rev.* 63:247–58.

Population, Capital, and Growth: Selected Essays. New York: W.W.Norton.

1979 *Growth, Population, and Income Distribution: Selected Essays.* New York: W.W.Norton.

1989 *Economic Development, the Family, and Income Distribution.* Cambridge: Cambridge University Press.



FRANKLIN ASBURY LONG

July 27, 1910–February 8, 1999

BY FRED W. MCLAFFERTY, BARRY K. CARPENTER, AND JERROLD MEINWALD

Frank Long's research made fundamental, unique contributions to a surprising variety of important scientific subjects. He applied his extensive background and deep intuition in physical chemistry, in combination with his creative instrumentation skills and keen awareness of new experimental techniques, to yield important discoveries in other research areas. These included basic reaction mechanisms of organic molecules in solution, unimolecular dissociation of gaseous ions, and diffusion of organic vapors through polymer films.

These broad interests and his outgoing personality also led him into leadership positions in academe, government, industry, and public affairs. The cause of international arms reduction was especially close to his heart. He made friends readily, took on unpopular causes willingly, and fulfilled commitments promptly and with apparent ease. He was department chair, vice-president, and trustee at Cornell, on the President's Science Advisory Committee for Presidents Eisenhower, Kennedy, and Johnson, assistant director of the U.S. Arms Control and Disarmament Agency, co-chair of the U.S. Pugwash Steering Committee, and a director of several large corporations. Probably his most publicized ap pointment was the one he did not receive as Director of the National Science Foundation, withdrawn at the last minute when President Nixon learned of Long's criticisms of the antiballistic missile system.

Long was born July 27, 1910, in Great Falls, Montana, and was always proud of his origins in this "frontier state." He grew up in nearby Eureka, where his father was the town doctor, as well as a hopeful inventor (until his automated stump-boring machine found only five customers). His father died when Frank was 13; he and his sister and brother were raised by his widowed mother, who was a schoolteacher and later a school superintendent. Eureka borders a mountainous area where the principal industry was lumbering. Frank worked part time as a surveyor with the U.S. Forest Service, experience that provided a broad perspective for his career, as well as many stories of enjoyable adventures in a pioneer environment.

He received B.A. and M.A. degrees from the University of Montana in 1931 and 1932. He did graduate work in physical chemistry with Axel Olson at the University of California, Berkeley, where he gained his initial experience studying the mechanisms of organic reactions and the use of radioactive isotopes, an area he also pursued with Willard Libby. In commenting on Frank's unusually personable nature, Konrad Krauskopf of Stanford, a roommate at Berkeley, recalled: "One evening he was kind enough to include me on a double date with a couple of damsels from Mills College, and the relationship blossomed so that eventually one of the girls became his wife and the other became mine."

After receiving his Ph.D. in chemistry from the University of California, Berkeley, in 1935, Frank spent a year as an instructor there, and then moved to the University of Chicago the following year as instructor. There he was also a research assistant to W.D.Harkins, whom he accompa nied to the Chemistry Department at Cornell for Harkins' semester as Baker lecturer. Long stayed on at Cornell (again as instructor!), but his research efforts were interrupted by the war. He served, initially under George Kistiakowsky, as a research supervisor for the Explosive Research Laboratory of the National Defense Research Committee in Pittsburgh from 1942 until 1945. He returned to Cornell as an associate professor and was promoted to full professor in 1946. He was elected to the National Academy of Sciences in 1962 and the American Academy of Arts and Sciences in 1965 (vice-president, 1976–80). He received honorary degrees from the University of Minnesota in 1963 and from Columbia College in 1983.

When Peter Debye stepped down as Chemistry Department chair in 1950, Long took over and served in this position for a record 10 years. He extended and diversified the department's excellence in teaching and research, establishing a unique record in his selfless fostering of the careers of young faculty. He was faculty trustee during 1956–57. He served as vice-president of research and advanced studies at Cornell, 1963–69, and played a key role with Bob Morison in establishing the highly successful Biology Division. In 1969 he began a four-year tenure as director of a new Cornell academic program (Science, Technology, and Society) designed to study the impact of science and technology on the problems facing U.S. society. Between 1969 and 1979 he was Henry R.Luce Professor of Science and Society, and between 1976 and 1979 he was director of the Peace Studies Program. He was a member of the corporate Board of Directors for the Carrier Corporation, United Technologies Corporation, and the Exxon Corporation, for which he was also a member of the Executive Committee.

In 1988 he and his wife, Marion Thomas Long, "retired" away from Ithaca winters to southern California, where he served as adjunct professor of chemistry and social sciences at the University of California, Irvine, and continued to be active on national and international committees. Marion died in 1992, and Frank died February 8, 1999, in Pomona, California. He is survived by son, Franklin, a chemist of Claremont, California; daughter, Elizabeth, a professor of sociology at Rice University; brother, George, of Portland, Oregon; and a grandson.

Fertile ground for research can often be found at the borders between disciplines. So Frank Long confirmed when he began to bring the language, concepts, and experimental techniques of solution-phase physical chemistry to bear on problems of aqueous organic reactions. He was one of the pioneers who showed organic chemists that they had to think carefully about nonideality, activity coefficients, and ion pairing if they were interested in the mechanisms of such processes. These concepts formed the foundation of the worldwide interest in mechanisms of solvolysis reactions that began in the late 1940s and continued for nearly three decades.

Because many aqueous organic reactions occur in media of high acidity, it soon became clear to mechanistic chemists that a supplement to the pH scale so useful in dilute solutions would be necessary. When Louis Hammett proposed the H_0 acidity function to accomplish this end, Frank immediately saw the power of the approach and put it to good use in his studies of the hydrolyses of lactones, esters, and acetals. He extended the concept to mixed and nonaqueous solvents and proposed alternative acidity functions for use under specialized conditions.

Many of the mechanistic descriptions that we teach our undergraduates can be traced back to Long's work. When an ester or lactone undergoes hydrolysis, does the O-acyl or the O-alkyl bond break, and how can one find out? Which end of an unsymmetrical epoxide opens under hydrolytic conditions, and is the answer the same under all conditions? Long and Lewis Friedman pioneered the use of stable isotopic labeling with degradation and analysis in the mass spectrometer to tackle these problems. Early isotope labeling studies relied on the use of radioactive tracers, with chemical degradation of reaction products being used to locate the labels. In contrast, their new mass spectrometric technique made it possible to acquire the same information faster and without the use of radioactivity or chemical degradation.

Not only did Long use stable isotopic labels for tracer purposes, he studied the change in kinetics that could accompany the introduction of such isotopes either into the molecule of interest or into the solvent in which the reaction occurred. His work on H_2O/D_2O solvent isotope effects showed the way to generations of researchers studying the mechanisms of biologically relevant reactions. The important proton inventory techniques that have elucidated some key enzymatic mechanisms can trace a good part of their ancestry to Long's work.

Mass spectrometry had previously been used largely for the determination of accurate atomic weights and isotopic abundances, and for the quantitative analysis of hydrocarbons. Long and Friedman were pioneers in characterizing reaction products by vaporizing them into the mass spectrometer to form gaseous organic ions; they were among the first to study the unimolecular decompositions of these ions, particularly for alkanes, lactones, alcohols, and esters. In a first for mass spectrometry, they used this chemistry in 1953 to confirm the molecular structure of ketene dimer, a highly publicized controversy of the time. Long's pioneering physical chemistry studies of gaseous ions included appearance potentials, heats of formation, and the statistical theory of their dissociations. Notable was his classical example of the nonergodic dissociation of ionized fluoroethylenes that occurs before the input energy can be statistically randomized.

Long contributed to early work in polymer chemistry at Cornell with definitive studies of the diffusion of organic vapors into polymer films that demonstrated dramatic effects of polymer crystallinity. Such research provided a critical part of the scientific basis for the now extensive food wrap and packaging industry.

Reviews citing Long's work invariably refer to it as "thorough," "careful," or "detailed." These qualities are obviously necessary if the data being reported are to be considered reliable, but Frank had the rare ability to combine a painstaking approach to his experimental work with a real penchant for innovation. This unusual combination ensured that his contributions to the mechanisms of solution-phase reactions would remain classic studies in the field of physical organic chemistry, as indeed they have.

Long's ability to be effective simultaneously in research and public service is illustrated by a story from Zafra Lerman:

> As a postdoc with Frank, one day in his office we began to discuss the entropy of activation in a proton transfer reaction. As Frank began his sentence with "This entropy must be negative," his secretary told him that both George Kistiakowsky and Jerry Wiesner were on the phone to discuss a *New York Times* article on antiballistic missiles. In the ensuing conversation I felt as if I were transported to another world in the company of people who were running the planet. I lost all track of time and my surroundings. When Frank finally hung up, he looked at me and said, "I'm sure it's negative." I had no idea what he was talking about and asked, "What is negative?" He responded, "The entropy of activation."

Frank Long's interest in arms control and other public issues began early, aroused initially by his military research during World War II, for which he was awarded the U.S.

Certificate of Merit in 1948. He was chair of the Advisory Committee for Chemistry, Office of Naval Research, 1949– 52; trustee of Associated Universities, 1947–1993; consultant, Ballistics Research Laboratory, Department of the Army, Aberdeen, Md., 1953–59; member, Science Advisory Board, Department of the Air Force, 1956–60; member, Ballistic Missiles Advisory Committee, Office of the Secretary of Defense, 1957–60; chair, Chemistry Advisory Committee, Air Force Office of Scientific Research, 1959–63; and member of the President's Science Advisory Committee under Presidents Eisenhower, Kennedy, and Johnson.

When the U.S. Arms Control and Disarmament Agency was formed in 1962, he was its first assistant director for science and technology, serving also as consultant, 1963–73 and 1977–79. As a member of the U.S. group that went with Averell Harriman to the Soviet Union in 1963, Long took a leading role in the effort of the United States, the United Kingdom, and the Soviet Union to negotiate a comprehensive nuclear test ban treaty. Intense negotiations over an extended period resulted in agreements on almost everything except the number of on-site inspections; the Soviets insisted on three per year versus the U.S. demand of seven. The historical compromise, the Limited Test Ban Treaty, prohibited testing in the atmosphere, the oceans, and in space, but permitted underground testing. He was a director of the Arms Control Association, 1971–77, and co-chair of the U.S. Pugwash Steering Committee, 1974–79 (the Pugwash Conferences received the Nobel Peace Prize in 1995). He was a member of the Board of Directors of the Albert Einstein Peace Prize Foundation and a member of the Board of Trustees of the Fund for Peace.

His aggressiveness in arms control efforts is best illustrated in his opposition to the antiballistic missile project, as delineated in a 1968 publication stating that ABM mis sile development would create "strong pressure toward acceleration of the arms race." In 1969 he was nominated by a board of scientists to be director of the National Science Foundation, and he went to Washington D.C., one morning presumably to receive the appointment from President Nixon in the White House Rose Garden that afternoon. Upon arrival, however, presidential science advisor Lee DuBridge told Long that the situation had changed—that the ceremony was cancelled. International publicity produced an immediate outcry from a wide variety of concerned citizens, including many prominent scientists. In a letter to *The New York Times,* S.E.Luria and Victor Weisskopf stated, "the implication is that the government desires scientific advice only from men who agree with the policies of the government. Science deals with truths, often unpleasant truths. In a world where the destinies of men and nations are forged by science and technology, a nation that puts only yes-men in its science councils might well court intellectual decay, technological paralysis and ultimate catastrophe." Later the White House relented, but Long then declined the President's offer.

Long contributed to two important studies on defense issues carried out under the auspices of the American Academy of Arts and Sciences. In the 1970s he and George Rathjens edited a volume on *Defense, Defense Policy, and Arms Control* (1976), and in the 1980s he led a study of President Reagan's program for ballistic weapon defense (Star Wars) that resulted in the edited volume *Weapons in Space* (1986). From 1983 to 1988 he served as chair of the American Academy of Arts and Science's Committee on International Security Studies.

Long served from 1947 until 1993 on the Board of Trustees of Associated Universities, Inc., a consortium of nine private universities founded to establish and operate

Brookhaven National Laboratory (BNL) and the National Radio Astronomy Observatory. He contributed uniquely to the unusual success of BNL. In addition to his unparalleled board activities, Long was also extensively involved in BNL research activities, especially with scientists Jacob Bigeleisen, Max Wolfsberg, Lewis Friedman, and Gerhart Friedlander. Long arranged for Jake and Max to spend semesters at Cornell, and he spent a semester at BNL in active research collaborations.

Long also played a major role in science and technology transfer to underdeveloped nations, including India, South Korea, Latin America, Malaysia, and Indonesia, in part as a member of the National Academy of Sciences' Board on Science and Technology for International Development. He was U.S. co-chair for the Indo-U.S. Sub-Commission on Education and Culture; a member of the U.S. Overview Committee for Indo-U.S. Science and Technology Initiative of the National Research Council started in 1983 by Prime Minister Indira Gandhi and President Ronald Reagan; a member of the Council on Foreign Relations, 1964–89; and co-chair of the Joint U.S.-Korea Advisory Committee for Science of the National Academy of Sciences, 1972–76. In 1975 he received the Order of Civil Merit and Dongbaeg Medal from the President of the Republic of Korea for contributions to the development of science and technology in Korea.

Only a few prizes are available to scientists for outstanding public service. Two of the most prestigious of these are the Charles Lathrop Parsons Award from the American Chemical Society, which Long received in 1985, and the Philip Haug Abelson Prize of the American Association for the Advancement of Science, which he received in 1990.

Frank Long will be remembered in science for his public service as well as his research accomplishments. His early fundamental contributions to the mechanisms of solvolytic reactions that utilized key concepts of physical chemistry provided a firm scientific basis for this important field. He was also a pioneer in understanding the physical principles and mechanisms of the reactions of gaseous organic ions, applying these in the mass spectrometer with stable isotopic labeling for the structural characterization of organic molecules and their basic reactions. Long was unusually effective and dedicated in public service, especially in his long-term efforts for arms control among the world's nuclear powers. His outstanding leadership and advisory board service greatly enhanced the research productivity at Cornell, Brookhaven National Laboratory, the President's Science Advisory Committee, other federal research agencies, and third world countries. At a Cornell University symposium in memory of Franklin Long on October 1–2, 1999, funded by a grant from the John D. and Catherine T. MacArthur Foundation, these contributions were remembered in talks by Dale Corson, Robert Hughes, George Rathjens, John Harvey, George Lewis, Jeremiah Sullivan, David Wright, Richard Garwin, Matthew Evangelista, Lisbeth Gronlund, Anne Cahn, Nikolai Sokov, Tom Christenson, Sarah Mendelson, and Judith Reppy.

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SELECTED BIBLIOGRAPHY

1934 With A.R.Olson. The mechanism of substitution reactions. *J. Am. Chem. Soc.* 56:1294.

1936 With A.R.Olson, W.F.Libby, and R.S.Halford. An improvement on the quantitative determination of radioactivity. *J. Am. Chem. Soc.* 58:1313.

1939 A study of the interchange between chromioxalate ion and oxalate ion, using radio-carbon. *J. Am. Chem. Soc.* 61:570.

1950 With L.Friedman. Determination of the mechanism of γ-lactone hydrolysis by a mass spectrometric method. *J. Am. Chem. Soc.* 72:3692.

1951 With L.Mandelkern. Rate of sorption of organic vapors by films of cellulose acetate. *J. Polym. Sci.* 51:457.

With W.F.McDevit and F.B.Dunkle. Salt effects on the acid-catalyzed hydrolysis of γ-butyrolactone. I. Chemical activity and equilibrium. II. kinetics and the reaction mechanism. *J. Phys. Colloid Chem.* 55:813, 829.

1952 With R.J.Kokes and J.L.Hoard. Diffusion of acetone into polyvinyl acetate above and below the second-order transition. *J. Chem. Phys.* 20:1711.

1953 With L.Friedman. Mass spectra and appearance potentials of ketene monomer and dimer: Relation to structure of dimer. *J. Am. Chem. Soc.* 75:2837.

1954 Kinetics of reactions in solution. *Annu. Rev. Phys. Chem.* 5:219.

1956 With J.G.Pritchard. Hydrolysis of substituted ethylene oxides in $H_2{}^{18}O$ solution. *J. Am. Chem. Soc.* 77:2663.

1957 With L.Friedman and M.Wolfsberg. Ionization efficiency curves and the statistical theory of mass spectra. *J. Chem. Phys.* 26:714.

With M.A.Paul. H_0 and related indicator acidity functions. *Chem. Rev.* 57:935.

1959 With J.Bigeleisen. Correlations of relative rates in the solvents D_2O and H_2O with mechanisms of acid and base catalysis. *Trans. Faraday Soc.* 55:444.

1961 With E.A.Halevi and M.A.Paul. Acid-base equilibria in solvent mixtures of deuterium oxide and water. *J. Am. Chem. Soc.* 83:305.

1964 With P.Salomaa and L.L.Schaleger. Solvent deuterium isotope effects on acid-base equilibria. *J. Am. Chem. Soc.* 86:1.

1965 With C.Lifshitz. Appearance potentials and mass spectra of fluorinated ethylenes. III. Calculations based on the statistical theory of mass spectra. *J. Phys. Chem.* 69:3737.

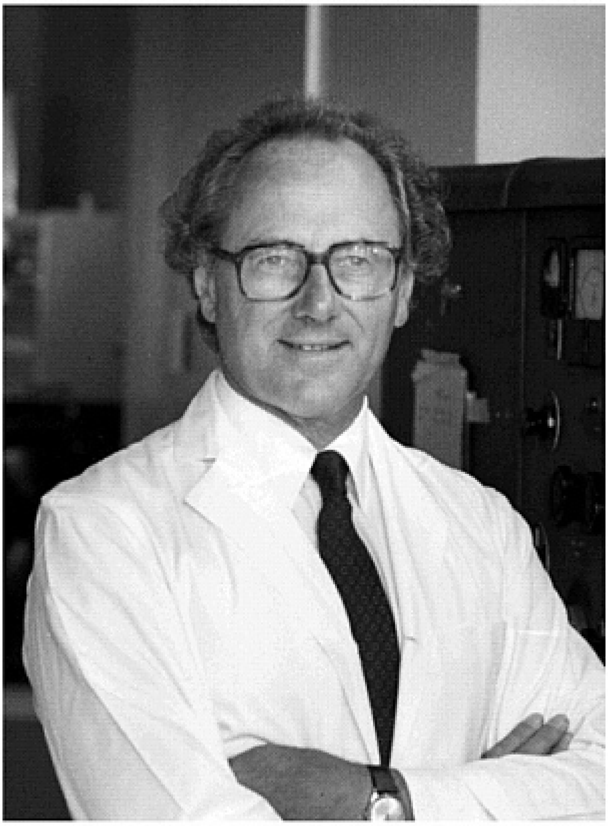
1968 Strategic balance and the ARM. *Bull. At. Sci.* 24:2.

1969 Support of scientific research and education in our universities. *Science* 163:1037–40.

1976 Arms control from the perspective of the nineteen-seventies. In *Arms, Defense Policy and Arms Control,* eds. F.A.Long and G.W. Rathjens, pp. 1–222. New York: Norton

1980 With A.Oleson, eds. *Appropriate Technology and Social Values. A Critical Appraisal.* Cambridge, Mass.: Ballinger.

1986 With D.Hafner and J.Boutwell, eds. *Weapons in Space.* New York: Norton.



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HANS JOACHIM MÜLLER-EBERHARD

May 5, 1927–March 3, 1998

BY ALEXANDER G. BEARN

HANS JOACHIM MÜLLER-EBERHARD was born in Magdeburg, Germany, on May 5, 1927. There were no scientists in his family; his father, Adolph Müller, was a successful businessman. Two years after the outbreak of war, Hans's brother, Eberhard, was killed on the Russian front at the age of 21. Hans's father changed his family name to Müller-Eberhard after World War II to memorialize his son.

Although the atmosphere in the Müller-Eberhard household was not academic, there was much discussion of religious and political matters. His father was distinctly anti-Nazi and frequently propounded his conviction that a clique of criminals had assumed control of the government. He warned young Hans that he should not tell others about his views on Hitler, or he would be sent to a concentration camp. Hans was the only member of his class not to join the Hitler youth. When in later years a classmate asked him why he did not join, he said, simply, that he had no wish to associate with criminals.

Hans's class at school was sent to an anti-aircraft battery on the outskirts of Magdeburg where they replaced regular army units. These military activities decreased the time allowed for a normal education. At the age of 17 he was drafted into the army and sent to Hungary to serve on the eastern front. Toward the close of the war he was captured by the Russians. He managed to escape the Russians, who were marching him eastward, by hiding in a ditch during the day and traveling by night through forests. He ultimately reached the Danube, where he was captured by the U.S. armed forces. He eventually rejoined his family in Altenau in the Harz Mountains, to which they had fled to avoid being in the Russian zone.

Although it was always Hans's intention to become a physician, he undertook formal studies to become a painter. While in Altenau, he also began studying with increasing pleasure textbooks of chemistry and physics. He augmented his meager financial resources by climbing fir trees to harvest the cones, a very hazardous occupation since the best seeds were frequently at the top of trees 10 to 15 meters tall. A number of Hans's fellow climbers were killed in falls.

In the spring of 1948 Hans entered the University of Göttingen to study medicine. His entry to medical school was contingent on his passing an examination, and so to further his education, he took classes at the Robert Koch Gymnasium in Clausthal-Zellerfeld, the birthplace of Robert Koch. It was a matter of quiet pleasure to Eberhard that some 40 years later he received the Robert Koch Medal in gold at the University of Bonn for a lifetime of achievement in medical research.

While in Altenau, Eberhard read widely in philosophy as well as science. By chance he read *Man the Unknown* by Alexis Carrel and first learned of the existence of the Rockefeller Institute for Medical Research. The intellectual atmosphere of Göttingen was of a high order. Hans's entry examination to the medical school had required an essay on the integration of Rutherford's model of the atom and Planck's quantum theory. In addition to his medical studies, he attended lectures given by major scientists at the univer sity. He was also greatly influenced by neo-Kantian Nicolai Hartmann, who lectured on philosophy. His reading companions included books by Hartmann, Heidegger, Jaspers, and the poetry of Rainer-Maria Rilke. In this way, the young Eberhard became a well-rounded intellectual, as well as a physician. To the regret of his friends, he seldom sketched or painted after becoming a physician. Nevertheless, on rare occasions he could be induced to sketch his colleagues, which he accomplished with great sensitivity and accuracy. A self-portrait was brilliantly executed in a fashion resembling the works of Augustus John.

During a medical tour of the United States, Eberhard's medical teacher Fritz Hartmann visited Henry Kunkel at the Rockefeller Institute, who in the course of conversation suggested that Hartmann might like to send one or two of his students to work at the Rockefeller in a postdoctoral capacity. Interestingly, Eberhard was not the first student recommended by Hartmann; his first recommendation was Hartwig Cleve, who declined but later came to work with Alexander G.Bearn at the Rockefeller Institute and became professor of human genetics at Munich. At the time, Kunkel was interested in the pathogenesis of liver disease, but was already focusing his lifelong attention on the gamma globulins of serum.

The environment was greatly to Eberhard's liking. For him, emerging from war-torn Germany, it was an effervescent community of scholars, both young and old. His initial studies at the Rockefeller concerned the carbohydrate component of gamma globulin; he discovered that the carbohydrate content of gamma globulin was entirely represented by the 19S component. This observation demolished the previous belief that 19S gamma globulin was merely an aggregate. This component of gamma globulin was later designated IGM. Eberhard also went on to prove that rheu matoid factor commonly present in the blood of patients with rheumatoid arthritis is a 19S antibody to 7S gamma globulin.

Returning to Göttingen after three years with Kunkel, Eberhard found the Department of Medicine lackadaisical and uninspiring. While at the Rockefeller, he had met Gunnar Wallanius of Sweden. Learning of Eberhard's mood upon his return to Germany, Wallanius invited him to spend some time with him in the Department of Clinical Chemistry in Uppsala, where he was alone in the laboratory and left to follow his own interests. In Uppsala Eberhard turned his attention to the nature of complement and determined the future direction of his research. While at Rockefeller he had reviewed the pertinent literature on complement, because complement, ill defined as it was, had in common with RF its combination with antigen-antibody complexes, as Michael Heidelberger had shown when he measured protein nitrogen.

In Uppsala the cardinal question, therefore, was: Can the serum protein be identified that combines with antigen-antibody complexes? In the 1950s Pierre Grabar at the Pasteur Institute in Paris had introduced immunoelectrophoresis as a new method to analyze complex mixtures of proteins. He decided to use this method to compare the pattern obtained of untreated human serum with that of serum incubated with an immune precipitate to activate complement. Careful inspection reproducibly revealed an electrophoretic shift of a minor component within the β-globulin region of the treated serum that was not occurring when the incubation was performed in the presence of chelating agent EDTA. He decided that the only way to elucidate the nature of the complement pathway was to identify in molecular detail the protein components that constitute the pathway. He called the component beta-1C globulin and its product B1A. After the isolation of both components, he obtained convincing evidence that B1C-globulin was an essential constituent of the hemolytic complement system. Beta-1C was subsequently named C3c and the major physiological degradation product of C3 was called C3c. Working with C3, Eberhard identified an active enzyme called C3gb convertase, responsible for C3 activation. Later evidence indicated that C3 was involved in immunological mechanisms, and he showed that although the absence of C3 in the blood of individuals predisposed them to recurrent infections, surprisingly, such individuals do not develop autoimmune disease. Eberhard's studies on C3 were not universally accepted, but its existence was beyond doubt.

After two productive years in Uppsala, Eberhard rejoined Kunkel in 1959 at the Rockefeller University, where he stayed for the next four years. He returned briefly to Uppsala to defend successfully his Ph.D. thesis, and subsequently became the first docent of immunochemistry in Sweden. Using immunoelectrophoresis, Eberhard investigated the pattern obtained from normal serum with serum incubated with an immune precipitate to activate complement. After electrophoresis on a supporting median, which Eberhard did much to develop, a minor component in serum became evident. This shift in mobility was abolished by a chelating agent. The principal fragment was named BA and the fragment BC, later to be called C3 and C3A, respectively. Eberhard isolated and purified these proteins. The first demonstration and purification of a specific protein in the complement system, this was a critical event, for it was the beginning of a series of molecular identifications of the proteins of the complement system. As Maclyn McCarty noted in 1971 on presenting him the Helen Hay Whitney Duckett Award, "You have lifted complement out of its primordial slime."

Working with C3, Eberhard identified an active enzyme called C3B convertase, which converts C3 to C3A. Later evidence indicated that C3 was involved in immunological mechanisms. He further showed that absence of C3 in the blood of individuals predisposed them to recurrent infections, although surprisingly, such individuals do not develop autoimmune disease.

After six years in the Kunkel laboratory, Eberhard was recruited by Frank Dixon to join the Scripps Clinic and Research Foundation in La Jolla. While at Scripps, Eberhard dissected still further the complement reaction and described its mode of action in exquisite molecular detail. His elegant Harvey Lecture in 1970 was one of the best and clearest summaries of the biology of complement at that time. His review in *Annual Reviews of Biochemistry* on the complement system also revealed the rigorous clarity of thought that was an essential feature of Eberhard's scientific papers, both oral and written. Eberhard, during his studies on complement, did much to elucidate the alternate pathway, identifying its initiating mechanisms and control. Eberhard was always generous in attributing certain aspects of the complement cascade to other workers in addition to himself.

At Scripps Eberhard was appointed to the Cecil H. and Ida M.Green Chair in Medical Research in 1972 and became chairman of the Department of Immunology in 1972 and associate director of research in 1978. He was also appointed adjunct professor in the Department of Pathology at the University of California at San Diego.

While in La Jolla, Eberhard was frequently invited to accept senior positions in molecular biology in Switzerland and Germany. Although tempted, he decided to remain at Scripps, where he was soon to be associate director of the institute as well as head of the Department of Immunology. One opportunity intrigued him, however; for more than two years he discussed the possibility of returning to Germany to head the Bernhard Nocht Institute for Tropical Disease in Ham burg, a distinguished institute that had not taken advantage of new developments in science. Eberhard had been given to understand that he would succeed Frank Dixon at the Scripps Institute, but this did not happen. Moreover, the new administration took the extraordinary action of removing him, without any discussion, from his named professorship. In 1988, with an atmosphere at Scripps increasingly hostile, he returned with mixed feelings to Germany, where he quickly invigorated the almost defunct Bernard Nocht Institute. The reinvigoration of this historically important institute was a formidable task. In reviving the institute, Eberhard showed administrative capabilities of a high order. The institute required considerable structural change, and Eberhard took a close interest in these architectural changes and brought to the table his sound aesthetic judgment. During his tenure, Eberhard obtained funds to create a new and modern library, a modern auditorium, and many major alterations in the existing laboratories.

Before Eberhard arrived there was very little communication between the institute's clinical and investigative sides. Indeed, there was much unprofitable bickering. This Eberhard was determined to change. His arrival resulted in a marked increase in morale and closer and more effective working relationships. The recruitment of young molecular biologists, virologists, protein chemists, and individuals well versed in DNA research was rapidly and successfully accomplished. Soon the institute became admired by colleagues in the field throughout the world. In addition, he greatly impressed the German government, which provided generously for the institute. The Federal Ministry of Research and Technology provided ample sums allowing for 30 "hard" money positions for scientists. In 1987 there were some 250 scientists; in 1995 there were more than 380. In addition, there were 61 students working for the Ph.D. degree.

Two research programs were particularly effective. The first dealt with the protozoan disease invasive ameobiasis, which is caused by *Entamoeba histolytica*. Only 10 percent of about 5 million individuals infected with the organism develop the disease. This was explained by Eberhard, who discovered marked DNA differences between pathogenic and non-pathogenic isolates of *E. histolytica*. Further work in his laboratory demonstrated the differences in both structure and function in the gene products that confer pathogenicity. Research on another disease, onchocerciasis, for which 80 million people are estimated to be at risk, centered on the identification of larval antigens that provide immunoprotection. This program could be carried out only by using the institute's newly created research facilities in Liberia. The civil war in Liberia endangered the program, but with tact and persuasion Eberhard initiated contacts with other African nations and the continuity of the work was maintained. Eberhard's success in revitalizing the institute was remarkable, and he received many awards during his time there. It is worth emphasizing that he was always concerned with human disease and, although not primarily a physician, his interest in the welfare of the patients was a major concern.

In 1990 the Bernhard Nocht Institute observed its ninetieth anniversary. In the year 2000, the institute celebrated its centenary. It is greatly to be regretted that Eberhard died before the celebration of this milestone in the life of the institute.

Eberhard had one more move in his scientific career, which was unfortunately brought to a premature close by his early death. He was asked by the University of Texas at Houston to develop a new institute to be called the Institute of Molecular Medicine for the Prevention of Human Diseases. His recruitment to Houston was largely due to the efforts of James Willison, who helped provide the initial resources that Eberhard required. Somewhat surprisingly, Eberhard proved to be an effortless but highly successful fundraiser within the Texan business world.

It was greatly to the disadvantage of the institute and to the misfortune of his many friends that carcinoma of the prostate was diagnosed even before his arrival in Houston. His courage during this illness was an example to his many friends. He did not flag in his enthusiasm for the institute despite the increasing pain of bone metastases. Despite aggressive medical therapy, during which Eberhard considered but did not elect to have a therapeutic immunological approach, he died at the age of 70 in 1998.

Until the end of his life, Eberhard kept the future of the institute in the forefront of his mind. Even while in the hospital he continued to work on plans for the future and took his briefcase wherever he went. Sadly, toward the end of his life he had not the strength to open it. Müller-Eberhard was married three times and leaves two daughters from his first marriage to Ursula Flech Müller-Eberhard, who had been a fellow medical student at Göttingen. Irma Gigli, his wife of 15 years and a distinguished immunological dermatologist, shared his scientific interests and was assistant director of the institute in Houston. She provided a warm and graceful home environment that he loved and that enabled him to refresh and flourish.

This generous and brilliant medical investigator greatly influenced the field of immunology; he was as imaginative and talented in the laboratory at the age of 70 as he was as a young man in his thirties. In addition to his love of science, his knowledge of art and philosophy enlarged his intellectual horizon and entranced his friends. His courage and defiance of the Nazi regime was but one indication of his unwavering determination to live a life in which loyalty and concern for his friends never flagged, even during the last painful months of his life.

Hans Müller-Eberhard was of medium height with kind but piercing blue eyes; he was always impeccably dressed in suit and tie, reserving blazer and sports jacket for the weekend. He never yielded to the casual life in California. He was a charming and excellent host at his home, where he regularly entertained colleagues from the laboratory and many visitors from overseas. Guests and friends knew they would enjoy with him his exquisite taste in music and the wines of California.

He worked in the laboratory with his own hands and on his own projects until the end of his life. In the laboratory he exuded confidence and exhibited great technical skills. His office was never cluttered; his door always open. He was as tidy in administrative matters as he was in the lab. His interest in his students was steadfast and even after they left his laboratory he took much pleasure in their successes. Although he had many admiring acquaintances throughout the world, he made only a few deep and enduring friendships, but for them no request went unheeded, and he spent many vacations and holidays with them. His loyalty followed the advice of Polonius, “The friends thou hast, and their adoption tried, grapple them unto thy soul with hoops of steel.” He did indeed.

THIS MEMORIAL greatly benefited from its thoughtful review by Dr. Irma Gigli.

SELECTED BIBLIOGRAPHY

1956 With H.G.Kunkel. The carbohydrate of γ-globulin and myeloma proteins. *J. Exp. Med.* 104:253.

1960 With U.Nilsson and T.Aronsson. Isolation and characterization of two β_1-glycoproteins of human serum. *J. Exp. Med.* 111:201.

With U.Nilsson. Relation of a β_1-glycoprotein of human serum to the complement system. *J. Exp. Med.* 111:217.

1966 With U.Nilsson, A.P.Dalmasso, M.J.Polley, and M.A.Calcott. A molecular concept of immune cytolysis. *Arch. Pathol.* 82:205.

1967 With W.S.Rodman, R.C.Williams, Jr., and P.J.Bilka. Immunofluorescent localization of the third and the fourth component of complement in synovial tissue from patients with rheumatoid arthritis. *J. Lab. Clin. Med.* 69:141.

With M.J.Polley and M.A.Calcott. Formation and functional significance of a molecular complex derived from the second and the fourth component of human complement. *J. Exp. Med.* 125:359.

1968 With M.J.Polley. The second component of human complement: Its isolation, fragmentation by C`1 esterase and incorporation into C`3 convertase. *J. Exp. Med.* 128:533.

1969 With P.Perlmann, H.Perlmann, and J.A.Manni. Cytotoxic effects of leukocytes triggered by complement bound to target cells. *Science* 163:937.

With V.A.Bokisch and C.G.Cochrane. Isolation of a fragment (C3a) of the third component of human complement containing anaphylatoxin and chemotactic activity and description of an anaphylatoxin inactivator of human serum. *J. Exp. Med.* 129:1109.

Complement. In *Annual Review of Biochemistry,* vol. 38, ed. E.E. Snell, p. 389. Palo Alto, Calif.: Annual Reviews, Inc.

1970 With D.B.Budzko. Cleavage of the fourth component of human complement (C4) by C1 esterase: Isolation and characterization of the low molecular weight product. *Immunochemistry* 7:227.

1971 With M.J.Polley and J.D.Feldman. Production of ultrastructural membrane lesions by the fifth component of complement. *J. Exp. Med.* 133:53.

With O.Götze. The C3-activator system: An alternative pathway of complement activation. *J. Exp. Med.* 134:90s.

Biochemistry of complement. In *Progress in Immunology,* vol. I, ed. B. Amos, p. 553. New York: Academic Press.

1972 The molecular basis of the biological activities of complement. In *The Harvey Lectures,* series 66. New York: Academic Press.

With L.G.Hunsicker, S.Ruddy, C.B.Carpenter, P.H.Schur, J.P. Merrill, and K.F.Austen. Metabolism of third complement component (C3) in nephritis, involvement of the classic and alternative (Properdin) pathways for complement activation. *N. Engl. J. Med.* 287:835.

1973 With W.P.Kolb, J.A.Haxby, and C.M.Arroyave. The membrane attack mechanism of complement: Reversible interactions among the five native components in free solution. *J. Exp. Med.* 138:428.

1974 With V.A.Bokisch and F.J.Dixon. Complement—A potential mediator of the hemorrhagic shock syndrome (dengue). In *Advances in the Biosciences. Schering Symposium on Immunopathology,* vol. 12, ed. G.Raspé, p. 417. New York: Pergamon Press.

1975 Complement. In *Annual Review of Biochemistry,* vol. 44, ed. E. E, Snell, p. 697. Palo Alto, Calif.: Annual Reviews, Inc.

With W.P.Kolb. Neoantigens of the membrane attack complex of human complement. *Proc. Natl. Acad. Sci. U. S. A.* 72:1687.

1976 With E.R.Podack and W.P.Kolb. The C5b-9 complex: Subunit composition of the classical and alternative pathway generated complex. *J. Immunol.* 116:1431.

With O.Götze. The alternative pathway of complement activation. *Adv. Immunol.* 24:1.

1978 Molecular dynamics and regulation of the complement system. In *Versatility of Proteins; Proceedings of the International Symposium on Proteins,* ed. C.H.Li, p. 373. New York: Academic Press.

1982 With E.R.Podack and J.Tschopp. Molecular organization of C9 within the membrane attack complex of complement. Induction of circular C9 polymerization by the C5b-8 assembly. *J. Exp. Med.* 156:268.

1984 With R.J.Ziccardi and B.Dahlbäck. Characterization of the interaction of human C4b-binding protein with physiological ligands. *J. Biol. Chem.* 259:13674.

1987 With Z.Fishelson. Regulation of the alternative pathway of human complement by C1q. *Mol. Immunol.* 24:987.

1992 With M.Leippe, E.Tannich, R.Nickel, G.Goot, F.Pattus, and R.D. Horstmann. Primary and secondary structure of the pore-forming peptide of pathogenic *Entamoeba histolytica. EMBO J.* 11:3501.

1994 With M.Leippe and J.Andrä. Cytolytic and antibacterial activity of synthetic peptides derived from Amoebapore, the pore-forming peptide of *Entamoeba histolytica. Proc. Natl. Acad. Sci. U. S. A.* 91:2602– 2606.

With M.Leippe, J.Andrä, R.Nickel, and E.Tannich. Amoebapores: A family of membranolytic peptides from cytoplasmic granules of *Entamoeba histolytica:* Isolation, primary structure, and pore formation in bacterial cytoplasmic membranes. *Mol. Microbiol.* 14(5):895–904.

Photo by Arthur Kravetz, Baltimore, Maryland

DANIEL NATHANS

October 30, 1928-November 16, 1999

BY DANIEL DIMAIO

DANIEL NATHANS, A SCIENTIST whose pioneering use of restriction endonucleases revolutionized virology and genetics and whose personal qualities had a profound impact on those who knew him, passed away in November 1999 at the age of 71. He was the University Professor of Molecular Biology and Genetics at the Johns Hopkins University School of Medicine, where he served on the faculty for 37 years, and a senior investigator of the Howard Hughes Medical Institute since 1982. Dan is survived by his wife, Joanne; three sons, Eli, Jeremy, and Benjamin; and seven grandchildren.

Dan was born and raised in Wilmington, Delaware, the youngest of eight children of Russian Jewish immigrants. He attended the University of Delaware, initially living at home and commuting by hitchhiking, and graduated with a degree in chemistry in 1950. He then entered medical school at Washington University in St. Louis, largely because, he claimed, his father saw him "as the last chance to have a doctor in the family." Dan began medical school with the intention of returning to Wilmington as a general practitioner, but a summer job in a local hospital bored him and made him rethink these plans and return early to St. Louis for a research position in Oliver Lowry's laboratory. While at

Washington University, Dan caught the attention of another of his professors, W.Barry Wood, who was later to move to Johns Hopkins and recruit Dan to join him in Baltimore.

After completing medical school in 1954 Dan did a medical internship at the Columbia-Presbyterian Hospital in New York City. He remembered this year as one of his most valuable because of the real-life problems he faced and the real responsibility he had for patients, but this was also a year that reinforced his decision to enter the laboratory. Dan then spent two years as a clinical associate at the National Cancer Institute, caring for patients and carrying out research on the synthesis of immunoglobulin by myeloma tumors. During this time, Dan met Joanne Gomberg and after a whirlwind courtship they were married. After returning to Presbyterian Hospital for two more years as a medical resident, Dan realized that his calling lay in medical research, and he finally dropped his plans to practice clinical medicine, much to his father's bewilderment.

Dan began his basic research career at the Rockefeller Institute in 1959 with Fritz Lippman. He initially enrolled in a Ph.D. program, which he abandoned because he decided he did not want to sit through any more lectures. Dan began by studying the mechanism of protein synthesis in myeloma cells, but he soon turned his attention to the more tractable *E. coli* system. These were the days before the discovery of messenger RNA and the elucidation of the genetic code, and Dan investigated the soluble factors that catalyzed the transfer of amino acids from amino acyl-tRNA to the growing polypeptide chain. He soon made his first major research contribution, the development of a bacterial cell-free system that supported protein synthesis. He then got wind of the discovery of RNA bacteriophage in Norton Zinder's laboratory and showed that phage RNA could support the synthesis of viral coat protein in a cell-free system. This was the first example of a purified mRNA that directed the synthesis of a specific protein. Many laboratories extended these initial observations, leading to a number of fundamental insights into the mechanism of protein synthesis. This important early work already displayed the rigor, clarity of thought, and impact that characterized Dan's entire body of work.

Dan continued his studies on bacteriophage and protein synthesis after he was recruited to Johns Hopkins in 1962 by Barry Wood, who was by then chairman of the Department of Microbiology. During his early years on the Hopkins faculty Dan carried out important studies on the regulation of bacteriophage translation by the viral coat protein, and he demonstrated that puromycin inhibited protein synthesis by being incorporated into the growing polypeptide chain, resulting in premature termination of translation. In experiments that presaged his later studies with restriction enzymes, he showed that 5-fluorouracil-substituted phage MS2 RNA generated subgenomic viral RNA fragments that encoded specific viral proteins.

In the late 1960s Dan's animal virus colleagues, Bernard Roizman and Robert Wagner, left Hopkins, and Barry Wood asked Dan to teach medical students about these viruses. Dan accepted this assignment with trepidation, because he knew little about the topic, but he was soon struck by the dramatic effects that tumor viruses had on cells. At this time, molecular studies of animal viruses were in their infancy, but the basic tools of propagation of animal viruses in cultured cells, plaque assays, and in vitro transformation systems had been developed. Dan saw the parallels with the bacteriophage, the analysis of which had spawned molecular biology, and he realized that the study of simple animal viruses would provide important insights into carcinogenesis and the biology of animal cells. What was lacking were the powerful genetic techniques of bacterial systems; during the next decade, it was Dan who provided the tools that allowed detailed molecular genetic analysis of mammalian viruses and cells.

Dan decided to redirect his research effort to the analysis of animal viruses, and after some thought he selected the simplest DNA tumor virus, SV40, as the object of his attention. Even though the SV40 genome was only about 5,000 base pairs of double-stranded circular DNA, a small size Dan found comfortable, this virus had the ability to grow lytically in monkey cells and to cause permanent tumorigenic transformation of rodent cells. To learn how to grow and handle SV40, Dan spent a sabbatical leave in 1969 with Leo Sachs and Ernest Winocour at the Weitzman Institute. While in Israel, in one of those wonderful moments we all dream about, Dan received a letter from his Hopkins colleague Hamilton Smith describing a new enzymatic activity from the bacterium *Hemophilus influenzae* that degraded DNA from foreign cells but did not degrade its own DNA. Ham also mentioned preliminary evidence suggesting that this enzyme cleaved DNA at specific nucleotide sequences. Perhaps with his studies of 5-fluorouracil-fragmented-phage RNA in mind, Dan immediately realized the implications of this discovery. “Well, that set me off thinking that we could use restriction enzymes to dissect the genome of a small papovavirus and learn something about how the virus works…and perhaps learn something about what genes are required for transformation.”[1]

Dan returned to Hopkins with some radiolabeled SV40 DNA in his luggage, and he set about testing his ideas. With Stuart Adler, a medical student, he surveyed the ability of all known restriction enzymes to cleave SV40 DNA. Early attempts to use the *E. coli* B restriction enzyme were unsatisfactory because it did not cleave DNA at specific sites. But then Ham Smith and his postdoctoral fellow Thomas Kelly showed definitively that the *H. influenzae* restriction enzyme cut DNA at specific recognition sites consisting of short defined nucleotide sequences.[2] (Actually, it turned out that the cleavage activity was due to a mixture of two restriction enzymes, HindII and HindIII.) In Dan's words, here were the "trypsins and chymotrypsins for DNA" that could be used to reduce an apparently featureless DNA molecule into homogeneous, manageable pieces derived from specific regions of the viral genome, onto which individual genetic activities could be mapped. Years later, Tom Kelly admitted that he and Ham Smith found the specific sites, but they had not fully appreciated the significance of the specific fragments.

Dan and his student Kathleen Danna focused on Ham Smith's enzyme, showing that it did in fact cleave SV40 DNA into 11 specific pieces. These results were published in 1971 in the *Proceedings of the National Academy of Sciences,* in a paper that ushered in the modern era of genetics. Figure 1 was standard fare and showed that cleavage altered the sedimentation profile of SV40 DNA. But Figure 2 crossed the divide: The DNA fragments were separated and revealed by polyacrylamide gel electrophoresis. In the discussion, with Dan's characteristic understatement, the New World came into view.

> The availability of pieces of SV40 DNA from specific sites in the molecule should be helpful for the analysis of the function of the SV40 genome. For example, when the order of fragments in the genome is known, it should be possible to map "early" and "late" genes and those genes that function in all transformed cells. It may also be possible to localize specific genes by testing for biological activity, e.g., T-antigen production or abortive transformation. If specific deletion mutants become available, the analysis of restriction enzyme digests may…[allow] mapping of such mutants. Comparison of restriction endonuclease digests by polyacrylamide gel electrophoresis has also provided a new method for detecting differences in DNA… It should [also] be possible to…obtain quite small, specific fragments useful for the determination of nucleotide sequence."[3]

This vision was soon transformed into reality in work that was often breathtaking in conception and elegance. Together with Kathy Danna and George Sack, a medical fellow, Dan determined the specific order of each fragment in relation to the others and constructed the first cleavage map of a viral genome. This map, which was to serve as a framework for localizing functional elements of SV40 DNA, was constructed by isolating overlapping partial digestion products and determining their constituent fragments—an approach developed in the analysis of proteins was applied to DNA with brilliant insight and success. Indeed, one of Dan's great strengths was his ability to adapt approaches developed in other fields to the study of genes. This is nicely illustrated by the identification of the origin of SV40 DNA replication, the first genetic signal to be positioned on a eucaryotic viral genome. Here, he designed a gradient-of-label experiment, modeled on the experiment of Howard Dintzis to map the direction of protein translation in vitro, to determine the temporal order of synthesis of specific viral DNA fragments in infected cells. In a figure that told a story of a thousand words, the results were displayed, mapping the origin and terminus of viral DNA replication and establishing that replication was bi-directional and proceeded symmetrically.

In the following years, Dan and his colleagues and collaborators devised a series of approaches to exploit the specific cleavage of DNA by restriction enzymes to dissect the genome of SV40. Restriction-fragment DNA fingerprinting was used to map sequence differences between different strains of SV40 DNA (and hence uniquely identify these strains) and to follow the genetic changes that occurred during virus evolution. A marker rescue approach using restriction fragments was developed and used in conjunction with the cleavage map to locate the position of mutations that resulted in temperature-sensitive defects in virus replication. In collaboration with George Khoury and Malcolm Martin, viral transcription units were mapped to specific segments of the viral genome in lytically infected and transformed cells. This work established many important features of the SV40 genome and life cycle, including the identification of the early and late genes and the demonstration that they were transcribed in divergent directions.

The early work from Dan's laboratory used restriction enzymes to map various functions of the viral genome; however, there was soon a subtle shift from using these reagents to map viral RNA and DNA to using them to actually generate viral mutants and reconstruct the viral genome. The altered genomes were then reintroduced into cells and assayed for biological activity. Initially, specific restriction fragments were deleted to generate viral mutants lacking defined segments of the genome, leading to the identification of the large T antigen as the product of the viral A gene. Later, Dan's laboratory developed more sophisticated methods of site-directed deletion and point mutagenesis to analyze SV40 regulatory signals and proteins to infer the function of individual viral proteins and *cis*-acting signals. These studies led to the precise localization of the DNA replication origin (and even the identification of individual nucleotides in the origin that controlled the rate of viral DNA replication) and the demonstration that the SV40 large T antigen was a multifunctional protein with independently acting domains. Gone were the days of random mutagenesis followed by the laborious task of separating the interesting mutants from the chaff, replaced by a more directed approach of deliberately manipulating the genome to generate the desired mutant. In a particularly elegant demonstration of the power of combining directed mutagenesis techniques with more classical approaches, Dan and his students provided con vincing genetic evidence that the ability of the SV40 large T antigen to recognize the viral origin underlay the role these two elements played in the initiation of viral DNA replication. Although the techniques developed in Dan's laboratory were superseded by new methodology made possible by advances in oligonucleotide synthesis, these early experiments alerted the scientific community to the power of this "new genetics."

This work galvanized the scientific community, and soon many laboratories were exploiting restriction enzymes to analyze DNA. Of particular importance were Paul Berg's identification of Eco RI as an enzyme that cleaved SV40 DNA at a unique site, defined by Dan as ground zero on the Hind cleavage map, similar analysis of SV40 by Joseph Sambrook, and the application of these techniques to bacteriophage ϕ X-174 DNA by Clyde Hutchinson. In addition, Dan was generous in distributing his reagents and information widely, a practice that bore early fruit in the determination of the complete nucleotide sequence of SV40 DNA by Walter Fiers and Sherman Weissman and their co-workers.

Dan freely admitted that he did not foresee the recombinant DNA revolution made possible by the in vitro manipulation of DNA. Nevertheless, many of the techniques developed by Dan's laboratory in the 1970s helped form the foundation of the nascent field of genetic engineering that was being developed by Paul Berg, Stanley Cohen, Herbert Boyer, and others. Indeed, in a certain sense, a main goal of genetic engineering was to amplify segments of cellular DNA in SV40-size packets so that they could be analyzed by the restriction enzyme-based methods developed to study SV40 itself. Dan was quick to recognize the uses and potential risks of this technology. He was a signatory of the letter calling for a moratorium of certain recombinant DNA experiments, but he was also among the first to use molecular cloning to construct and to propagate replication-defective animal virus mutants in bacteria.

In the latter part of his scientific career Dan studied the cellular response to growth signals and isolated and characterized some of the first cellular genes whose expression was regulated by growth factor treatment. Dan was struck by the fact that the genes induced most rapidly by growth factors were often transcription factors, and he pointed out the parallel between these transcription factors and viral immediate-early proteins that orchestrated the sequential program of viral gene expression and genome replication. Dan was particularly intrigued by the ability of variant proteins, such as those produced by alternative splicing, to modulate the activity of the full-length form. Some of his final publications concerned the DNA binding specificity of these cellular transcription factors, work that mirrored his early interests in SV40 large T antigen and sequence-specific recognition of the viral replication origin.

This work brought Dan fame and great recognition, including election to the National Academy of Sciences, numerous honorary degrees, the National Medal of Science, and the 1978 Nobel Prize for physiology or medicine. He greeted the news of his Nobel Prize with characteristic skepticism, insisting on independent confirmation before he would comment on the award, and humility, paying tribute to his wife, Joanne, whose main job, he stated, was to make sure that his head didn't get too large for his hat. The day Dan learned of the Nobel Prize, he deferred departmental celebrations until he had led his regularly scheduled laboratory session for a small group of medical students (although reports had it that little instruction occurred that day). In what was undoubtedly a refreshing break from custom, Dan, at a celebratory university assembly, declined to answer a question from the audience about a matter of public policy by gently reminding the questioner that he was not an instant expert on topics unrelated to his research simply because he had won a Nobel Prize! He was delighted to share the Nobel Prize with Ham Smith and Werner Arber, who carried out the early genetic analysis of restriction and modification in bacteria and who predicted the existence of restriction enzymes. The Nobel citation recognized the role this work played in the birth of modern genetics and predicted much of the genetic revolution that is still underway.

Dan's impact was not restricted to his published work. Because of his fairness and insight, his counsel was widely sought, first by students, colleagues, the staff who washed the petri dishes and swept the floors; later by presidents of the United States, when he was a member of the Presidential Council of Advisors on Science and Technology, and even by the Pope, when Dan was called to Vatican City to provide advice to the Holy See on scientific matters. In these duties, Dan was served well by his interests and knowledge in a wide range of areas, including history, politics, literature, and the arts, which he shared with his wife, Joanne.

Dan's gifts were also recognized at Johns Hopkins, where he was chairman of the Department of Microbiology for many years. He viewed the ideal department to be one the size of a small extended family, and his main role as chairman to be one of *paterfamilias,* fostering the careers of his junior faculty. Dan also served for one year as interim president of the Johns Hopkins University and led the university through a challenging time that saw the successful redefinition of the relationship between the School of Medicine and the Johns Hopkins Hospital. He compared the presidency to his year as a medical intern at Columbia-Presbyterian Hospital, which also forced him to make quick decisions based on limited data, but he tackled it with characteristic thoughtfulness, fairness, good sense, and grace. A genera tion of administrators learned what the scientists had known all along—that Dan was a man of few words who invariably saw the core of the problem and had the vision to find solutions. As aptly put by Jeremy Berg, chairman of biophysics at Johns Hopkins, Dan had the highest signal-to-noise ratio of anyone he had ever met. Most importantly, because he put the interests of the Johns Hopkins University and the biomedical research endeavor first and never sought self-aggrandizement, Dan was able to marshal the support of diverse constituencies. In short, he had the moral authority to lead.

Dan was also a wonderful teacher, particularly in a one-on-one setting, when he would wander through the laboratory, sit down, and ask, “What’s new?” He was always intensely interested in the science and wanted to see the data, and weekend mornings would often find him patiently passaging monkey cells in the tissue culture room. But this interest carried with it a risk. If you hadn’t thought through your results, Dan could solve your problem on the spot. We quickly learned to analyze our own results carefully before showing them to Dan, lest we be scooped by the boss! Dan also would not accept facile explanations or hand waving, and instead he would insist, “Well, what’s your experiment?” He embraced young scientists, even those of us who did not immediately grasp how the analysis of DNA fragments, defined by the arbitrary cleavage specificities of bacterial enzymes, would revolutionize genetics. Dan taught us his approach to science, one that entailed reducing a problem to its essential features and then attacking it at its core, and we soon learned not to be satisfied with the surface nuggets along the streambed, but to dig a mine and find the mother lode.

As Dan approached his seventieth birthday he looked forward to completing his term as university president and returning to the laboratory. He told me, “I’m ready to come back full-time to being a professor, to do some teaching, and to continue with my research. I’m thinking about what new areas of science I want to get into. I’m hoping that Howard Hughes Medical Institute will want to consider to support me for a little while, and I am looking forward to continuing what I consider a privileged life.”[1]

The following year Dan was diagnosed with acute myelogenous leukemia. He continued to come to the laboratory between courses of chemotherapy and hospitalizations, and he particularly enjoyed long walks through his Mt. Washington neighborhood with Joanne. He was also enormously proud of the accomplishments of his family. For many years, Joanne was a lawyer serving in the City of Baltimore’s Department of Legislative Reference. Benjamin is on the faculty of the University of Pennsylvania, Eli is a lawyer who has returned to graduate school at Hopkins to obtain a Ph.D. in history, and Jeremy is a neuroscientist who had joined Dan on the faculty in the Department of Molecular Biology and Genetics at Hopkins. On the night of November 16, 1999, Dan passed away at home.

Dan Nathans changed the way we viewed viruses and genes. When he began his studies dissecting the genome of SV40 in 1970, genes were *terra incognita*. The coastline had been roughly charted by classical genetic experiments, but the vast unbroken interior stretched on toward a distant horizon. Dan taught us how to draw lines of longitude and latitude on this map, and gave us the first lessons on how to fill in all the glorious detail. The true measure of this work is that today we can barely imagine how to analyze viruses and genes without using the approaches pioneered in Dan’s laboratory. Challenge a student to design a molecular genetic experiment that doesn’t entail the use of restriction enzymes or molecular cloning. You might as well ask for bricks without straw.

Despite the enormous importance of his scientific contributions and administrative service, those who knew Dan will remember him chiefly for his personal qualities. He was gentle, soft-spoken, modest, scrupulously fair, and unswervingly honest. His success was leavened by his humility, and his intelligence by his wisdom. For as long as I can remember, conversations about Dan focused not on his scientific accomplishments but on these extraordinary human characteristics. To work closely with Dan Nathans was a privilege beyond measure, an experience that forever shaped our science and our lives.

I FIRST MET Dan Nathans when I arrived at Johns Hopkins as a medical student in 1974, and I got to know him well beginning in 1977, when I entered his laboratory to carry out Ph.D. dissertation research. This memoir is based largely on my personal recollections of Dan and his laboratory dating from this exciting time. I was greatly assisted by an audiotape interview that I conducted with Dan in 1996, in which he reflected at length on his background, scientific career, and administrative duties.[1] Another valuable source of information was the article he published on the occasion of his being awarded the 1978 Nobel Prize in medicine or physiology entitled, “Restriction Endonucleases, Simian Virus 40, and the New Genetics” (1979). I am also greatly indebted to Thomas Kelly, Thomas Shenk, and Steven Desiderio, who encouraged me to commit my memories and thoughts to paper; to my friends and colleagues who shared their recollections of Dan with me; and to Keith Peden and Charles Radding, who provided helpful suggestions on this manuscript.

NOTES

1. Audiotape interview of Daniel Nathans conducted in July 1996 in the series “Leaders of American Medicine,” sponsored by Alpha Omega Alpha.

2. T.J.Kelly and H.O.Smith. A restriction endonuclease from *Hemophilus influenzae*. II. Base sequence of the recognition site. *J. Mol. Biol.* 53(1970):393–409.

3. K.Danna and D.Nathans. Specific cleavage of simian virus 40 DNA by restriction endonuclease of *Hemophilus influenzae*. *Proc. Natl. Acad. Sci. U. S. A*. 68(1971):2913–17.

SELECTED BIBLIOGRAPHY

1961 With F.Lipmann. Transfer of amino acids from aminoacyl-sRNA to protein on ribosomes of *E. coli. Proc. Natl. Acad. Sci. U. S. A.* 47:497–504.

1962 With G.Notani, J.H.Schwartz, and N.D.Zinder. Biosynthesis of the coat protein of coliphage f2 by *E. coli* extracts. *Proc. Natl. Acad. Sci. U. S. A.* 48:1424–31.

1964 Puromycin inhibition of protein synthesis: Incorporation of puromycin into peptide chains. *Proc. Natl. Acad. Sci. U. S. A.* 51:585–92.

1968 With Y.Shimura and H.Kaizer. Fragments of MS2 RNA as messengers for specific bacteriophage proteins: Fragments from fluorouracil-containing particles. *J. Mol. Biol.* 38:453–55.

1969 With K.Eggen. Regulation of protein synthesis directed by coliphage MS2 RNA. II. In vitro repression by phage coat protein. *J. Mol. Biol.* 39:293–305.

1971 With K.Danna. Specific cleavage of simian virus 40 DNA by restriction endonuclease of *Hemophilus influenzae. Proc. Natl. Acad. Sci. U. S. A.* 68:2913–17.

1972 With K.J.Danna. Bidirectional replication of simian virus-40 DNA. *Proc. Natl. Acad. Sci. U. S. A.* 69:3097–3102.

With K.J.Danna. Studies of SV40 DNA. 3. Differences in DNA from various strains of SV40. *J. Mol. Biol.* 64:515–18.

1973 With W.W.Brockman and T.N.H.Lee. Evolution of new species of viral DNA during serial passage of simian virus-40 at high multiplicity. *Virology* 54:384–97.

With K.J.Danna and G.H.Sack. Studies of simian virus-40 DNA. 7. Cleavage map of SV40 genome. *J. Mol. Biol.* 78:363–76.

With G.Khoury, M.A.Martin, T.N.H.Lee, and K.J.Danna. A map of simian virus 40 transcription sites expressed in productively infected cells. *J. Mol. Biol.* 78:377–89.

1974 With P.Berg, D.Baltimore, H.W.Boyer, S.N.Cohen, R.W.Davis, D.S.Hogness, R.Roblin, J.D.Watson, S.Weissman, and N.D. Zinder. Potential biohazards of recombinant DNA-molecules. *Science* 185:303.

With C.J.Lai. Mapping temperature-sensitive mutants of simian virus 40—rescue of mutants by fragments of viral DNA. *Virology* 60:466–75.

With W.W.Brockman. Isolation of simian virus 40 variants with specifically altered genomes. *Proc. Natl. Acad. Sci. U. S. A.* 71:942–46.

1975 With G.Khoury, M.A.Martin, and T.N.H.Lee. Transcriptional map of SV40 genome in transformed cell lines. *Virology* 63:263–72.

1976 With W.A.Scott and W.W.Brockman. Biological activities of deletion mutants of simian virus-40. *Virology* 75:319–34.

1977 With K.Rundell, J.K.Collins, P.Tegtmeyer, H.L.Ozer, and C.-J. Lai. Identification of simian virus-40 protein-A. *J. Virol.* 21:636–46.

1978 With D.Shortle. Local mutagenesis: A method for generating viral mutants with base substitutions in preselected regions of viral genome. *Proc. Natl. Acad. Sci. U. S. A.* 75:2170–74.

1979 Restriction endonucleases, simian virus-40, and the new genetics. *Science* 206:903–909.
With D.R.Shortle and R.F.Margolskee. Mutational analysis of the simian virus-40 replicon—pseudorevertants of mutants with a defective replication origin. *Proc. Natl. Acad. Sci. U. S. A.* 76:6128–31.
1980 With K.W.C.Peden, J.M.Pipas, and S.Pearson-White. Isolation of mutants of an animal virus in bacteria. *Science* 209:1392–96.
1982 With D.DiMaio. Regulatory mutants of simian virus-40—effect of mutations at a T-antigen binding-site on DNA-replication and expression of viral genes. *J. Mol. Biol.* 156:531–48.
1983 With D.I.H.Linzer. Growth-related changes in specific messenger RNAs of cultured mouse cells. *Proc. Natl. Acad. Sci. U. S. A.* 80:4271–75.
1985 With L.F.Lau. Identification of a set of genes expressed during the G0/G1 transition of cultured mouse cells. *EMBO J.* 4:3145–51.
1991 With Y.Nakabeppu. A naturally occurring truncated form of FOSB that inhibits fos jun transcriptional activity. *Cell* 64:751–59.

WILLIAM HARRISON RIKER

September 22, 1920-June 26, 1993

BY BRUCE BUENO DE MESQUITA AND KENNETH SHEPSLE

WILLIAM RIKER WAS A VISIONARY scholar, institution builder, and intellect who developed methods for applying mathematical reasoning to the study of politics. By introducing the precepts of game theory and social choice theory to political science he constructed a theoretical base for political analysis. This theoretical foundation, which he called "positive political theory," proved crucial in the development of political theories based on axiomatic logic and amenable to predictive tests and experimental, historical, and statistical verification. Through his research, writing, and teaching he transformed important parts of political studies from civics and wisdom to science. Positive political theory now is a mainstream approach to political science. In no small measure this is because of Riker's research. It is also a consequence of his superb teaching—he trained and influenced many students and colleagues who, in turn, helped spread the approach to universities beyond his intellectual home at the University of Rochester.

THE EARLY YEARS

Bill, as he was known to his friends, was born in Des Moines, Iowa, on September 22, 1920. He was the muchcherished only son of Ben and Alice Riker. Ben, after whom Bill would later name one of his own sons, owned a bookstore in Des Moines. The father's love of books was shared with his son, who was taught to read at the age of three. Bill's ability to learn, precociously revealed, continued with him until his last breath.

In a pre-Depression depression in Iowa the Riker family bookstore failed in 1925. Facing hard times, the family moved to Battle Creek, Michigan, and then on to Detroit. Bill's favorite recollection from his Michigan years was that he was given an air rifle for perfect attendance at Baptist Sunday School. The family's fortunes improved following a move to Indianapolis, Indiana, in 1932. There Ben Riker established a fine bookstore at L.S.Ayres, the well-known and innovative Indianapolis department store. Presaging his son's later prominence and intellectual rigor, Ben Riker himself became a highly influential book dealer. When John Bartlow Martin, a well-known journalist, later speechwriter for Adlai Stevenson, John Kennedy, Lyndon Johnson, Robert Kennedy, Hubert Humphrey, and George McGovern, and ambassador to the Dominican Republic, wrote a personal history of Indiana, Alfred Knopf, Sr., consulted Ben Riker for advice on the book's merits. Bill's father disliked the manuscript, noting that Martin allowed his judgment to be influenced by his "political, social, and economic prejudices." He went on to note that "Most literate Hoosiers—who are the only ones who buy books and in whom I am chiefly interested—will not accept the book as a true picture of Indiana…." (http://www.indianahistory.org/pub/traces/jbmart.html). The father's passion for even-handed objectivity seems to have been inherited by his son. Just such dispassionate even-handedness and analytic objectivity were the driving passions of Bill Riker's intellectual life.

Following graduation from Shortridge High School in

1938, Bill went to DePauw University, from which he graduated in 1942. Bill worked for RCA following his graduation. There he learned to understand something about how complex organizations function, a subject that continued to fascinate him during his years as a Ph.D. student at Harvard (1944–48), where he wrote a dissertation on the Congress of Industrial Organizations.

Bill married Mary Elizabeth Lewis (M. E.) in 1943, a loving union that lasted for 50 years until Bill's death. M.E. and Bill had four children: two daughters and two sons. One son, Ben, died tragically in an automobile accident in the summer of 1973 while returning with friends from a vacation in Hudson's Bay. This tragedy made even stronger the deep ties of affection that made and make the Riker family such a wonderful group of people. Bill's merits in no small part are due to the support and encouragement he had at home. That encouragement was tempered as well by M. E.'s ability to keep Bill's feet firmly rooted to the ground. On one occasion, for instance, one of us (B.B.dM.) vividly recalls sitting in the Riker living room as Bill explained that he had kept track of his score in over 250,000 games of Solitaire because he was interested in whether randomness really existed. M. E. quickly pointed out that Bill was too cheap to replace the deck of cards (this was before computer Solitaire), so that the cards stuck together when he shuffled, facilitating patterns across games. Alas, he had to admit it was true.

During his years at Harvard, Bill established himself as an independent-minded, innovative intellect. Richard L.Park, a classmate at Harvard, recalled that the other graduate students thought Bill both brilliant and extremely odd. Indeed, he was odd. At a time when other political scientists were absorbed with descriptive case studies Bill was struggling with how to study politics more analytically. He was searching for a method that would serve as the platform upon which to build a science of politics. That method was to begin to take shape in his mind a few years later.

Following completion of his doctorate in 1948 Bill became an assistant professor at Lawrence University (then Lawrence College) in Appleton, Wisconsin. He remained at Lawrence until 1962, having risen to the rank of professor. Bill maintained close ties with friends at Lawrence and sustained a deep affection for the opportunity Lawrence gave him to explore his ideas about politics. Lawrence University returned the admiration and affection, awarding Riker an honorary doctorate in 1975.

While at Lawrence, Bill studied a 1954 paper by L.S. Shapely and Martin Shubik in which they developed a mathematical argument for what they called a “power index.” The power index offered a mathematical formula expressing a legislator’s power as a function of his ability to swing decisions by turning a losing coalition into a winning coalition. It exemplified a new vein of literature that addressed political processes in the language of mathematics, including the work of John von Neumann and Oskar Morgenstern, Duncan Black, Kenneth Arrow, and Anthony Downs. Riker rapidly introduced this work into his curriculum at Lawrence and used it as the basis for his new science of politics. He had the vision to see how these strands of research, derived mostly from economics but ironically with little impact in that discipline at the time, could be put to powerful use in building a science of politics. The remainder of his professional life was devoted to developing this science through research, teaching, and institution building.

BUILDING A POSITIVE THEORY OF POLITICS

In the mid-1950s Riker adopted and built upon a significant array of approaches to the study of political phenom ena, including methodological individualism, an emphasis on micro-foundations, game theory, spatial models, axiomatic set-theoretic treatments of rational action, and generalized Condorcet results, questioning the validity of processes for collective decision making. Between 1957 and 1959 Riker wrote three formal papers that indicated his initial steps toward his eventual theoretical synthesis. Two papers drew on Shapely and Shubik's formulation of the power index and a third paper set about determining whether Arrow's Possibility Theorem, which predicted that n-person voting procedures for more than two outcomes should demonstrate an inherent instability, pertained to actual voting practices (1957, 1958, 1959). Whereas these papers were mathematical and attempted to draw generalized conclusions by combining theoretical deduction with empirical tests, they did not as yet put together the pieces that would later characterize positive political theory. Notably, even though Riker was engaging in experiments in coalition formation using a game-theoretic structure, neither game theory nor an explicit "rational action" model was relevant to these early papers.

Riker also wrote two papers published in philosophy journals before the close of the decade. These papers discuss the importance of carefully circumscribing the events defining a scientific study and the need to base science on "descriptive generalizations" (1957, 1958). In these articles Riker challenged the standard view in political science that promoted the study of the idiosyncratic details of rare and influential events. This challenge to the case study method and to so-called thick description remains at the core of methodological debates today.

By 1959, when he was selected as a fellow at the Center for Advanced Study in the Behavioral Sciences, Riker had a clear and explicit vision of the theoretical approach he was to pioneer. In his application to the Center he wrote, "I describe the field in which I expect to be working at the Center as 'formal, positive, political theory.'" He elaborates, "By Formal, I mean the expression of the theory in algebraic rather than verbal symbols. By positive, I mean the expression of descriptive rather than normative propositions." This document is telling of Riker's own sense of intellectual development, and his reflective and unabashed program for political science. He states,

> I visualize the growth in political science of a body of theory somewhat similar to…the neo-classical theory of value in economics. It seems to be that a number of propositions from the mathematical theory of games can perhaps be woven into a theory of politics. Hence, my main interest at present is attempting to use game theory for the construction of political theory.

Riker spent the 1960–61 academic year at the Center. In this fertile year away from the responsibilities of teaching he wrote *The Theory of Political Coalitions* (1962), which served as a transforming study in political science. In *The Theory of Political Coalitions,* Riker deduced the size principle, introducing the idea of *minimal* winning coalitions in the study of electoral and legislative politics as an alternative to the view of vote maximization expressed in Downs (1957). The size principle states that in n-person, zero-sum games, where side-payments are permitted, where players are rational, and where they have perfect information, only minimum winning coalitions occur.

Downs argued that politicians are primarily office seekers rather than policy makers or allocators of resources. As such, they maximize electoral support and, therefore, forge coalitions as large as possible. Riker's decision makers make authoritative allocation decisions and so seek to minimize the number of claimants on the distribution of resources. A vast literature on coalition formation and government stability has grown out of the debate between Riker and Downs.

The Downsian model indicates that on unidimensional issues and in winner-take-all elections, politicians adopt (usually centrist) policy positions in order to maximize their vote share. Downs's politicians care only about winning office. They do not concern themselves with the policy or private goods concessions they must make to others in order to win.

Riker, in contrast, argued that maximizing votes is costly. Voters are attracted to a candidate by promises about personal benefits. Candidates have preferences of their own about the distribution of scarce resources in the form of private goods to their backers and leftover resources for their own use. To attract votes, politicians must pay a cost by sacrificing some personal interests or granting private side-payments to prospective supporters in an effort to avoid alienating potential voters. Riker argued that rational politicians, motivated primarily by a desire to control resources, seek to attract just enough votes to win and no more, subject to variation above minimal winning size only because of uncertainty about the preferences of voters or their loyalty. By forming minimal winning coalitions politicians make as few concessions as possible, while still controlling sufficient support to maintain governmental authority and pass legislation.

Riker's theory of political behavior marked a sharp departure from standard political science views and an equally sharp departure from views standard in economics. Political scientists at the time frequently wrote normative treatises on governance or attributed political decisions to psychological forces and attitudinal factors. For economists concerned with exchange in the marketplace collective outcomes were seen as a fairly mechanical adding machine equating supply and demand, with neither the marginal buyer nor marginal seller able to influence the market price. Riker drew a fundamental distinction between collective outcomes in economics and in politics. He saw collective outcomes in politics as the product of conscious strategic processes. This is a crucial distinction because the rational actor in political arenas intentionally calculates how to achieve aims in a strategic environment with other strategically acting agents, making game theory the central analytic tool for modeling political processes.

When *The Theory of Political Coalitions* was published, the book created a significant stir precisely because Riker not only exhorted the discipline to become more scientific, but because he showed how to do it. As one reviewer noted, "Although Riker's particular approach is not the answer to all of the discipline's woes, he has certainly succeeded in challenging us by example. Those who would accept the challenge had better come prepared with a well sharpened kit of tools. For, either to emulate or attack, nothing less will suffice" (Fagen 1963, pp. 446–47).

Riker was the first political scientist, and indeed the first non-RAND theoretician, to recognize the potential of game theory to understand political interactions. It was Riker who bestowed upon game theory the promise of a new life after RAND defense strategists concluded the theory was of little merit for studying warfare and after economists rejected the hopes and promises of von Neumann and Morgenstern. A later generation of economists grasped its promise for grounding a new mathematics of the market, launching the "non-cooperative revolution" in economics.

THE ROCHESTER TRANSFORMATION: INSTITUTION BUILDING

The year 1962 marked a major turning point in Bill's life and in the future of political science. Not only was *The*

Theory of Political Coalitions published, but the Riker family moved to Rochester, New York, where Bill became chair of the Department of Political Science at the University of Rochester.

The University of Rochester hired Riker with the understanding that he would have the resources and freedom to build a program modeled after his intellectual vision. Rochester was true to its word, forging a loyalty to the university on Bill's part that was the stuff of legend. Whenever a colleague was tempted by an offer elsewhere, Bill, as department chair from 1962 to 1977, simply could not imagine how anyone could prefer to be anywhere else. Apparently he was right. Hardly anyone left. The cold, long winters of Rochester were no problem given the lively, intellectually stimulating, entertaining, and engaging informal daily exchanges between faculty and graduate students—all treated and feeling absolutely as equals—over bag lunches.

Immediately upon his arrival in Rochester, Riker set about outlining a strategy for building the Rochester political science department. His strategy emphasized both behavioral methods and positive theory. The result was 14 new courses and seminars, an entirely new curriculum unlike those found anywhere else at the time. The new Ph.D. requirements stressed quantification and formal analysis. He shifted the emphasis common in other programs from the literature to his focus on developing the tools necessary to do rigorous research into the theoretical properties and empirical laws of politics. The effort succeeded. One decade later, the unranked department Bill inherited was ranked fourteenth in the country, despite never having a faculty larger than 13 during those years (Roose and Andersen, 1970). Another decade later, the department, still small by comparison with its competitors, was ranked among the top 10 and placed its students at the most prestigious universities, in the mean time helping to build sister centers of positive political theory at such institutions as Caltech, Washington University, and Carnegie-Mellon.

Riker's efforts on behalf of positive political theory extended beyond the confines of his home department at the University of Rochester. He maintained an active publication record, contributing so many articles to the flagship journal of political science, the *American Political Science Review,* that its editor wrote to him, "There is some danger of turning this journal into the 'William H.Riker Review.'" Among the more distinguished was a paper on power (1964), several on experimental methods (1967, 1970) —the latter with his student William Zavoina—and his seminal and controversial theory of the calculus of voting with another of his students Peter Ordeshook (1968).

In addition to his major contributions of original research during this period Riker sought to further establish his method through co-authorship with Peter Ordeshook of a textbook that elucidated the parameters of positive political theory. This text, entitled *An Introduction to Positive Political Theory* (1973), was aimed at advanced undergraduates and beginning graduate students, and was an important step in defining positive political theory for a widespread audience. It introduced the assumption of rationality and the formal account of preference orderings, and it demonstrated the positive approach to political science through its application to such political problems as political participation, voting and majority rule, public goods, public policy, and electoral competition. The text also contained discussions on formal theory and deductive results from formal theory including n-person and two-person game theory, the power index, and the size principle.

Riker did not limit his efforts to the development of positive political theory at Rochester or to the impact of his own research. Together with other like-minded scholars, Bill formed a community that fostered the rise of rational choice theory as a cross-disciplinary phenomenon. In the early 1960s a meeting of minds occurred, resulting in the founding of the Public Choice Society. Researchers active in these early meetings included subsequent Nobelists Herbert Simon (economics and public administration), John Harsanyi (game theory), and James Buchanan (public finance), as well as Gordon Tullock (public finance), Mancur Olson (economics), John Rawls (philosophy), James Coleman (sociology), and of course, William Riker. The Public Choice Society is noteworthy for helping to generate the critical mass required to establish the rational choice approach as an academy-wide method of inquiry. In founding the society, members ensured that their newly wrought discipline would benefit from an active network of similar-minded intellects. To further this end, the society held annual meetings and initiated an enduring journal, *Public Choice.*

RECOGNITION

Riker personally met with career successes and external honors that established his intellectual legacy and served as community recognition of the significant role he played in remaking political science. In 1974 Riker was elected to the National Academy of Sciences and thus was among the first political scientists to be inducted into this community. Soon other Rochesterians were in his midst, including Fenno, Shepsle, McKelvey, and Fiorina, as well as "fellow travelers" like John Ferejohn.

Riker was elected to the American Academy of the Arts and Sciences in 1975 and in 1983 was chosen to serve as president of the American Political Science Association. Additionally, he was honored, as mentioned earlier, by Lawrence University with an honorary degree. DePauw Uni versity, his undergraduate school, likewise honored him in 1979, as did the State University of New York, Stony Brook, in 1986. In 1977 Upsala University in Sweden chose Bill for an honorary doctorate as part of the university's five-hundredth-anniversary celebration. Bill also was the recipient of numerous distinguished fellowships and awards, including a Guggenheim Fellowship in 1983, National Science Foundation grants from 1967 to 1973 and again for 1985–87. He was the Fairchild fellow at Caltech in 1973–74, a visiting professor at Washington University in 1983–84, and the recipient of three teaching awards: one at Lawrence (in 1962) and two at Rochester (in 1988 for undergraduate teaching and in 1991 for graduate teaching). After leaving the department chairmanship, Bill went on to serve as dean of graduate studies at Rochester from 1978 to 1983 and continued to teach an overload even after becoming professor emeritus.

RESEARCH IN THE LATER YEARS

At the time Bill became president of the American Political Science Association, his research interests were drawn to the role political institutions and political campaigns play in shaping outcomes. His seminal work, *Liberalism Against Populism* (1982), laid out a fresh and controversial theory of democracy. In it Bill used strategic logic to challenge the idea that democracy leads to especially good and representative public policy, suggesting instead that it had little advantage over other forms of governance on that dimension. Democracy's great advantage lay in the ease with which one could throw the rascals out. This naturally led him to inquire into what politicians do to avoid such a result. A series of papers followed exploring democracy, two-party competition, and the nature of representative government. In 1984 he focused the attention of the discipline on these issues in his article "The Heresthetics of Constitution Making." Here, coining the term "heresthetics" to refer to the manipulation of the structure of issues for political advantage, Bill undertook research that occupied the remainder of his life.

He built a theory of how politicians use issues and linkages across issues for strategic advantage. This led him to inquire into how and why campaigns matter. An easily accessible first approximation of an answer was provided in his book *The Art of Political Manipulation* (1986). His final treatments of issue formation and the rhetoric of campaigning were the centerpieces of his last two books. The first, an edited volume entitled *Agenda Formation* (1993), was published only days before Riker died. The collection of essays examined how agenda control, political institutions, and political structure induce equilibria to avert chaos in public policy.

In his last book, the posthumously published *The Strategy of Rhetoric* (1996), Riker brought together his concern for heresthetic maneuvering with his concern for political persuasion. He examined the campaign to ratify the U.S. Constitution, using innovative statistical techniques to test his new theory of political persuasion. Most rational choice scholarship takes the institutional structure in which preferences are aggregated as a given in the model. Riker, however, drew attention to the significance of the proactive role of politicians in structuring the environment in which preferences are coordinated into a collective outcome. Thus, Riker contrasted heresthetics with rhetoric. Whereas rhetoric involves persuasion, heresthetics involves strategic manipulation of the setting in which political outcomes are reached; it is in essence a strategy of rhetoric. *The Strategy of Rhetoric* is a monumental work. It provides an entirely new way to think about strategic uses of rhetoric and campaigning that is defining the research agendas of scholars across the various sub-specialties of political science.

THE MAN

William Riker's intellectual accomplishments were prodigious. He served as an academic exemplar for anyone who knew him. He was a brilliant and highly productive scholar. He was a dedicated and committed teacher of undergraduates and graduate students. He was a remarkable administrator and institution builder. But above all, he was an astounding human being. We cannot end without speaking of the man beyond the scholar.

We have mentioned Bill's loyalty to Rochester and his abiding affection for Lawrence. Bill remained in touch with virtually every Ph.D. student with whom he had worked. He regularly purchased stock through a former student who became a broker. He traveled the world to assist his students in building programs wherever they were. On his seventieth birthday, the political science department at Rochester threw a party and two-thirds of the students who had ever received a Ph.D. from the department came to participate in the celebration. They came at their own expense from places as far away as India, Korea, and Europe. Bill Riker inspired such devotion because he himself was so devoted.

As an individual his multidimensional creativity was apparent and permeated well beyond his specialization in the social sciences. He had a photographic memory, recalling precise details from newspaper articles from his childhood or specific paragraphs in books he had read 50 years earlier. His creativity, however, extended beyond this remarkable ability. A simple example illustrates the point. Everyone is familiar with the song, "The Twelve Days of Christmas." Bill, bored with hearing the song on his car radio (he eventually decided he didn't need a radio in his car), but never one to turn away from an analytical or interpretive puzzle, thought about the song, solved the gift-giving algorithm, and discovered that 364 gifts are given, one for each day of the year, except Christmas day, which presumably already had the gift of Christ. An easy enough problem, but only someone of distinct creativity in everything would think to question the meaning of this seemingly trivial song.

Consider this second illustration, developed more fully in Riker's *The Art of Political Manipulation*. Bill had always regarded C.P.Snow's *The Masters* as one of the great political novels (ranking it second only to Robert Graves's *I, Claudius*). Nominally, it is a story about the campaign and election of an Oxbridge college master, a contest pitting a humanist against a scientist and thus a vehicle freighted with that very same symbolism and ideological clash found in any national campaign between Tory and Labour or Democrat and Republican. Most readers assume that Eliot, a relatively junior tutor in the college—as much observer as participant in the unfolding political drama and the disinterested narrator of the tale—is the voice of Snow himself. One of the more senior residents of the college, Chrystal (all are identified only by surnames), is the personification of the political insider and most important of all is *pivotal* to the outcome; he will make the next master according to how he ultimately decides. In the final scene each elector in the college rises, first announcing his own full name and then declaring for whom he supports with his vote. Chrystal rises and declares himself Charles Percy Chrystal. Or, as Riker notes, C.P.Chrystal—a small play on the author's own name, C.P.Snow. It is Chrystal, not Eliot, who is the voice of the author! Snow, whether consciously or not, fancies himself the insider, the pivot, the maker and breaker of leaders, not the mere observer and narrator. The novel is a truly exciting story of political intrigue; that in itself is sufficient unto the day for most of us interested in politics. Bill Riker went deeper than most of us with the insight that behind the drama of politics is introspection, calculation, personal ambition, even hubris. This may not be powerful literary criticism, but it is first-rate political intuition. It is the product of an uncommon mind.

Bill's skills as an administrator included the great subtlety with which he managed his department. Bill often dropped into the offices of his colleagues to chat, frequently taking them for walks in parkland owned by the University of Rochester (the trustees' garden). Naturally, assistant professors were especially flattered by the attention, even more so when, as it happened with one of us (B.B.dM.), it resulted in a jointly written article. Years later, when that former assistant professor became department chair, he asked Bill what the chair does. Bill replied that the chair drops in causally on junior faculty, chats with them, takes them out occasionally, and that way knows whether they are on a good path toward tenure. The chair helps steer junior colleagues so that they do the best they can. That is, even in the most informal moments part of him was thinking about how to help others succeed.

On his deathbed, Bill Riker continued his devotion to helping others. Hospitalized, knowing that his death was imminent, he asked a colleague to let a student know that he had read her paper and thought it was excellent. Remarkably, he apologized that he was unable to give her written comments. At 10 p.m. on the night he died in a hospice, Bill, extremely weak and barely audible, reminded one of us (B.B.dM.) of advancements and honors he desired for a former student and long-time colleague at Rochester. He died a few hours later. His last three days, when he knew he would not survive the weekend, were lived with as much grace and generosity of spirit as any of us could hope for in a lifetime.

Bill Riker was a once-in-a-century man. He was a superb and truly beloved colleague, friend, and teacher. Future generations may well mark him as the founder of modern political science. Those of us privileged to have known him will never forget him. All future generations of political scientists will be shaped by his vision.

M.E.RIKER GENEROUSLY provided insights into Bill's early years. We benefited as well from the study by Amadae and Bueno de Mesquita (1999).

REFERENCES

Amadae, S.M., and B.Bueno de Mesquita. 1999. The Rochester School: The origins of positive political theory. *Annu. Rev. Polit. Sci.* 2:269–96.

Downs, A. 1957. *An Economic Theory of Democracy.* New York: Harper & Row.

Roose, K.D., and C.Andersen. 1970. *A Rating of Graduate Programs.* Washington, D.C.: American Council on Education.

Shapley, L.S., and M.Shubik. 1954. A method for evaluating the distribution of power in a committee system. *Am. Polit. Sci. Rev.* 48:787–92.

SELECTED BIBLIOGRAPHY

1953 *Democracy in the United States*. New York: Macmillan.

1955 The senate and American federalism. *Am. Polit. Sci. Rev*. 49:452–59.

1957 Events and situations. *J. Philos.* 54:57–70.

With R.Schaps. Disharmony in federal government. *Behav. Sci*. 2:276–90.

1958 The paradox of voting and congressional rules for voting on amendments. *Am. Polit. Sci. Rev*. 52:349–66.

Causes of events. *J. Philos.* 56:281–92.

1959 A method for determining the significance of roll calls in voting bodies. In *Legislative Behavior,* eds. J.Wahlke and H.Eulau, pp. 337–83. Glencoe, Ill.: Free Press.

A test of the adequacy of the power index. *Behav. Sci.* 4:120–31.

1961 Voting and the summation of preferences. *Am. Polit. Sci. Rev*. 55:900–11.

1962 *The Theory of Political Coalitions.* New Haven: Yale University Press.

1964 *Federalism: Origin, Operation, Maintenance.* Boston: Little-Brown.

Some ambiguities in the notion of power. *Am. Polit. Sci. Rev*. 58:341–49.

1965 Arrow's theorem and some examples of the paradox of voting. In *Mathematical Applications in Political Science,* ed. J.M.Claunch, vol. I, pp. 41–60. Dallas: Southern Methodist University Press.

1967 Bargaining in three-person games. *Am. Polit. Sci. Rev.* 61:342–56.

1968 With P.Ordeshook. A theory of the calculus of voting. *Am. Polit. Sci. Rev.* 62:25–42.

1970 With W.Zavoina. Rational behavior in politics. *Am. Polit. Sci. Rev.* 64:48–60.

1973 With P.Ordeshook. *Introduction to Positive Political Theory.* Englewood Cliffs, N.J.: Prentice-Hall.

1976 With Richard Niemi. The choice of voting systems. *Sci. Am.* 234(June):21–27.

1980 Implications from the disequilibrium of majority rule for the study of institutions. *Am. Polit. Sci. Rev.* 74:432–46.

1982 The two-party system and Duverger's Law: An essay on the history of political science. *Am. Polit. Sci. Rev.* 76:753–66.

Liberalism Against Populism: A Confrontation Between the Theory of Democracy and the Theory of Social Choice. San Francisco: Freeman.

1984 The heresthetics of constitution making: The presidency in 1787, with comments on determinism and rational choice. *Am. Polit. Sci. Rev.* 78:1–16.

1986 *The Art of Political Manipulation.* New Haven, Conn.: Yale University Press.

1993 *Agenda Formation.* Ann Arbor: University of Michigan Press.
1996 *The Strategy of Rhetoric* (published posthumously with the assistance of R.Calvert, J.Mueller, and R.Wilson). New Haven, Conn.: Yale University Press.

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RICHARD C. STARR

August 24, 1924–February 3, 1998

BY ANNETTE W. COLEMAN AND JEFFREY A. ZEIKUS

RICHARD STARR WAS THE outstanding freshwater phycologist of the last half century. He early recognized the value of pure cultures of algae, not just to study life histories but for biochemical, physiological, and genetic work as well. The importance of clones of documented usage led him to establish the Culture Collection of Algae in America, which became the premier collection in the world and the foundation of modern research on algae. While shepherding the collection through its first 47 years and teaching courses both winter and summer, Richard Starr conducted an active research program that yielded significant insights into life history events of algae, including isolation and identification of several plant sexual hormones. His professional contributions—and collaborations and associations that arose from them—were worldwide, earning him major prizes and awards, all richly deserved. His research continued until the day of his death, only a few months after his full retirement from teaching.

Richard Cawthorn Starr was born in Greensboro, Georgia, on August 24, 1924. The Great Depression and the early death of his father left the family in straitened circumstances, and his mother had to take a job to help support young Richard and his sister. Perhaps this influenced his lifelong concern with caring for his mother, and Georgia was always considered home. After high school, Richard attended Georgia Southern Teacher's College (B.S. in secondary education in 1944), fully intending to teach high school. This he did, briefly, but somewhere along the line he decided to take a master's degree at George Peabody College (M.A. in 1947). That led to enrollment at Vanderbilt University in the Ph.D. program. The seminal influence came here, for he met and chose to study under Harold C.Bold, a charismatic mentor and one of the very few phycologists in the United States at that time who had met such European scholars as F.E.Fritsch, a fellow of the Royal Society. For Richard, from then on, the study of algae became the love of his life. Beginning with single green algae cells isolated from soil samples, the favorites of his own major professor Harold C.Bold, his interests progressed to the morphologically elegant desmids and finally to the beautifully motile Volvocales.

Starr worked out the life cycle of *Chlorococcum,* a green soil alga, for his Ph.D. He did this not just from collected samples but also from material brought into the laboratory and cultured through its various life stages. The life history characteristics of such simple soil algae were only revealed by establishing and studying pure cultures, using techniques previously developed by others for bacterial and fungal research. This new approach to understanding protistan organisms was in its infancy. A major developer and pioneer proponent was E.G.Pringsheim, then at Cambridge University in England, where he had found shelter after fleeing Prague with several hundred cultures of algae. Pringsheim was to be the second seminal influence on Starr, for Richard obtained a Fulbright Fellowship to support a year (1950–51) in England with Pringsheim during his doctoral period. There he learned not only the most recent details of Pringsheim's culture techniques but he also brought back to the United States samples of Pringsheim's algal collection, samples that later contributed to the core of the U.S. collection.

Upon his return from Cambridge and completion of his thesis at Vanderbilt in 1952, Starr took a teaching position in the Botany Department of Indiana University, where he rose rapidly through the ranks. Here a year later he formally established the Culture Collection of Algae, making these strains available at minimal cost to anyone. This collection was supported throughout the years by grants from the National Science Foundation and in turn so were the Ph.D. programs of the early graduate students well into the 1960s and beyond. The list of cultures published with and distributed by the *Journal of Phycology* included far more information than simply a listing of the species available. The isolator and collecting location were given where known. Starr also included precise details on how one could isolate individual algae, what formulae were most appropriate for culture media, and the best light and temperature conditions for growth. For several different algae, Starr described in the list how instructors could demonstrate sexual reproduction in living cultures in the classroom, a dynamic subject that always elicited the interest of the general biology student. With the passing years, thanks to his developing habit of driving around the countryside sampling pig ponds, drainage basins, pools and streams, trees, soils, and even hoof prints, additional clonal isolates of a wide variety of algae accumulated in the collection.

Indiana University was the home of some remarkable biologists of the mid-century, including Herman J.Muller of *Drosophila* fame and T.M.Sonneborn of *Paramecium* fame. Constant exposure to their activities gave Starr a continuous infusion of knowledge on genetics and on protozoa. By

1954 he had published his first paper on genetics of algae, an analysis of a "natural" mutant of the desmid *Cosmarium*. His growing interest in the Conjugales led to his second algal foray abroad, to the laboratory of Paavo Kallio in Turku, Finland, in the summer of 1956. *Spirogyra, Cosmarium, Netrium, Closterium, and Micrasterias* became subjects of graduate studies (M.A.Allen, L.Tews, P.W.Cook, P.J.Biebel, B.E.Lippert, and R.Korn).

The edge of the approaching wave of Volvocales was already in the laboratory, however. Starr's collecting habits had turned up a sample of *Gonium sociale* that, upon cloning, proved to be homothallic, forming zygotes within a clonal culture. Colonial green flagellates and related unicells arrived in collection after collection over the next 20 years, often along with a graduate student dedicated to each genus and species (A.W.Coleman, N.J.Lang, M.E.Goldstein, A.E.Brooks, R.Carefoot, W.H.Darden, D.O.Harris, G.E.Kochert, R. Lynn, M.D.McCracken, E.G.Palmer, W.Vande Berg, R.F. Meredith, J.W.Heimke, J.A.Zeikus, R.Palmer, R.O'Neil, M.A.Messina, C.E.Miller, J.H.Allensworth, E.R.Jones, and M.Wood). Analyses of life cycles and nutrition led to ever-improved methods of controlling sexual reactions in culture. He made certain that his students learned all the techniques of isolating and establishing clonal populations of algae they had collected in the field, including how best to induce their asexual and sexual reproductive phases to reveal hitherto unsuspected events. For the Volvocacean family particularly, a vast foundation of information was compiled and numerous isolates were added to the culture collection. Augmented by isolates from collections made during everyone's travels, *Pandorina, Eudorina, Volvulina, Platydorina,* and *Pleodorina* flourished and were soon joined by *Gonium* and *Astrephomene* brought by J.R.Stein during her visit for a year. With these organisms, culture methods both for the propagation and for the analysis and manipulation of sexual cycles were perfected, and comparisons revealed for the first time how genetically diverse many similar morphologies might be.

If a student wished to pursue a problem somewhat aside from the typical ones being done by other students, Starr was amenable to such explorations. Examples of atypical student research topics were deriving mathematical expressions for growth patterns in algae; establishing how fungal parasites attack and destroy algal cells while carrying out their own reproduction; and comparing the ultrastructure of genera within the same taxonomic family to detect similarities and differences. Funding for student research came from his own grants or else he made suggestions on fellowship application procedures. Years after a student had left for a permanent faculty position elsewhere, he could always be depended upon for a glowing letter of support. Even a cash loan to a financially strapped graduate student was not unusual for Richard Starr.

From the smaller members of the Volvocales it was an obvious step to *Volvox,* but one that took another foreign trip, to Dr. Hirose in Kobe, Japan, where collecting provided the famous *Volvox carteri* f. *nagariensis* strains. These continue to this day as the premier material for developmental and genetic studies. The *Volvox,* species presented new problems in controlling gametogenesis, for here a clear influence of male “induction” of female sexual development was observable. While his continuing line of graduate students handled the various *Volvox* species, Starr concentrated on the developmental patterns of *V. carteri* f. *nagariensis,* a readily mutable and promising object for analysis of development. In 1975 he published a careful analysis of cell lineage during development.

Again, a trip abroad led to a major discovery. In 1972-73 an Alexander von Humboldt-Stifting senior award allowed Starr to visit the Max Planck Institute in Koeln, where he developed a collaboration with Prof. Lothar Jaenicke, a collaboration both lifelong and full of mutual appreciation. The symbiosis was the more amazing because Jaenicke was the consummate biochemist and Starr happily declared that his biochemistry text was the Sigma Catalog. The major scientific consequences of this association were twofold. The first was the isolation and identification and eventually the cloning and sequencing of the gene responsible for the "inducing" material in *Volvox carteri*. Two decades later the same duo solved the chemical nature of the pheromones in *Chlamydomonas allensworthii,* responsible for sperm attraction to the egg.

Through these busy years of research and graduate teaching, Starr remained a tireless and dedicated teacher of undergraduates, both in courses and as the hired hands in his laboratory. Starr was not just a dynamic lecturer. His stylish and very accurate drawings on the chalkboard lent visual interest for students once they became accustomed to his being left-handed. An almost unbroken string of summers from 1952 to 1963 found Starr at Woods Hole Marine Biological Laboratory, teaching the marine phycology course, a situation where his teaching influenced a large proportion of the coming generations of phycologists. He brought in outstanding scholars to present lectures on their particular subjects of specialization, among whom were G.F.Papenfuss of Berkeley, John Kingsbury of Cornell, Walter Herndon of Tennessee, and Tyge Christensen of Denmark. Starr made certain that scholarship money was available for his graduate students to attend a summer session, because it was his opinion that one could not be considered a well-educated phycologist without a period of study of marine algae in their natural habitats.

Teaching algae or cryptogamic botany, Starr was known for both the early hour of his laboratory sessions and for the living, performing laboratory materials he provided through careful and clever manipulation of growth beforehand. Laboratory sessions were not somber affairs though, and he was capable of asking such questions as: Why would P.T.Bamum be interested in having *Oedogonium* in his collections? Answer: Because it produces dwarf mates. As a major professor, Richard Starr was demanding of excellence of scholarship, long hours spent in the lab, and diligent seminar attendance. He made it possible for all his students to attend national meetings to give oral or poster presentations, and he went out of his way to introduce students to famous senior scientists whenever possible.

After Starr moved himself and the algae collection to the University of Texas at Austin in 1976, he received both student and faculty awards recognizing his excellence in teaching. His scientific prominence led to his appointment to the Ashbel Smith Professor chair, and at its inception in 1987 to the Harold C. and Mary L.Bold Regents Professor of Cryptogamic Botany chair. At Texas his broadening interests added graduate studies on Glaucophytes and fungi (T.S.Kantz and J.F.White) to the continuing line of Volvocalean work, but he never missed an opportunity to initiate a culture of a new or unusual organism. The cyanobacterial genus named in his honor by a former student was discovered by Starr in a soil sample he had collected from near the Great Ruins in Zimbabwe. This soil sample was but one of many collected during his worldwide trips seeking *Volvox*. After he first saw the obviously undescribed organism, he successfully established clonal cultures of it for further study. To date, *Starria zimbabweensis* is still known only from these cultures.

By the time of the move to Texas, Starr's reputation as a scholar and researcher had earned him election to the National Academy of Sciences (1976). This honor was preceded by the Darbaker Prize (1955) and the Merit Award of the Botanical Society (1973), followed by the Gilbert Morgan Smith Medal of the National Academy of Sciences (1985) and the Phycological Society of America Award of Excellence (1997). His talents as farsighted organizer were also in steady use, as treasurer, vice-president, and president (1959–60) of the Phycological Society of America, as secretary, vice-president, and president (1971) of the Botanical Society of America, as secretary of the International Phycological Society, and as chair of the Botany Section of the National Academy of Sciences. They also led to his chairmanship of the organizing committee for the first International Phycological Congress (1978), and his joining the first delegation of American botanists to visit China after the Cultural Revolution. The Chinese academic community had suffered greatly through the policies of the Cultural Revolution, and Starr helped with both lectures and personal encouragement to restore the Chinese phycological community. This led to numerous exchanges of scholars, welcomed both at Texas and other U.S. sites. Altogether Starr's contributions to international scientific cooperation, particularly in phycology, closely rival in importance even his culture collection.

Researcher, teacher, scholar, head of the culture collection and its constant advisor, promoter of international scientific discourse—all these were Richard Starr. He was a gifted microscopist and his remarkable research results with algae introduced many to the advantages of their study. His infectious love of the algae and his model presentations in lectures and symposia enticed even more researchers to these organisms. Because his scientific standards were high he was never shy about expressing an opinion, but he remained a consummate gentleman. His early students called him (not to his face, of course) Uncle Dickie or Pookey, but his standard appellation was "Doc," and Doc was the constant source of almost infinite information on the algae.

Starr was also an excellent scientific microphotographer both in black and white and color using a variety of microscopes, and his living cultures were subjects of magnificent color films involving time-lapse views of dynamic processes such as colony inversion in *Volvox* and gamete fusion in *Spirogyra*. He taught all his graduate students to use the darkroom and the fruits of this instruction are well demonstrated in their beautifully illustrated dissertations and subsequent publications.

He was a boon companion wherever he traveled in the world, a talented raconteur with a broad sense of humor. His foster dogs, wide-screen TV, and love of classical music, but not excluding Dolly Patron, gave him relaxation. But nowhere was he happier than when he sat down at his microscope with a freshly collected sample from a cow pond to see what was there. He would pull some pipettes and isolate individual cells or organisms. Each subsequent morning, long before others of the department even arrived, he could be found moving slowly along the hanging line of tubes in the light room armed with his pocket magnifier, checking the meniscus and sides of each tube for the appearance of growth. His newly collected soil samples from Australia and New Zealand were awaiting attention on the day he died.

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TAXA NAMED IN HONOR OF RICHARD STARR

Starria gen. nov. (Cyanophyta, described by N.J.Lang. *J. Phycol.* 13(1977):288–96.

Chlorococcum starrii sp. nov. (Chlorophyta, described by F.R. Trainor and P.A.Verses. *Phycology* 6 (1967):237–39.

Cystomonas starrii, transferred by H.Ettl and G.Gartner. *Nova Hedwigia* 44(1987):509–17.

SELECTED BIBLIOGRAPHY

1949 A method of effecting zygospore germination in certain Chlorophyceae. *Proc. Natl. Acad. Sci. U. S. A.* 35:453–56.

1954 Inheritance of mating type and a lethal factor in *Cosmarium botrytis* var. *subtumidum Wittr. Proc. Natl. Acad. Sci. U. S. A.* 40:1060–63

1955 A comparative study of *Chlorococcum* Meneghini and other spherical, zoospore-producing genera of the Chlorococcales. *Indiana University Science Series,* No. 20.

Sexuality in *Gonium sociale* (Dujardin) warming. *J. Tenn. Acad. Sci.* 30:90–93.

1958 The production and inheritance of the triradiate form in *Cosmarium turpinii. Am. J. Bot.* 45:243–48.

1962 A new species or *Volvulina* Playfair. *Arch. Microbiol.* 42:130–37.

1968 Cellular differentiation in *Volvox. Proc. Natl. Acad. Sci. U. S. A.* 59:1082–88.

1969 Structure, reproduction, and differentiation in *Volvox carteri* f. *nagariensis* Iyengar, strains HK 9 and 10. *Arch. Protistenk.* 111:204–22.

With D.O.Harris. Life history and physiology of reproduction of *Platydorina caudata* Kofoid. *Arch. Protistenk.* 111:138–55.

1970 *Volvox pocockiae,* a new species with dwarf males. *J. Phycol.* 6:234–39.

With M.D.McCracken. Induction and development of reproductive cells in the K-32 strains of *Volvox rousseletii. Arch. Protistenk.* 112:262–82.

1971 Sexual reproduction in *Volvox africanus*. In *Contributions to Phycology,* eds. B.C.Parker and R.M.Brown, pp. 59–66. Lawrence, Kan.: Allen Press.

Control of differentiation in *Volvox. Symp. Soc. Study Dev. Growth* 29:59–100.

With W.J.Vande Berg. Structure, reproduction and differentiation in *Volvox gigas* and *Volvox powersii. Arch. Protistenk.* 113:195–219.

1972 A working model for the control of differentiation in *Volvox carreri* f. *nagariensis* Iyengar. *Mem. Soc. Bot. Fr.* 1972:175–82.

1974 With L.Jaenicke. Purification and characterization of the hormone initiating sexual morphogenesis in *Volvox carteri* f. *nagariensis* Iyengar. *Proc. Natl. Acad. Sci. U. S. A.* 71:1050–54.

With R.C.Karn and G.A.Hudock. Sexual and asexual differentiation in *Volvox obversus* (Shaw) Printz, strains Wd3 and Wd7. *Arch. Protistenk.* 116:142–48.

1975 With R.Meredith. The genetic basis of male potency in *Volvox carteri* f. *nagariensis. J. Phycol.* 11:265–72.

1979 With J.W.Heimke. The sexual process in several heterogamous *Chlamydomonas* strains in the subgenus Pleiochloris. *Arch. Protistenk.* 122:20–42.

1980 With J.A.Zeikus. The genetics and physiology of noninducibility in *Volvox carteri* f. *nagariensis* Iyengar. *Arch. Protistenk.* 123:127–61.

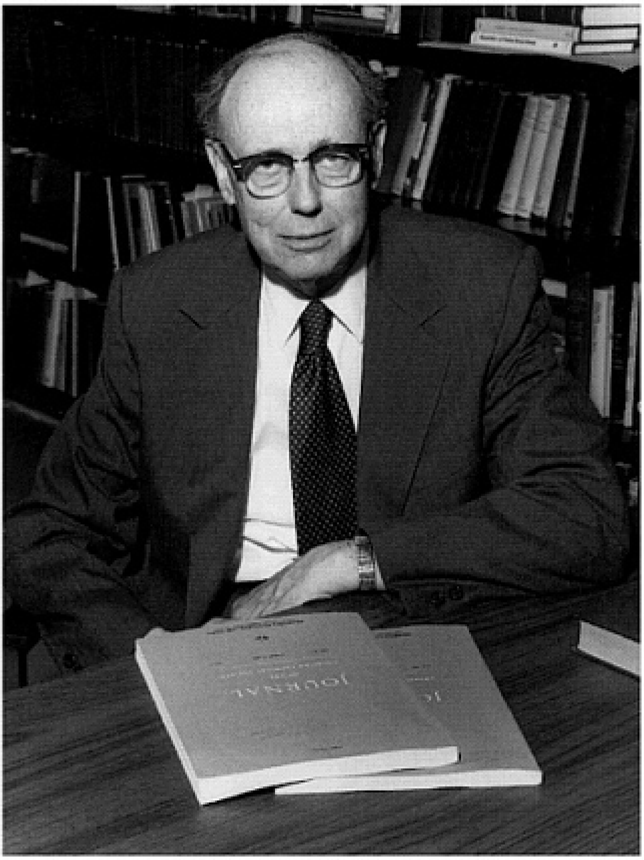
1981 With C.E.Miller. The control of sexual morphogenesis in *Volvox capensis. Ber. Deutsch. Bot. Ges.* 94:357–72.

1984 Colony formation in the algae. In *Encyclopedia of Plant Physiology N. S.,* vol. 17, eds. H.F.Linskens and J.Heslop-Harrison, pp. 261–90.

1986 With L.Jaenicke, R.Gilles, and C.E.Miller. Signals for the timing of differentiation in *Volvox:* Amino acids and glycoproteins as messenger molecules. *Nova ACTA Leopoldina NF* 56:467–72.

1995 With F.J.Marner and L.Jaenicke. Chemoattraction of male gametes by a pheromone produced by female gametes of *Chlamydomonas. Proc. Natl. Acad. Sci. U. S.. A.* 92:651–55.

1996 With L.Jaenicke. The lurlenes, a new class of plastoquinone-related mating pheromones from *Chlamydomonas allensworthii* (Chlorophyceae). *Eur. J. Biochem.* 241:581–85.



Courtesy of William Tarbell, Bolingbrook, Illinois

Dean Stanley Tarbell

DEAN STANLEY TARBELL

October 19, 1913–May 26, 1999

BY NELSON J. LEONARD

DEAN STANLEY TARBELL had a distinguished career in research and teaching in organic chemistry. His contributions to physical organic chemistry included elucidation of addition reactions to olefins, determination of intermediates in the Claisen rearrangement of allyl aryl ethers, and quantitative comparison of the behavior of organo sulfur versus organo oxygen compounds. He discovered new categories of organic compounds, including mixed carboxyliccarbonic anhydrides, and delineated their chemistry. He established the structures of important natural products, notably those of colchicine, which arrests the process of cell division in plants and animals, and the antibiotic fumagillin, which has emerged as an inhibitor of angiogenesis.

In the course of his research, Tarbell also contributed substantially to the methodology of organic synthesis. The University of Rochester and Vanderbilt University, in turn, benefited greatly from his presence on their faculties, and he was most effective in his role as a teacher and a director of research for many, many students. He also established himself, along with his wife, Ann, as a biographer of chemists and historian of science. A true scholar of language as well as history, he could read Latin, French, German, Classical

Greek, and Arabic, and he enjoyed such reading, especially in his retirement.

Stanley Tarbell was born on October 19, 1913, in Hancock, New Hampshire, on a farm that had been in the family since the settlement of the village. His older sister Irene and he constituted the seventh generation of the family to have lived there. The earliest Tarbell in the colonies was one Thomas Tarbell, who lived near Boston around 1650. When Stan was studying Caesar's Commentaries in high school, he was amused to read of an obscure tribe called the Tarbelli who lived in the Pyrenees, but the potential link to the forebears' name in England was not established! The descendants of Thomas Tarbell moved to Groton, Massachusetts, and worked their way westward along the New Hampshire-Massachusetts border. Stan's grandfather, Joseph A.Tarbell, married Amaret Lakin of the ancestral farm in Hancock. Stan's father, Sanford McClellan Tarbell, remained on the farm and raised hay, apples, hens, and Morgan horses, while establishing himself as a harness maker and forger. Stan's mother, Ethel Milliken Tarbell, was born in Alstead, New Hampshire, the daughter of Charles A. and Eva Strickland Milliken. The Milliken family could also be traced to pre-revolutionary times, and ancestors on both sides of Stan's family fought in the Revolutionary and Civil Wars.

Neither parent had received much formal education, but they sacrificed in order to provide it for Irene, Stan, and his younger sister, Elva. The family moved to Antrim, New Hampshire, and into a house near the school in that village. After two years there was another move, this time to Winchester, New Hampshire, to a large house that remained in the family until 1995. Stan went through Winchester schools until he started college. He recalled for us in his self-published 1966 *Autobiography* the many seasonal family chores for which he was responsible. He was paid for help ing the neighbors, pumping the bellows for the pipe organ in the Universalist Church, and also loading and aiming the trap for clay pigeon shooting at the local gun club. His childhood fascination with baseball and books grew into major hobbies in later life. In the case of baseball, that meant attendance at the games of the professional team located wherever he lived.

Thayer High School in Winchester had excellent teachers. The college preparatory course consisted of four years of Latin, French, English, and mathematics, along with courses in history and physics. Stan learned some German by studying informally with the Reverend Mr. Houghton of the Universalist Church, who, along with Stan's mother, father, and sister Irene, encouraged him to apply to Harvard College and to take the College Boards, which qualified him for admission. A tuition scholarship of $400 from the New Hampshire Harvard Club and $750 in savings supported Stan's freshman year. He was sustained in subsequent years by scholarships, savings from summer work at a YMCA camp and in a tannery, and by a loan from Irene (which he repaid within the family by a loan to Elva when she attended Middlebury College).

At Harvard, a course in organic chemistry taught by Louis Fieser led Stan to consider specializing in that subject, but he was proudest of his performance in a German course devoted to the reading of Goethe, which he took in his junior year. He felt fortunate also to have taken a course in advanced organic chemistry with E.P.Kohler in his senior year, which reaffirmed his previously aroused interest. Any real pleasure as an undergraduate seemed to be derived mainly from Stan's friendships at Lowell House and its excellent library and record collection. His acquaintance with symphonic music was enhanced by regular appearances of Serge Koussevitzky and the Boston Symphony in Sanders

Theatre. As Stan approached graduation, he did not receive any guidance in applying for a job or for a graduate assistantship at Harvard or elsewhere. However, through a series of fortunate coincidences (his words), he was provided with a tuition fellowship for one year of graduate work at Harvard. Stan earned or borrowed money necessary for living expenses. He elected to do research with Paul Bartlett, with whom he received training in physical organic chemistry and chemical kinetics. Employed by Bartlett during the summer after his first graduate year, Stan worked on a project that indicated the addition of halogens to a carbon-carbon double bond was a two-stage process; the first stage was an electrophilic attack by halogen. During his second year, Stan obtained results on the halogenation of dimethylmaleic anhydride that reinforced the earlier findings. The papers, published in the *Journal of the American Chemical Society,* that described the halogenation work were cited in 1938 when Bartlett received the Langmuir Prize of the American Chemical Society.

During Stan's third graduate year at Harvard, he obtained an assistantship at Radcliffe College, where he taught laboratory courses in organic chemistry. There he met his future wife, Ann Tracy, who graduated from Radcliffe that year and subsequently qualified for a Ph.D. degree with Robert C.Elderfield at Columbia University. Stan spoke warmly of the friends he had during the graduate years, including Charles Stauffer, Charles C.Price III, and Charles K.Bradsher, with whom he shared the interests of tennis, squash, and, in the case of the third Charlie, travel by bicycle through Germany in the summer of 1937. This Charlie and Stan had actually completed their Ph.D. theses and examinations half way through their third year. In September they set out together for the University of Illinois and postdoctoral positions, Charles with Reynold C.Fuson and Stan with

Roger Adams. After a year at Illinois, Stan felt more attached to that university than he did to Harvard (his words). He found that the organic chemistry faculty members consisting of Adams, Marvel, Fuson, and Shriner were notable for the harmonious way they worked together and for their scientific performance. Also striking was the size of the Illinois group of graduate students, their very high morale, and their devotion to the school and its faculty (again, his words).

Stan obtained a teaching position in 1938 at the University of Rochester, where W.Albert Noyes, Jr., head of the Department of Chemistry, also presented him with the challenge of building an outstanding program in organic chemistry. This he did in the course of his almost 30 years on the Rochester faculty. During his first year at the university, Stan had one graduate student, Clay Weaver, and worked diligently in the laboratory himself. He collaborated with John F.Kincaid, a new instructor in physical chemistry, with whom Stan shared an office, in a kinetic study of the Claisen rearrangement of allyl aryl ethers in solution. They applied transition-state theory to the reaction and obtained its entropy of activation, which was apparently the first time this had been done for an organic reaction. They learned that the reaction was first-order and unimolecular for migration of the allyl group to both the ortho and para positions. The results indicated a highly ordered transition state, which they suggested to be the same for both ortho and para migrations. This conclusion was shown subsequently to be correct by an accumulation of evidence from other laboratories.

Stan trained new graduate students on problems concerned with novel aspects of the Claisen rearrangement, while emphasis on the kinetic aspects became secondary to the synthesis and determination of the scope of the reaction. Other investigations included the finding that the reaction of phenyl isocyanate with phenols was catalyzed by Lewis acids and bases. The observation of catalysis was important in the later development of polyurethane polymers from diisocyanates and polyhydroxy compounds. Stan and his students discovered a new method for the synthesis of sulfilimines, $R_2SNSO_2R`$, and determined the products of the rearrangement of benzyl ethers of representative salicylic acids. With the entrance of the United States in the Second World War, Stan became involved in defense contract research that included methods for the detection of toxic agents, in particular arsenical compounds, and synthesis and testing of compounds for antimalarial activity.

Beyond the 1942–45 responsibilities remained the obligations of building the Rochester faculty in organic chemistry, helping to raise a family, and continuing a program of outstanding research and teaching.

BUILDING THE ROCHESTER FACULTY

Theodore Cairns, with a Ph.D. from the University of Illinois, was added to the faculty in 1939, but he left in 1941 for the beginning of a distinguished career at DuPont. Warren McPhee, with a Northwestern Ph.D. followed by a postdoctoral year with Roger Adams, was his replacement, and Marshall Gates, who received his Harvard Ph.D. with Louis Fieser, was added in that same year. True to Fieser's expectation, Marshall would become a leader in American chemistry. Robert Carlin, another University of Illinois postdoctorate who followed McPhee as an instructor in organic chemistry, left to take a position at Carnegie Institute of Technology. His position was then filled by Virgil Boekelheide, a Minnesota Ph.D. with C.F.Koelsch, who was in 1946 an instructor at the University of Illinois. Virgil had the added responsibility of looking after Stan's research program while Stan activated a war-delayed Guggenheim

Fellowship of a year at the University of Oxford. Stan regarded this a "superb appointment," and here is a quotation from Virgil Boekelheide, reprinted with his permission.

> After I moved to Rochester, Stan and I worked together extremely well. Our ideas of how things should be done were in complete agreement. So he went off to Oxford on his Guggenheim Fellowship, and I took over the supervision of his graduate students as well as my own. The excellent relationship between Stan and me continued in the following years…. In 1960 the University of Oregon offered me an appointment of a Professorship… If I moved to Oregon my long-standing relationship with Stan Tarbell would be broken and this would be a considerable loss…. Eventually, I chose the challenge (1960) of Oregon even at the cost of weakening my close relationship with Stan Tarbell.

The triumvirate of Tarbell, Gates, and Boekelheide guaranteed a Rochester tradition for organic chemistry and for further outstanding faculty appointments.

HELPING TO RAISE A FAMILY

In 1942 Stan married Ann Tracy, whom he had met when he was lecturing at Radcliffe, as mentioned earlier. The Tracy forebears were numerous, far flung, and distinguished. Her parents were William and Edith Jackson Tracy, and Ann was born in Helena, Montana. Following her undergraduate and graduate work, Ann had returned to Radcliffe for two years of postdoctorate research in biochemistry prior to her marriage. With the move to Rochester, she was recruited to teach a laboratory course in biochemistry in the medical school of the university and, further, to set up an analytical laboratory (for a division of the Manhattan Project) that had been organized to study the toxicity and pharmacology of substances involved in the atomic bomb program. She ran the laboratory successfully for nearly two years, until the end of the Second World War and the beginning of the family: William in October 1945, Linda in July 1948, and Theodore in November 1950. The usual domestic, school, and community activities were supplemented by hikes, baseball, and sailing on Lake Ontario, a family displacement to Stanford University during Stan's second Guggenheim Fellowship, 1961–62, and later travel through Europe. The family's move to Nashville, Tennessee, proceeded smoothly with Stan's appointment as a distinguished professor at Vanderbilt.

CONTINUING A PROGRAM OF RESEARCH AND TEACHING

Stan was a splendid teacher, whether assisting in the organic chemistry laboratory at Rochester (his first assignment), giving advanced lectures for graduate students (his second assignment), or instituting departmental and research group seminars (including self-assigned presentations). He had a remarkable memory and an enthusiasm tinged with the appropriate amount of scientific skepticism. His droll sense of humor stimulated the more perceptive students. He believed that self-education was the best education, and he inspired, occasionally goaded, students to think for themselves. In pursuing his goal of developing a recognized center for training and research in organic chemistry at both undergraduate and graduate levels, Stan concentrated on supplying the necessary physical resources, such as library, stockroom, research equipment, and advanced instrumentation. He introduced undergraduates to research and found appointments for them in other graduate schools while recruiting the best possible graduate students for Rochester. The roster of Stan's coauthors is replete with the names of presently wellknown professors and industrial, especially pharmaceutical, researchers of established reputation. I rely on the words of Sidney M.Hecht, presently John W.Mallet professor of chemistry and professor of biology at the University of Virginia, for providing a sense of the research training environment at Rochester:

> I had the good fortune to be able to join Stan Tarbell's research group following my second year in college at the University of Rochester. Stan was deeply involved in the chemistry of fumagillin and I was given a project exploring some of the transformations envisioned as part of an eventual total synthesis, as well as a graduate student mentor in the laboratory (David Brust) to guide my initial day-to-day efforts. The choice of projects reflected Stan's thorough, scholarly style. Although less obvious at the time, it also reflected his ability to identify important problems; fumagillin has emerged as an intensively studied inhibitor of angiogenesis, apparently operating by inhibition of one isozyme of methionine aminopeptidase.
>
> Stan was an excellent mentor, always willing to listen to new research results and provide advice, always supportive of his students. He previewed my first public research presentation personally and made several suggestions about the timing and style of my talk, a couple of which I sometimes quote to my own students. Along with his wife, Ann, and whichever of his children were at home, he also hosted a number of social events for his group, including picnics in the summer and dinners at his home during the December holidays.
>
> Throughout my time in the Tarbell laboratory, there was a steady stream of visits from his former students. Stan's determination to stay in touch with his former coworkers was reflected in his policy of encouraging his coworkers to take their notebooks with them when they left; if there was any need for clarification of experiments that had been run, or access to data or procedures, Stan knew how to get in touch with each former student. Therefore, it was a constant source of pleasure but no surprise that Stan and I kept in touch, through correspondence and visits, for more than 25 years after my graduation from Rochester. Ambitious undergraduate researchers have always been welcome in my laboratory, as a reflection of my gratitude to Stan for the opportunity I was given.

Let me return to the research highlights that marked Stan's Rochester years. He became interested in colchicine, a compound that is isolated from the bulbs of the autumn crocus. It arrests the process of division in plant and animal cells and is used medically in the treatment of gout. The

Rochester team provided independent evidence for the presence of the seven-membered B ring and experimental evidence to support Dewar's postulate that ring C was a seven-membered ring of the tropolone type, which was of special interest. Stan followed the structural work with a study of the reactions of colchicine and with syntheses directed toward colchicine and its derivatives. Over a 10-year period, Stan and his students determined the contrasting behavior between series of organic sulfur compounds and the corresponding organic oxygen compounds, including the discovery of the generality of isomerization by base of alkyl allyl sulfides to alkyl propenyl sulfides and elucidation of the mechanism. Another ongoing investigation was concentrated on the synthesis, isolation, thermal decomposition, and reactions of mixed anhydrides: carboxylic carbonic anhydrides, carboxylic dithiocarbamic anhydrides, formic carbonic anhydride, carboxylic thiocarbonic anhydride, dicarbonates, and tricarbonates. This investigation added another dimension for understanding the differences in behavior of sulfur- versus oxygen-containing compounds. A major contribution was Stan's demonstrated use of di-t-butyl dicarbonate (di-t-butyl pyrocarbonate) for 1°-amino protection. His reagent now finds universal use for amino acid protection in automated peptide synthesis.

In 1950 Stan started to work on the structure of the antibiotic fumagillin, which had anti-parasitic and anti-tumor activity and which had been given to him by Abbott Laboratories. Only near the end of the problem could conventional structure establishment by degradation, analysis, partial synthesis, and direct comparison of the separate moieties be augmented by nuclear magnetic resonance spectroscopy. The compound and most of its derivatives had no characteristic ultraviolet or infrared spectra, many were non-crystalline, separable only by chromatography, and detectable by optical rotation. Nevertheless, the combined efforts of graduate and undergraduate students and postdoctorates explored the novel chemistry thoroughly and accumulated sufficient evidence for the assignment of the complete structure and absolute stereochemistry. A massive paper combined all of the chemical conversions and intermediate structures in a magnificent analysis of the chemistry of fumagillin. Examination of other natural products included the erythrina alkaloids that had muscle-relaxing activity. An initial cooperative study with Virgil Boekelheide was continued in depth by Virgil while Stan maintained an observant interest.

It was about this time, in 1964, that Stan acquiesced to become chairman of the Department of Chemistry and to plan to meet the needs of space and money. The administration of the university responded positively to a 50-page report, prepared by a faculty committee under Stan's chairmanship, that made recommendations for the future direction of the chemistry department. A visiting committee, of which I happened to be a member, helped to convince President Allen Wallis that the funds allocated for a new building for chemistry and related sciences should be augmented by a reasonable percentage to provide necessary new equipment. The report, without much change, was also used in an application to the National Science Foundation for a Center of Excellence grant that was successful during Stan's chairmanship and was fully implemented under his successor, William H.Saunders, Jr.

Another university, however, namely Vanderbilt, had also received Center of Excellence grant that contained provision for making a senior appointment in chemistry at the newly created grade of distinguished professor, which was offered to Stan. Although he did not particularly care for the title, he and Ann finally decided to leave Rochester for the challenges of a different university and city, a different section of the country, new colleagues to work with, and a new community to know. The graduate students and two postdoctorates who accompanied Stan from Rochester soon had a lively research program going and were joined by Vanderbilt undergraduate and graduate students. The Tarbells were received most cordially by the university people. Ann joined the Nashville chapter of the Tennessee Ornithological Society and became an active bird watcher and licensed bird bander. She also did volunteer work for the Vanderbilt Children's Hospital, for example, tutoring a girl patient in chemistry to enable her to obtain her high school diploma. Stan's teaching responsibilities were similar to those he had had at Rochester. Travels out of Nashville were associated mainly with family occasions and visits to see children and grandchildren, in addition to Stan's professional travels to meetings and for lectures at various colleges in Tennessee and adjoining states. His research continued to provide new methodology for synthesis, both general and specific. He developed further the chemistry of organic dicarbonates and tricarbonates. To all this he added fundamental studies on the carbon basicity of nitrogen in organic compounds and on the hydrolysis of ethers and anhydrides, which he followed by ^{18}O-labeling. Stan's interest was aroused by another antibiotic available from Abbott Laboratories, ristocetin. He initiated a study of its structure and chemistry at Rochester and continued the investigation at Vanderbilt, but then turned the problem over to his colleagues Thomas M.Harris and Constance M.Harris, who ably unraveled the complicated structure. This was consistent with Stan's feeling, developed after some years at Vanderbilt, that Ph.D. students would be better off working for his colleagues rather than for him.

His sustained interest in history in general was behind his decision to write a history of organic chemistry in the

United States from 1875 to 1955. Stan and Ann together approached this task with the knowledge, diligence, and thoroughness that characterized their previous work in science. They examined practically every paper on organic chemistry that had been published by an American in U.S. or foreign publications during the selected 80-year period, starting with the recognition of chemistry as a profession. The product was an eminently readable collection of essays that recounts the genesis and development of important ideas and experiments and takes into account the social milieu in which the science was done in the United States. To cement Stan's purpose to switch to history, he had joined the History of Science Society and the History Division of the American Chemical Society upon their return from a sabbatical leave in 1974. Both Tarbells began giving papers on leading American organic chemists and they published full articles based upon these presentations. They wrote about discoveries and developments that were crucial to the field. Possibly their greatest joint contribution was the definitive biography of Roger Adams, which actually appeared while they were accumulating material for the volume on the history of organic chemistry in the United States. The Dexter Award of the Division of the History of Chemistry of the American Chemical Society was bestowed in 1989.

Stan was of special service to Vanderbilt in chairing a committee to study the Ph.D. programs at the university. The report made specific recommendations to the Vanderbilt administration, many of them requiring additional funds for graduate work. Although the administration received the report with reserve (Stan's words), many of the recommendations were implemented gradually over the years. The report provided a statement of accomplishments in the past, a charter for the present, and some solid goals for the future. In keeping with academic practice, visiting committees examined the programs of the individual departments, and I again had the opportunity of serving on a visiting committee for chemistry.

June 15, 1981, was "Stan's Day" at Vanderbilt University and consisted of "a modest tribute to a distinguished American chemist, D.Stanley Tarbell, by a few of his friends and colleagues" to mark his retirement. It would also have been appropriate to call it a distinguished tribute to a modest American chemist, for such were the characteristics of the speakers and the honoree. David J.Wilson and Thomas M. Harris have given me permission to quote from their memorial statement to the faculty of the College of Arts and Science on May 26, 1999, after Stan had died following a long illness:

> Stan was a true scholar with wide-ranging interests. At one point in his youth, he learned Arabic so that he could read the *Koran*. Another time he learned classical Italian so that he would be able to read Dante's *Inferno*. He was a music lover and a lifelong baseball fan. He became a loyal supporter of the Sounds upon his move to Nashville. We loved Stan for his dry wit and deeply respected him as a colleague. He was a man of few words but the words he spoke were always important. He could be relied on for his level head and excellent judgment on University affairs. He would go to great lengths to help his students, even many years after they had departed. He was very generous to the younger members of the faculty. An excellent example of this occurred when we were trying to hire him away from Rochester. The Dean asked Stan how much salary it would take to get him to move here. Stan replied he did not need a raise and that he would prefer to have the money given to the assistant professors.

Stan was generous with his time and his wisdom in service on many national boards: National Science Foundation selection committees, pre- and postdoctoral; National Institutes of Health, Medicinal Chemistry Study Section B, of which he was the chair during 1964–68; National Research Council Advisory Committee to the U.S. Quartermaster Corps

Laboratory, Natick; American Chemical Society Committee on Professional Training and chairman of the Division of the History of Chemistry; National Cancer Chemotherapy Committee; a panel of the Walter Reed Army Institute of Research; the Marshall Scholarships Selection Committee, southeast region; and the advisory board of the Beckman Center for the History of Chemistry, University of Pennsylvania. He was elected to the National Academy of Sciences and the American Academy of Arts and Sciences. He was fundamentally a scholar and a teacher, and he brought both personae to every enterprise of which he became a part. In considering his own career, Stan deemed it lucky, varied, absorbing, and productive.

I AM MOST GRATEFUL to Virgil Boekelheide, Sid Hecht, Tom Harris, Dave Wilson, and Bill and Ted Tarbell for the information they provided. I was also guided by the material that Stan himself placed on file in the Office of the Home Secretary of the National Academy of Sciences and, of course, by Stan's lucid *Autobiography*. It was my pleasure to serve under Stan's chairmanship on the NIH Medicinal Chemistry Study Section B, which gave me faith in the peer judgment process, and to see him at innumerable chemistry meetings and symposia during our parallel careers in the profession.

SELECTED BIBLIOGRAPHY

1936 With P.D.Bartlett. The mechanism of addition reactions. A kinetic study of addition of methyl hypobromite to stilbene. *J. Am. Chem. Soc.* 58:466–74.

1939 With J.F.Kincaid. The Claisen rearrangement. I. A kinetic study of the rearrangement of allyl *p*-tolyl ether in diphenyl ether solution. *J. Am. Chem. Soc.* 61:3085–89.

1940 With J.F.Kincaid. The Claisen rearrangement. II. A kinetic study of the rearrangement of allyl 2,6-dimethylphenyl ether in diphenyl ether solution. *J. Am. Chem. Soc.* 62:728–31.

The Claisen rearrangement. *Chem. Rev.* 27:495–546.

1941 With C.Weaver. The condensation of sulfoxides with *p*-toluenesulfonamide and substituted acetamides. *J. Am. Chem. Soc.* 63:2939– 42.

1942 With R.C.Mallatt and J.W.Wilson. Acidic and basic catalysis in urethan formation. *J. Am. Chem. Soc.* 64:2229–30.

1948 With H.R.V.Arnstein, H.T.Huang, and G.P.Scott. The structure of ring C of colchicine. *J. Am. Chem. Soc.* 70:1669.

1950 With G.P.Scott. Studies in the structure of colchicine. An infrared study of colchicine derivatives and related compounds. *J. Am. Chem. Soc.* 72:240–43.

1951 With D.P.Harnish. Cleavage of the carbon-sulfur bond in divalent sulfur compounds. *Chem. Rev.* 49:1–90.

1955 With J.C.Godfrey and V.Boekelheide. The structure of α-erythroidine. *J. Am. Chem. Soc.* 77:3342–48.

With P.Hoffman, H.R.Al-Kazimi, G.A.Page, J.M.Ross, H.R. Vogt, and B.Wargotz. The structure of fumagillin. III. *J. Am. Chem. Soc.* 77:5610–17.

1958 With N.A.Leister. The stability of mixed carboxylic-carbonic anhydrides. *J. Org. Chem.* 23:1149–52.

1959 With R.M.Carman, D.D.Chapman, N.J.McCorkindale, F.H.L. Varino, R.L.West, and D.J.Wilson. The nature of the side chain in fumagillin. *J. Am. Chem. Soc.* 81:3151–52.

With E.J.Longosz. Thermal decomposition of mixed carboxyliccarbonic anhydrides; factors affecting ester formation. *J. Org. Chem.* 24:774–78.

1960 With R.M.Carman, D.D.Chapman, K.R.Huffman, and N.J. McCorkindale. The structure of fumagillin. *J. Am. Chem. Soc.* 82:1005– 1007.

1961 With R.M.Carman, D.D.Chapman, S.E.Cremer, A.D.Cross, K.R.Huffman, M.Kunstmann, N.J.McCorkindale, J.G.McNally, Jr., A.Rosowsky, F.H.L.Varino, and R.L.West. The chemistry of fumagillin. *J. Am. Chem. Soc.* 83:3096–113.

1962 With J.R.Turner. The stereochemistry of fumagillin. *Proc. Natl. Acad. Sci. U. S. A.* 48:733–35.

With R.P.F.Scharrer. Decomposition of mixed carboxylicdithiocarbamic anhydrides. *J. Org. Chem.* 27:1972–74.

1969 The carboxylic carbonic anhydrides and related compounds. *Acc. Chem. Res.* 2:296–300.

1972 With J.R.Fehlner, R.E.J.Hutchinson, and J.R.Schenck. Structure of ristocetin A. *Proc. Natl. Acad. Sci. U. S. A.* 69:2420–21.

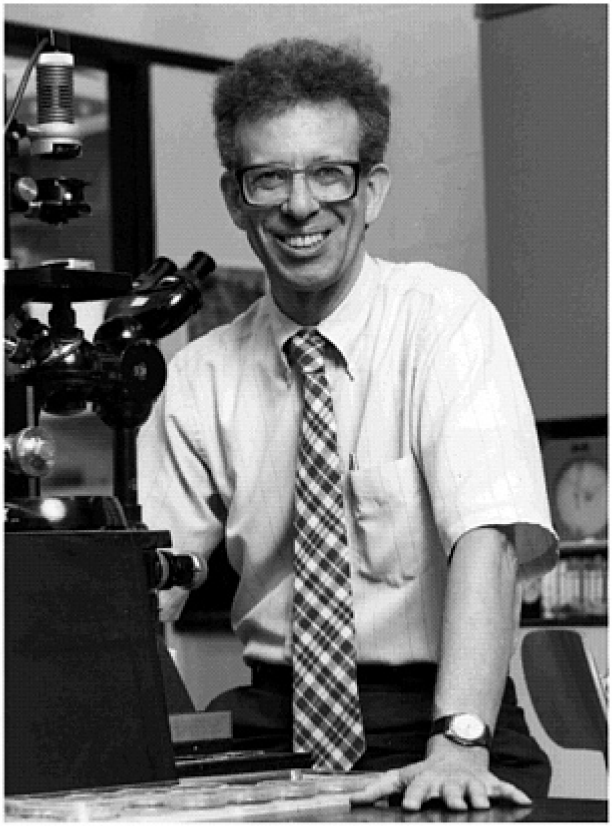
1975 With T.M.Harris, J.R.Fehlner, and A.B.Raabe. Oxidative degradation of ristocetin A. *Tetrahedron Lett.* 2655–58.

1978 With B.M.Pope, S.-J.Sheu, R.L.Stanley, and Y.Yamamoto. Synthetic and kinetic studies on tricarbonates and dicarbonates. *J. Org. Chem.* 43:2410–14.

1980 With A.T.Tarbell. The development of the pH meter. *J. Chem. Educ.* 57:133–34.

1981 With A.T.Tarbell. *Roger Adams, Scientist and Statesman*. Washington, D.C.: American Chemical Society.

1986 With A.T.Tarbell. *Essays on the History of Organic Chemistry in the United States, 1875–1955*. Nashville, Tenn.: Folio Publishers.



Howard M Temin

HOWARD M. TEMIN

December 10, 1934–February 9, 1994

BY BILL SUGDEN

HOWARD TEMIN LOVED knowledge, its acquisition, and its sharing. He pursued research where the logic of his experiments led him, independently of the scientific community's initial skepticism toward his findings. He applied his expertise to improve public health policy to minimize smoking and to maximize benefits from research on the human immunodeficiency virus (HIV).

This recounting of Howard Temin's scientific career reflects my appreciation of his work as a tumor virologist. We shared lunch on Tuesdays for 20 years and gradually grew to be friends. Howard classified himself as a virologist and taught his students to be virologists. He taught the prominent course on animal virology on the University of Wisconsin's Madison campus for 30 years. (I filled in for him when I first came to the McArdle Laboratory for Cancer Research while he traveled to Stockholm to accept the Nobel Prize. Typically, he insisted that I give several lectures before he left so that he could gauge whether I could lecture adequately and to coach me. I passed his test and I teach that course today.)

During the first week I was in McArdle, Howard invited me to have lunch with him, Paul Kaesberg, and Roland Rueckert. These lunches were squeezed in for one-half hour before the weekly seminar on tumor virology—a training ground for formal presentations by graduate students and postdoctoral fellows that Howard had organized. I learned much from and about Howard at those lunches. He usually determined the subjects to be discussed but wanted our contributions. He valued science enormously while savoring the peccadilloes of its practitioners. These lunches, our frequent discussions about our faculty colleagues in McArdle, and our shared participation on many graduate student committees led us from formal collegiality to informal friendship. The uncited interpretations and motivations I ascribe to him come from these times together.

Many of us who grew to know Howard professionally valued him personally. Rayla Greenberg Temin warmly described his rich personal life.[1] Here I shall outline the depth and breadth of his scientific contributions. It is these contributions, coupled with his commitment to reason in all facets of his professional life, that made Howard Temin a major force in biology during the latter half of the twentieth century.

THE PROVIRUS HYPOTHESIS

Quite early in life Howard Temin was a devotee of science in general and biology in particular. He published his first paper at the age of 18 in 1953. He began the research he would follow professionally as a graduate student with Renato Dulbecco in Cal Tech in 1957. Not long before, Dulbecco and Margarite Vogt[2] had developed a method to plaque poliomyelitis virus in cell culture; that is, they learned how to enumerate infectious virus particles in a stock of virus by detecting one focus of dead cells per infectious particle. The infected cells were lysed by expanding rounds of infection, viral replication, and cell death. This assay was the foundation for quantitative studies of lytic viruses in cell culture. As Howard began work in Dulbecco's group, Mannaker and Groupé[3] described an assay in which Rous sarcoma virus (RSV) altered the morphology of cells infected in culture. Here each focus of infection did not result from ensuing rounds of cell death but rather in survival of cells with altered phenotypes of shape. This in vitro assay was exciting because it could reflect in vitro the known ability of RSV to cause cancers in vivo soon after its inoculation into newborn chicks. Howard, working with Harry Rubin, a postdoctoral fellow in Dulbecco's group, refined this assay and used it to investigate "morphological transformation" of cells by RSV in culture.

Temin and Rubin (1958) refined the assay for RSV by overlaying chick embryo fibroblast (CEF) cells with agar soon after their exposure to dilutions of a virus stock. This overlay minimized the spread of progeny virus from an initially infected cell to distant cells, thereby confining the progeny from initial infections each to a single focus. The agar also helped to restrain the infected cells, which became less adherent to their initial site. Overlaid, infected cells yielded foci that enlarged exponentially with time, and this enlargement resulted primarily from division of the infected cells (1958). These foci arose linearly as a function of the dilution of the virus stock assayed over a large range of dilutions; these results indicated that a single particle of RSV is competent to initiate a focus (1958).

Rubin and Temin (1959) used this quantitative focus assay for RSV to analyze its initiation of infection radiologically. They compared the sensitivities to exposure to X rays and ultraviolet (UV) light of RSV and New Castle disease virus (NDV) in initiating or maintaining infection. NDV infects CEF cells only lytically and has an RNA genome, as RSV was then thought to have. (Bather[4] found RNA in semi-purified RSV. Crawford and Crawford[5] developed an isopycnic method to purify RSV further and confirmed its genome as being RNA). They found that infection by NDV was resistant to previous exposure of the host cells to X rays or UV light, while infection by RSV was exquisitely sensitive to similar treatments. Once cells were infected with RSV, their ability to produce progeny virus had an intermediate sensitivity to treatment with X rays. The exquisite sensitivity of RSV to initiate infection of radiologically treated cells equaled that of treated CEF cells to form colonies. This finding indicated that initiation of infection by RSV shared a common radiosensitive target with cell division, in marked contrast to the radiologically resistant, cytocidal NDV. The reduced sensitivity to radiological treatment of RSV production after establishment of its infection, coupled with its exquisite sensitivity for initiation of infection, appeared similar to those of the temperate phage (1959). These studies led them to hypothesize that "the genome of the Rous sarcoma virus must be integrated with that of the cell before virus production can begin" (1959). This hypothesis drove much of Howard Temin's research for the next 11 years.

Temin and Rubin[6] established the previously suspected model that cells in which RSV infection is established pass on to their progeny the capacity to release RSV. They analyzed single infected cells in microdrops and found both that the cells divided and that the daughter cells could release virus. This observation underscored the difference between RSV and lytic viruses such as EMC and NDV. RSV infection did not dramatically alter its host cell's survival, but it did affect it genetically; lytic viruses merely killed their host cells. This realization provided another similarity to the temperate phage, and a difference. Temperate phage pass on phage genomes from infected parent to infected daughter cell; however, they do not continuously release progeny phage.

In 1959 Harry Rubin moved to Berkeley, while Howard Temin continued his work at Cal Tech. Howard characterized isolates of RSV that conferred distinctive morphologies on their infected cells. He infected CEF cells that he had cloned to demonstrate that the distinctive cellular morphologies resulting upon infection with different isolates of RSV reflected genetic contributions of the viruses (1960). The capacity to endow an infected host cell with one morphology could mutate, the mutant virus then conferring on the cells it infects a new, distinctive morphology. Howard concluded that "the virus becomes equivalent to a cellular gene controlling cellular morphology." He also contemplated the possibility that the ability of RSV to control the morphology of cells infected in vitro was related to the virus's tumorigenic capacity in vivo.

In 1960 Howard moved to the McArdle Laboratory for Cancer Research, where he carried on his research for the rest of his life. By this time an appreciation of the functions of cellular RNAs was crystallizing. Two groups published their findings, indicating that ribosomal RNAs were stable, structural elements of ribosomes, whereas short-lived RNAs conveyed information from DNA to the ribosomes to encode protein synthesis.[7,8] This short-lived RNA is messenger RNA (mRNA). The other component of cellular RNA was transfer RNA (tRNA), small stable RNAs required to move amino acids to the ribosomes. The recognized functions of cellular RNAs did not include long-lived transfer of information. The means by which RSV, an RNA tumor virus, could stably affect the heritable morphology of infected cells was therefore enigmatic both for Howard and the scientific community at large.

At the McArdle Laboratory Howard continued to study RSV infection genetically. He isolated and characterized cells infected with RSV arising after a low multiplicity of infection, which were morphologically altered but did not in general produce virus. Virus production could be rescued by infection of these converted non-virus-producing (CNVP) cells with a different strain of RSV. These CNVP cells induced tumors in susceptible chicks, as did virus-producing cells (1963,1). These experiments separated virus production from virus-mediated morphological transformation of the infected host cell and tumorigenicity. They demonstrated that RSV-infected cells could maintain the information for producing virus in the absence of such production. The information in the infected cell necessary to produce virus was designated the provirus.

Howard analyzed the mechanism of infection by RSV biochemically. He assessed actinomycin D as an inhibitor of RSV infection and production. Actinomycin D had been recently shown to inhibit DNA-dependent RNA synthesis,[9] but not the replication of some RNA viruses.[10] At low concentrations (0.1 to 0.2 μg/ml), actinomycin reversibly inhibited infection by and production of RSV (1963,2). Concentrations up to 10 μg/ml had no effect on lytic infections by NDV (1963,2). Thus the effect of this inhibitor varied dramatically for the lytic RNA virus NDV and the transforming RNA tumor virus, RSV. Howard "suggested that the template responsible for synthesis of viral (RSV) nucleic acid either is DNA or is located on DNA" (1963,2). This unorthodox suggestion was a logical outgrowth of Temin's genetic and biochemical studies of RSV replication in cell culture. Similar experiments demonstrating the sensitivity of RSV infection to treatment with actinomycin D were also reported by other groups.[11] Temin tested his suggestion directly with two recently developed methods to detect specific RNA/DNA hybrids. He labeled RSV RNA with tritiated uridine by propagating infected cells in labeled medium, isolating released virus, and purifying its genomic RNA. This labeled RNA was then hybridized to cellular DNAs isolated from uninfected and infected cells. The results of these experiments indicated that more DNA in infected cells was detected by its hybridization to RSV RNA than DNA in uninfected cells (1964). The specific c.p.m. of labeled RNA hybridized to cellular DNAs were extremely low—too low to be compelling today. However, the small signals were consistent with the provirus of RSV being DNA, as Howard had hypothesized.

Howard analyzed the effects of serum on the proliferation of CEF cells in culture and recognized that the removal of serum inhibited the cells' proliferation.[12] He used this insight to manipulate cultures of cells such that they were partially synchronized within their proliferative cycle. He infected these partially synchronized cells with RSV and found that the capacity of infected cells to support virus production required the infected cells to pass through mitosis (1967). He found this requirement for mitosis when cultures were partially synchronized by removal of serum, by treatment with excess thymidine, or by treatment with colchicine (1967). In all cases, RSV was produced from infected cells after they passed through mitosis. These experiments did not allow him to distinguish between a requirement for mitosis to form the provirus or to activate the provirus to allow production of progeny virus. Additional experiments with synchronized cells did support the hypothesis that the provirus was composed of DNA. Howard treated cells arrested largely in the G2 phase of the cell cycle with cytosine arabinoside, an inhibitor of DNA synthesis. This treatment inhibited formation of the provirus as reflected by a failure to produce progeny RSV; the inhibition was abrogated by simultaneous treatment with deoxycytidine (1967). This and related observations indicated that formation of the provirus required DNA synthesis, but that DNA synthesis need not occur during the S phase of the cell cycle. The accumulated findings from Howard's experiments analyzing infection by RSV in cell culture were convincing to him, but still did not persuade virologists in general.

The years 1967 and 1968 were watershed occasions for animal virology; at least three findings with DNA and RNA viruses would eventually contribute to Howard's appreciation of the life cycle of RSV and to its general acceptance by virologists. Joe Kates and Brian McAuslan,[13] working with rabbit poxvirus, a member of the same family of DNA viruses as is smallpox, demonstrated that purified viral core particles contain a DNA-dependent RNA polymerase. The activity was detected only after intact viral particles were disrupted, was inhibited by actinomycin D, and synthesized RNA homologous to rabbit poxviral DNA. (It has since been demonstrated that poxviral DNA-dependent RNA polymerase is encoded by the virus and related to similar cellular enzymes.) In 1968 Aaron Shatkin and J.D.Sipe identified an RNA-dependent RNA polymerase in cores of reoviruses.[14] Reoviruses contain multiple distinct segments of double-stranded RNA within their inner core. Shatkin and Sipe found that they needed to remove the virus's outer protein shell to detect the polymerase activity, which was dependent on the addition of all four ribonucleoside triphosphates and synthesized RNAs homologous to reoviral genomic RNA. Thus, by the end of 1968 it was evident that both a DNA-and an RNA-containing animal virus house a template-dependent RNA polymerase activity.

Studies with the DNA tumor viruses, simian virus 40 (SV40) and polyoma (Py) in 1968 demonstrated that these tumor viruses affected their transformation of cells in culture by maintaining their DNA genomes integrated into their host cell's chromosomes. Joe Sambrook—a postdoctoral fellow with Howard's former mentor Renato Dulbecco—led a team of researchers who isolated chromosomal DNAs from SV40-and Py-transformed cells and showed by nucleic acid hybridi zation that these cellular DNAs had integrated copies of the viral DNAs.[15] Two approaches were critical to the success of their experiments. In one approach the isolated cellular DNAs were separated on alkaline sucrose gradients by velocity sedimentation, which minimized any fortuitous, non-covalent association of viral DNAs with large chromosomal DNAs. In all experiments the integrated viral DNAs were detected by hybridization with viral RNAs synthesized in vitro with DNA-dependent RNA polymerase isolated from *E. coli.* This latter approach permitted the radiolabeled RNA synthesized in vitro with purified viral DNA templates to be of high specific activity. The results from the hybridization experiments were thus compelling and demonstrated that certain DNA tumor viruses maintained their genomes as DNA integrated into the virally transformed host's chromosomes.

As these results with different animal viruses were being appreciated, David Boettiger began working as a graduate student at the McArdle Laboratory with Howard Temin. Colleagues at McArdle had been working previously with various halogenated nucleotides. Charlie Heidelberger had synthesized fluorodeoxyuracil (5-FU) and pioneered its use in chemotherapy for certain human cancers. Waclaw Szybalski had studied bromodeoxyuridine (5`-BUdR) and had shown that, on its incorporation into the DNA of bacteria, DNA became sensitized to damage induced by exposure of the cells to near ultraviolet or visible light. David, with Howard's guidance, rendered CEF cells stationary by withdrawing serum from their medium, infected them with RSV, treated them with 5`-BUdR, and exposed them to near UV light (1970). The stationary cells did not incorporate 5`-BUdR and were not detectably harmed by the near UV light. However, this regimen reduced infection by RSV to 5 percent of that of the untreated control. Importantly, increasing the multiplicity of infection twenty-fold significantly decreased the rate of inactivation of infection, indicating that multiple virus particles were inactivated independently within a single infected cell. This experiment provided powerful support for Howard's provirus hypothesis. It demonstrated that the incorporation of a light-sensitive DNA-nucleotide analogue soon after infection by RSV, followed by exposure to near UV light, inactivated that infection without damaging stationary host cells. This manuscript was submitted to *Nature* in March of 1970, but it was not immediately accepted.

While David Boettiger was optimizing his inactivation experiments, Satoshi Mizutani, a postdoctoral fellow with Howard, pursued the possibility foreshadowed by the findings with rabbit poxvirus and reovirus that RSV might contain a polymerase activity capable of copying RSV RNA into a precursor to its proviral DNA. Permeabilization of the envelope of the viral particle with a non-ionic detergent in the presence of dithiothreitol allowed detection of the activity soon to be dubbed reverse transcriptase. This enzyme could incorporate the four deoxyribonucleotides to yield DNA. Treatment of the disrupted virions with RNase A prior to their incubation with labeled deoxynucleotides abrogated subsequent DNA synthesis, indicating that RSV contained an RNA-dependent DNA polymerase. Mizutani and Temin submitted their findings to *Nature* on June 15, 1970. Their paper was published on June 27, 1970 (1970,1). David Baltimore at MIT published similar findings for murine RNA tumor viruses in the same issue of *Nature*.[16] He had submitted a manuscript in March to the *Proceedings of the National Academy of Sciences* relating his findings that vesicular stomatitis virus, VSV, a rhabdovirus, contained an RNA-dependent RNA polymerase, again focusing attention on the existence of template-dependent polymerases intrinsic to various families of viruses.[17]

The two reports of RNA-dependent DNA polymerase activity in avian and murine RNA tumor viruses caught the attention of much of the biological community. Howard's provirus hypothesis was accepted. The existence of this formerly undetected activity was consonant with his hypothesis, but uncountable years of research by many people would be needed to outline the mechanism by which reverse transcriptase and its associated activities could synthesize a provirus. In the interim, the inactivation experiments of Boettiger and Temin, which established the DNA nature of RSV's provirus, were published by *Nature* (1970,2) 8 months after its submission, not the 12 days needed to christen reverse transcriptase. The combined findings indicated that RNA tumor viruses copied their RNA genomes into DNA and that these proviral DNAs were integrated into infected cells' chromosomes, as were the genomic DNAs of SV40 and polyoma. RNA tumor viruses were themselves eventually rechristened retroviruses to underscore their intrinsic use of a "backwards" flow of information from RNA to DNA.

MULTIPLICATION-STIMULATING ACTIVITY (MSA)

Howard characterized cells infected with RSV in order to compare and contrast their proliferative abilities with those of uninfected parental CEF cells. He termed the infected cells converted; today they are termed transformed. He was motivated by his appreciation that RSV was an efficient tumor virus, causing rapidly growing, lethal tumors within 10 days when inoculated into susceptible, newborn chicks. He soon learned that both parental and transformed cells deplete culture media of required factors contained in serum.[18] The concentration of serum in a medium determined the saturation density cells achieved when they eventually ceased to proliferate.[19] Insulin could replace serum and support proliferation of parental and transformed CEF cells; the transformed cells could grow to a higher saturation density than their parental cells in a medium lacking serum but containing insulin.[19] These observations led Howard to hypothesize "that the increased multiplication in cell culture of converted [i.e., transformed] cells as compared with uninfected cells results from a decreased requirement by the converted cells for an insulin-like activity found in serum."[19] He pursued this hypothesis in tandem with his work on the provirus and argued that the reduced requirement of transformed cells for specific factors in serum contributed to their tumorigenicity in vivo.[20]

Embryo fibroblasts derived from chickens and ducks, but not rats, could deplete media of factors required for their proliferation,[20,21] and all three, when infected with RSV or a murine sarcoma virus (MuSV), could proliferate to higher saturation densities when serum was limiting than could their uninfected parents.[21] Transformed CEF cells multiplied to higher saturation densities than uninfected parental cells in limiting serum, because they passed through more cell cycles than did their parental cells, as scored by their prolonged ability to incorporate tritiated thymidine.[22] Transformed cells bound or depleted the multiplication-stimulating activity (MSA) in serum at the same rate as did their parental uninfected cells. These studies showed that medium with serum depleted by either cell type during increasing times of incubation supported proliferation of fresh cells to similar extents.[23] The increased capacity of transformed cells to multiply in limiting serum therefore reflected their ability to use MSA more efficiently than did untransformed cells.[23] These findings in cell culture provided a model with which to consider tumor growth in vivo. The growth of RSV-infected cells in vivo could reflect in part their capacity to proliferate efficiently in levels of MSA that did not support multiplication of uninfected or normal cells. This situation might arise, for example, when a nidus of infected cells expanded beyond their immediate blood supply.

Howard and his colleagues needed now to define MSA molecularly. The observation that rat embryo fibroblasts failed to deplete serum of MSA, as did chick and duck cells, led to the appreciation that some rat cell lines secreted MSA.[24] MSA was partially purified from calf serum[25] and from serum-free medium conditioned by growing in a line of Buffalo rat liver cells, BRL-3A (1973). It was purified to apparent homogeneity from conditioned medium with a final step of preparative electrophoresis in polyacrylamide gels containing sodium dodecyl sulfate (SDS).[26] MSA purified from conditioned medium stimulated DNA synthesis in treated cells, stimulated cell multiplication, stimulated glucose uptake, but did not contain insulin.[26] Thus, in 1974 Howard was poised to characterize MSA in detail molecularly and to explore the mechanism by which it stimulated multiplication of cells in culture. His original contribution focusing on the effects of serum to promote proliferation per se placed his imprint on this field. However, his commitment to understand the life cycle of RNA tumor viruses led him to focus his research on these viruses and not to pursue his work on growth factors such as MSA. His focus on RNA tumor viruses was also fostered by his own findings, which had heightened the growing interest of the community of cancer researchers in this family of viral carcinogens and placed him at its center.

AN EVOLVING STYLE

Howard Temin's research on RNA tumor viruses, his contributions to the elucidation of their replication, and his enunciation of and experimental support for the provirus hypothesis were not conducted in a vacuum. The Madison campus in general and the McArdle Laboratory for Cancer

Research in particular provided an intellectually rich and supportive milieu for his research. Harold Rusch directed the McArdle Laboratory when Howard joined it in 1960, and, together with the senior faculty, he worked to protect junior faculty from university responsibilities outside their research. Howard seized this opportunity and immersed himself in his own research. He worked with technicians and carried out many experiments himself. He guided his technical staff closely, observing their cells and findings daily. He accepted no graduate students for the first seven years of being a faculty member. Of the first 24 manuscripts he published from McArdle, he is the sole author on all but one. This singular dedication to his research, coupled with his exacting thought and speech, made him a formidable figure on the Madison campus.

As his research contributions grew to be appreciated beyond Madison, Howard devoted more of his time to mentoring graduate students and postdoctoral fellows. Having accepted a student into his group, Howard placed his highest priority on guiding that student; a growing list of local and national responsibilities did not challenge the priority he placed on training. After 1970 almost all his research papers were co-authored with graduate students, postdoctoral fellows, and technicians. Howard trained, in part, by example. He was engaged intellectually, socially, and professionally in all settings. Whether at the weekly tumor virology seminar in McArdle or the yearly retrovirus meeting in Cold Spring Harbor, he would be in the front row and ask questions of each speaker. He asked to understand, to seek help to solve a puzzling problem, and to provide insights. Speakers might fear his grilling and retrospectively delight in his having asked them questions from which they learned.

The general acceptance of his proviral hypothesis after the identification of reverse transcriptase activity in the virions of RNA tumor viruses(1970)[16] provided him the opportunity to consider that hypothesis in a broad context. Howard developed a protovirus hypothesis, which he described in three installments (1971).[27,28] The prefix proto is derived from Greek and means primitive or original. In contemplating the origin of RNA tumor viruses, Howard postulated that reverse transcription could contribute not only to the formation of RNA tumor viruses, but perhaps also to somatic development in and evolution of the species. Two of these speculations have proved, in part, correct.

In considering the origin of RNA tumor viruses, Howard distinguished between the RNA sarcoma viruses, which efficiently cause sarcoma but are rare in nature, and the RNA leukemia viruses, which rarely cause cancers but are common in nature. He wrote,[27]

> RNA sarcoma viruses have arisen *de novo* on several occasions. The most famous example is the original discovery of the Rous Sarcoma Virus (RSV) [32]. Since these viruses cannot replicate in a cell without transforming it into a tumor cell, and since these viruses are not ordinarily transmissible from one infected animal to another without experimental intervention, the RNA sarcoma viruses must have originally come from some preexisting entity which differed in at least one of these properties, that is, which was not an RNA sarcoma virus.
>
> RNA leukemia viruses are very widespread in natural populations of birds and mammals. They are very similar to RNA sarcoma viruses, both in the structure of the virion and in having a DNA intermediate for replication. Therefore, it seems likely that the RNA sarcoma viruses arose by mutation from the RNA leukemia viruses. In light of the previous discussion, the mutation would involve the genes making a product controlling the requirement for multiplication-stimulating activity for cell multiplication. In the sarcoma viruses this product would be effective in increasing the efficiency of utilization of multiplication-stimulating activity by fibroblasts, while in the leukemia viruses this product would not be active in fibroblasts.

We know now that the rapidly transforming RNA tumor viruses arise from the weakly transforming RNA tumor viruses' or RNA leukemia viruses' acquiring cellular proto-oncogenes (genes that, when mutated, can contribute to the risk of developing cancer) and together evolving through cycles of replication mediated through reverse transcription. Since 1970 Temin and his colleagues contributed much to this understanding. An enormous group of researchers have also contributed to the identification and characterization of more than 100 proto-oncogenes in the mammalian genome.

Howard presented his hypothesis for the generation of rapidly transforming RNA tumor viruses from weakly transforming parents partially in response to a proposal by Huebner and Todaro.[29] These authors speculated that cancers arise in animals, including human beings, from repressed RNA tumor viruses resident in germ cells of all mammals. In this model, these viruses are transmitted vertically and, when activated, induce cancer. Huebner and Todaro posited that carcinogenic information was incorporated in inherited but repressed RNA tumor viruses that must be activated by chemical or physical inducers (thought of as carcinogens) to cause cancers. Howard suggested, rather, that rapidly transforming RNA tumor viruses cause cancers by horizontal infections and arise from weakly transforming RNA tumor viruses when they acquire cancer-promoting mutations. These disparate notions were eventually resolved by seminal studies of Varmus, Bishop, and their colleagues. These virologists asked the question, "What information is present in Rous sarcoma virus but not present in related, weakly transforming avian RNA tumor viruses?" They demonstrated that nucleotide sequences derived from uninfected cellular DNA represented the transforming information in this rapidly transforming RNA tumor virus.[30] Subsequent analyses of this and other oncogenes captured by retroviruses have demonstrated that the viral oncogenes are derived from normal cellular genes now dubbed proto-oncogenes and are not linked to endogenous retroviruses. Proto-oncogenes contribute functions to normal cells and must be mutated and/or differentially expressed to evolve into oncogenes.

One tenet of the protovirus hypothesis held that uninfected cells would express RNA-dependent DNA polymerase activity (i.e., reverse transcriptase), which could contribute to the formation of RNA tumor viruses and to somatic development. Howard and his colleagues John Coffin, Chil-Yong Kang, and Satoshi Mizutani screened infected and uninfected CEF cells, infected and uninfected rat cells, and chicken embryos for reverse transcriptase activity.[31] They isolated appropriate particulate activities that were RNA dependent and synthesized RNA-primed DNA products unrelated to RSV RNA. However, Howard acknowledged, “it is easier to get biochemical evidence for the existence of RNA-directed DNA polymerase activity in cells than to show it has a biological role.”[32] In an addendum he wrote in 1979 to his protovirus hypothesis,[33] he no longer emphasized the speculation that reverse transcriptase would function widely in uninfected cells.

In considering the protovirus hypothesis in the context of somatic development, Howard speculated that in “normal development, this DNA→RNA→DNA information transfer could be used to identify cells as being of a particular type and to recruit other cells into a related or identical form” (1971). He noted that the addition of new information by copying pre-existing DNA via RNA synthesis and reverse transcription might, for example, contribute to the generation of antibody diversity. As far as I know, that suggested mechanism for somatic differentiation has not been observed; genomic alterations during development consist of deletions yielding new juxtapositions, but not duplications via reverse transcription.

Howard extended his protovirus hypothesis to include contributions of reverse transcription in the germ line to evolution of the species. Here his hypothesis is correct. Remnants of RNA tumor viruses (retroviruses), retrotransposons (elements that transpose via reverse transcription), and cDNA genes (copies of cellular genes arising via reverse transcription of RNA transcribed from these genes) are known now to comprise more than 10 percent of the human genome. The extent of information derived in the genome via reverse transcription makes Howard appear prescient in formulating his protovirus hypothesis.

Howard's professional style also evolved as he won international recognition for his research. He, David Baltimore, and Renato Dulbecco were awarded the Nobel Prize in physiology or medicine in 1975. He seized an opportunity at the Nobel banquet, which was filled with smokers, to note he was "outraged that the one major measure available to prevent much cancer, namely the cessation of smoking, has not been more widely adopted." This was not a lone gesture. He testified early in 1976 along with Renato Dulbecco before a Senate subcommittee chaired by Edward Kennedy in support of a tax of up to 50 cents per pack of cigarettes. Late in 1975 he argued before the Wisconsin State Health Council "that the deleterious effects of cigarette smoking can be considered the major health problem in the state of Wisconsin." The health council went on to support a measure that would curtail smoking in public places. He testified before the Senate Human Services Committee in 1979 that smoking "is the number one preventable health hazard in the United States today" to support the elimination of smoking in public places. Howard opposed smoking not only by giving testimony before governmental committees, but also personally. When eating at a university cafeteria, if he encountered faculty or students smoking in a no-smoking area, he would forcefully ask them to stop smoking or move.

His efforts, coupled with those of many like-minded public health advocates, have led to the outlawing of smoking in most public places in many states, in domestic airplanes, and to the recent consideration by the federal government to classify nicotine-containing cigarettes as addictive.

STRUCTURE OF THE PROVIRUS

With the acceptance of the provirus hypothesis and with the cancer research community's intensifying interest in retroviruses, Howard Temin's research evolved to characterize the provirus. Given that the provirus represents the DNA intermediate in the life cycle of retroviruses, what does it look like? A satisfying answer to this question would await much work from many scientists. It would also require the development of tools powerful enough to elucidate the structure of a specific sequence of 10^4 base pairs among an avian or mammalian genome of 10^9 to 10^{10} base pairs of DNA. These tools were discovered and refined throughout the 1970s. Kelly and Smith demonstrated that a prokaryotic restriction endonuclease cleaved DNA at a specific palindromic hexanucleotide[34]; a simple assay for such enzymes was developed by Sharp and others,[35] and the identification and characterization of hundreds of these potent tools ensued. Research in the 1960s had provided prokaryotic enzymes that synthesize kinase, phosphorylate, and ligate DNAs.[36] These enzymes, coupled with restriction endonucleases and prokaryotic plasmids encoding antibiotic resistance, formed the tools for recombinant DNA technology. In 1975 Ed Southern provided an effective means to couple restriction endonucleases with nucleic acid hybridization to detect and identify unique segments of DNA within a mass of isolated cellular DNA.[37] Technical developments during this decade were subsequently crowned with two methods to sequence DNAs efficiently.[38] The course of elucidating the structure of the provirus followed the development of these tools.

Even before the tools were available to study proviral DNAs physically, Hill and Hillova[39] introduced a means to study them biologically. They showed that transfection of DNA from infected cells into naïve cells yielded infectious retroviruses (that is, proviral DNAs can be infectious themselves). Their finding was a compelling confirmation of the provirus hypothesis. It also allowed studies of the provirus itself.

Cooper and Temin (1974) developed a quantitative assay to detect infectious proviral DNA of RSV and of spleen necrosis virus (SNV), a retrovirus of the reticuloendothelial virus group. Howard and his colleagues gradually switched their focus from RSV to SNV, perhaps because nucleic acids of SNV hybridized to DNA sequences in uninfected CEF less efficiently than did those of RSV.[40] Transfection of naïve cells with decreasing concentrations of DNA from infected cells yielded infected cells with a dose-response indicating that one proviral DNA mediated infection. Experiments with sheared DNA indicated that fragments between 10 and 15 kbp in length are required to encode an infectious provirus. Virion RNAs from retroviruses were known to migrate in velocity sedimentation analyses at 60–70S and upon denaturation at 35S.[41] A duplex DNA of 10 kbp could easily serve as a template for a retroviral RNA of 35S; the measured length of the provirus was roughly consistent with the length of RNA in retroviruses.

The assay for infectivity was coupled with physical analyses to analyze the structures of DNAs first synthesized from SNV retroviral RNAs and those eventually integrated as proviruses (1977). Early after infection, most infectious DNA was in the cytoplasm. Extraction of recently infected cells by the method of Hirt[42] separated small unintegrated DNAs from the large integrated DNAs. Most of the small unintegrated infectious retroviral DNA consisted of linear duplex molecules approximately 10 kbp in length (1977, Figure 4); little was circular in configuration. The linear duplex DNA was found to have a higher specific infectivity than did the circular molecules. The means by which these molecules were infectious was not clear. They could upon being transfected into naïve recipient cells move to the nucleus and be transcribed to yield progeny viral RNAs, or recombine and/or integrate and be transcribed after these events to yield progeny viral RNAs. These studies demonstrated that infectious DNAs are synthesized in the cytoplasm from incoming retroviruses and accumulate prior to the synthesis of detectable, infectious, integrated, or proviral DNAs. The cytoplasmic infectious DNAs were likely to be precursors to the integrated provirus. As expected, the infectious provirus was found in large DNAs (1977, Figure 6) linked to cellular DNAs with characteristic repeated sequences.

The structures of SNV viral DNAs, prior to integration and after integration, could be studied by Southern blotting with restriction endonucleases that cleaved within viral DNA. The cleaved viral DNAs were detected by hybridization with ^{125}I-labeled RNAs and “copy” DNAs of viral RNA (or cDNAs) synthesized with reverse transcriptase and ^{32}P-labeled triphosphates. The 3` end of viral RNA could be enriched by purification of small, partially degraded viral RNAs containing polyA. (The work of Joe Kates with vaccinia virus had detected polyA in viral RNAs.[43] PolyA was quickly shown to be a feature of the 3` ends of most eukaryotic messenger RNAs.) cDNAs of 3` ends of viral RNA detected the proviral DNA encoding those RNA sequences. Southern analyses of specifically cleaved, unintegrated, and SNV proviral DNAs demonstrated that both DNAs are terminally redundant and are collinear.[44] No differences were detected between infectious and non-infectious DNAs.

Mike Bishop, Harold Varmus, Peter Vogt, and their colleagues at the same time carried out extensive, similar analyses of the structures of unintegrated and proviral DNAs of strains of RSV.[45] They established that the terminal redundancy of these DNAs consists of sequences derived from both the 3` and 5` ends of the viral RNA. These repeat ends were termed long terminal repeats (LTR) and consisted of about 300 base pairs.

Howard's group isolated DNAs of SNV from acutely and chronically infected cells as recombinant DNAs cloned in a modified lambda phage, Charon 4a, and analyzed.[46] The lambda phage, Charon 4a, was developed on the Madison campus to facilitate the safe isolation of cellular genes.[47] Kunitada Shimotohno and Howard Temin analyzed these molecular clones in detail. They determined the DNA sequences of the LTRs and the cellular/proviral DNA junctions of six clones (1980).[48] Their analyses were revealing: The LTRs of SNV were 569 base pairs and encoded signals both for the initiation of RNA synthesis and addition of polyA. The structure of an LTR could be depicted as U3RU5 in which U3 and U5 represent unique sequences from the 3` and 5` ends of viral RNA respectively, and R represents the terminal redundancy of viral RNA as enunciated by Coffin.[49] A site for binding the cellular $tRNA^{Pro}$, which serves as a primer for reverse transcription, was mapped just downstream of the 5` LTR. The cellular/proviral DNA junctions of the isolated DNAs consisted of a 5-base pair direct repeat of cell DNA adjacent to a 3-base pair inverted repeat of viral DNA.[50] These structures were similar to those of integrated bacterial transposons and therefore supported the hypothesis that the formation of retroviral proviruses was related mechanistically to bacterial transposition. Howard was delighted by these findings: They were consistent with one facet of his protovirus hypothesis, in which he had suggested that retroviruses evolved from cellular elements involved in information transfer.

Structural determinations of the provirus demonstrated that the LTRs that flanked viral coding sequences contained most of the proviral *cis*-acting regulatory elements. The coding sequences of proviruses from different retroviruses generally consisted of a similar motif: viral internal structural genes *(gag)* -reverse transcriptase *(pol)* -viral glycoproteins *(env)*. Rapidly transforming viruses had a different motif, however. In working with reticuloendothelial viruses, Howard also studied a rapidly transforming member, Rev-T, which caused fatal leukemia in newly hatched chickens and turkeys. As with most rapidly transforming retroviruses, Rev-T was defective for replication and required a helper virus, RevA, closely related to SNV. Rev-T encoded the viral transforming gene v-*rel*. Howard and his colleagues analyzed v-*rel* and the avian cellular gene c-*rel* from which it evolved. They showed that v-*rel* consisted of multiple fused exons of c-*rel* that were inserted in place of much of *gag* and *pol* in RevA.[51] As RSV had captured the cellular *src* gene, Rev-T had acquired the cellular *rel* gene. These transforming viruses accommodated otherwise intractably large cellular genes in the compact form of DNA copies of the genes' spliced RNA transcripts. The structure of v-*rel* and other retroviral transforming genes indicated that reverse transcription of the spliced RNA of cellular proto-oncogenes contributed to the formation of rapidly transforming retroviruses. Shimotohno and Temin (1982) provided experiments in support of this finding. They constructed a retrovirus with part of the mouse α-globin gene in it and demonstrated that this model virus lost the introns of the α-globin gene upon its replication through multiple rounds of reverse transcription. Determination of the structures of proviruses, of retroviruses, and their rapidly transforming derivatives provided both the foundation for and the impetus to elucidate the mechanisms that underlie their formation. In a different tack, postdoctoral students with Howard—Tom Gilmore, Celine Gelinas, and Mark Hannink—analyzed v-*rel*, its expression, its protein product, and its product's function to demonstrate that it was a transcriptional activator belonging to the NF-kB family (1988).[52]

SYNTHESIS OF THE PROVIRUS

Solving two interrelated problems drove Howard to study the synthesis of proviruses. First, he sought to define the viral *cis*- and *trans*-acting elements that mediated retroviral replication. Second, he sought to use these elements to understand retroviral variation and evolution. Both of these problems led him and his colleagues to develop and characterize retroviral vectors and the helper cells on which they depend.

Rapidly transforming retroviruses are natural vectors for their derivatives of cellular proto-oncogenes. Most are defective for replication and depend on helper viruses for one or more *trans*-acting viral proteins. These natural vectors have all the *cis*-acting elements required for their replication. Identification of these elements would allow their incorporation into vectors engineered by virologists. Identification of the *trans*-acting viral factors required by the natural vectors would allow introduction of their genes into established cells such that these engineered helper cells would support replication of appropriately engineered vectors (i.e., they would substitute for helper viruses).

Howard's group identified and characterized retroviral elements required in *cis* for replication. Shimotohno and Temin[53] used a direct approach to probe sites within a viral genome that could tolerate added genes. They inserted multiple versions of the herpes simplex viral thymidine kinase gene *(tk)* at different positions in a proviral clone of SNV and tested two potential properties: Could it provide *tk* function to *tk*⁻ cells, and could it replicate with REV-A as a helper virus in CEF cells? They found that it was important to remove the 3` end of the *tk* gene for viral replication, probably because the gene's polyadenylation signal would lead to internal addition of polyA and truncation of the viral genome. They also found that *tk*-vectors that replicated in the presence of helper virus ranged from 5.7 to 10.6 kb in length. These *tk*⁺ viral vectors were powerful tools to identify other elements required in *cis* for efficient replication of retroviruses.

Small deletions within the provirus were used to identify an element termed "E" required for the encapsidation of the viral RNA by the viral capsid proteins.[54] "E" would have to be added to any vector to insure its being packaged within viral particles. Another feature of retroviruses required precise analysis to permit construction of cells such that they could synthesize the viral particles required by retroviral vectors. Retroviruses synthesize *gag* and *pol* from genomic viral RNA; *env* is synthesized from a spliced transcript. Splicing had been discovered in the mid 1970s. Most primary transcripts of eukaryotic cellular genes were processed post-transcriptionally to excise multiple tracts of intervening sequences (introns) and ligate the remaining sequences (exons), which could subsequently be exported to the cytoplasm to function as mRNAs. The structure and life cycle of retroviruses necessitates that their splicing be incomplete. The primary transcription of the provirus is the virion RNA—the RNA packaged in the viral particle. Were it to be efficiently spliced to yield only mRNA for *env,* then the intron required to synthesize *gag* and *pol* would be lost in the next generation of infection and reverse transcription. Shinichi Watanabe and Howard (1983) precisely mapped the 5` and 3` splice sites used to synthesize *env* mRNA. This mapping allowed them to construct independent expression vectors for *gag/ pol* and for *env,* introduce them into cells, and identify cells that expressed all of these viral proteins. The expression vectors were designed to lack "E" and have as few sequences as practical that could mediate recombination with introduced vectors. These helper cells could replace the functions of a helper virus and support the viral life cycle of their tk^+ vectors. Howard and his colleagues would go on to use these helper cells and a battery of carefully engineered vectors to measure and characterize rates and kinds of retroviral variation. These same helper cells formed a first generation of tools that would be essential for retrovirus-mediated gene therapy. They can support replication of vectors which themselves, when packaged, are infectious but do not yield infectious progeny on infection of non-helper cells. Parallel studies with murine retroviruses carried out by David Baltimore and his colleagues led to development of helper cells for murine retroviral vectors.[55]

Viral *trans*-acting functions in addition to *gag/pol* and *env* were likely to be required for retroviral replication. The similarity in structure between bacterial transposons and retroviral proviruses indicated that, like the transposons, retroviruses would contribute functions to mediate the integration of the provirus into host chromosomal DNA. Mutational analysis of coding information in SNV identified a virus that failed to integrate and was complemented by another mutant virus with *cis*-defects that eliminated its ability to integrate. With this former mutation, Nito Panganiban and Howard mapped the integrase gene of SNV to be at the carboxyl end of the polymerase gene.[56]

In Howard's early experiments with RSV, he had identified and exploited spontaneous viral mutants. From the time of those early experiments he wished to measure the rate of mutation during retroviral replication. During the 1960s and 1970s, accumulating research demonstrated that the cell regulates DNA synthesis and uses multiple mechanisms to insure the fidelity of that synthesis. During the same era, it became apparent that mutation rates in RNA viruses must be high. What was the rate of mutation in viruses that used both DNA and RNA as their genome? A barrier in measuring this rate had for years remained impassable. A rate reflects the number of mutations per cycle of replication, but the number of cycles of replication of retroviruses formerly could not be measured. Howard recognized that helper cells and their viral vectors could be used to support a single round of retroviral replication. The sum of mutations that accumulate during that single round would constitute a rate. Joe Dougherty and Howard devised a retroviral vector that expressed resistance to two drugs, G418 and hygromycin B. The G418-resistance gene termed *neo* was expressed from the full-length RNA and had inserted into it a termination codon that rendered it non-functional. The hygromycin gene was expressed from a spliced RNA in place of *env*. This vector was transfected into helper cells in the presence of neutralizing antisera, and the cells were cloned and screened for those that expressed the bona fide input vector. The packaged, released virus could be used at a low multiplicity to infect non-helper cells in which it would undergo a single round of reverse transcription and integration (1988,2, Figure 1). Such infected cells were selected for resistance to hygromycin B, the number of clones was enumerated, and the percentage of those also resistant to G418 was determined (1988,2). Resistance to G418 would reflect mutations that compensated for the termination codon introduced into the *neo* gene. These mutations arose frequently, and their basis was determined. Substitution mutations formed at a rate of 2×10^{-5} per base pair per replication cycle. Insertions arose at 1/500 of this frequency.

These mutation rates for base substitutions are on the order of a thousand-fold higher than those for DNA synthesis in mammalian cells measured by Howard's faculty colleague Norman Drinkwater.[57] They formed the basis for understanding the extraordinary variation of HIV observed in vivo and allowed John Coffin to posit confidently that HIV's observed variation necessitated efficiently repeated rounds of infection of naïve cells by HIV in vivo.[58] His model has been verified by studies measuring the overgrowth of resistant mutants in vivo after treatment of AIDS patients with new, potent antiviral drugs.[59]

The application of retroviral vectors and helper cells to study variation during a single round of replication was extended by Wei-Shau Hu and Howard to provide detailed insights into the mechanism of synthesis of retroviral proviruses.[60] Retroviruses encapsidate two 35s RNAs per viral particle. Hu and Temin introduced two vector DNAs into helper cells that encoded alternate resistances. One was neo^{-}/hyg^{+}, as was that used by Dougherty and Temin (1988), the other was neo^{+}/hyg^{-}. They characterized clones of the transfected helper cells to insure that each contained one bona fide copy of each of the vectors. Viruses released from these clones of helper cells would with some frequency contain heterodimers—one RNA molecule transcribed from each provirus. Recombination between packaged heterodimers would yield proviruses encoding resistance to both G418 and hygromycin B. The neo^{-} and hyg^{-} alleles were identified with specific restriction endonuclease sites. Wei-Shau infected cells with virus released from the clones of transfected cells and enumerated the number of infected cells resistant to one, to the other, or to both drugs. Recombinants arose at a rate of 2 percent per kbp, separating the mutant alleles per replication cycle—extremely frequently. The recombinants were analyzed for loss of the diagnostic restriction endonuclease sites; most had lost them and represented genomic recombinants.[60] Recombination within a retrovirus can be viewed to result from reverse transcriptase copying one template RNA or DNA and then switching to the other present in the viral particle. The high rate of recombination found by Hu and Temin indicates that such a template switch occurs once per every two or three cycles of retroviral replication.

Hu and Temin built on their initial study by using two vectors, *neo*$^-$/*hyg*$^+$ and *neo*$^+$/*hyg*$^-$, which were marked throughout their genomes with eight different restriction endonuclease sites. Evidence from work on disparate retroviruses from many groups provided a detailed model for the synthesis of the linear precursor to a provirus that Hu and Temin outlined (1990, Figure 2). They generated and analyzed recombinants between the marked vectors and interpreted their formation in light of the detailed model for the synthesis of the proviral precursor. The first step in synthesis of the precursor to the provirus is synthesis of DNA primed from the tRNA near the 5` end of the viral RNA. This DNA shortly runs out of template and can be isolated from in vitro reactions as strong-stop DNA. Hu and Temin (1990) identified which endonuclease restriction sites were present in recombinant proviruses. They used these analyses to show that strong-stop DNA, which could in theory transfer to the 3` end of the RNA molecule from which it was synthesized or to the 3` end of the other RNA molecule within the virus particle, could in fact transfer to either template. Once the first strand of DNA was synthesized, they found that the second strand was primed only from the first strand's template. Howard interpreted the high frequency of detected recombination during retroviral replication to result from the inherent ability of reverse transcriptase to switch its templates, an event essential to synthesis of the proviral precursor.[61]

Multiple studies with a variety of retroviral vectors and helper cells allowed Howard and his colleagues to prove the mechanism by which the provirus is synthesized. They now used this general approach to illuminate mechanisms by which retroviruses capture cellular proto-oncogenes to evolve into rapidly transforming derivatives. Jiayou Zhang developed helper cells with two non-homologous vectors. RNA synthesized from one would yield RU5 upstream of hyg^r but no U3 sequences. The other would yield RU5 upstream of *neo*^{r} along with U3R. Recombination within heterodimeric viruses released from these helper cells would be required to generate a functional 3` end of a *hyg*^{r} provirus (U3RU5 *hyg*^{r} U3RU5). Zhang and Temin (1993) infected cells with virus from characterized clones of helper cells with these proviruses and selected either for *neo*^{r} or *hyg*^{r}. *Hyg*^{r} cells arose at a frequency that indicated that nonhomologous recombination occurred at a rate of 0.1 percent to 1 percent of that of homologous recombination for retroviruses. They determined the sequence of the junctions of the recombinants and excitingly found a correlation with the kinds of junctions observed for sites at which retroviral sequences join viral oncogenes in rapidly transforming retroviruses.[62] For example, in a group of non-homologous recombinants they described as being general, they found one example of recombination without sequence identity, six with a short region of five to eight base pairs of sequence identity, and three with insertions at the site of recombination. Inspection of naturally occurring, highly transforming retroviruses revealed that their sites of recombination usually contained short stretches of sequence identity or insertions.[62] The non-homologous recombination they had characterized underlies the means by which retroviruses form their 3` ends while capturing cellular proto-oncogenes.

HUMAN RETROVIRUSES

Howard's hypothesizing the provirus, his work on its structure and on its synthesis involved avian retroviruses. RSV and REV-T were known to cause sarcomas and lymphomas in chickens at a time when human retroviruses were not identified, let alone shown to cause human disease. Confirmation of the provirus hypothesis, however, focused attention on retroviruses and helped to justify the National Cancer Institute's major investment in research in the 1970s on retroviruses in general and a search for human retroviruses in particular. Although he in some sense started this band, Howard did not follow its wagon. He continued to study avian retroviruses. By the end of the decade, Y.Hinuma, following a paradigm he developed to study Epstein-Barr virus, a human tumor virus in the herpes virus family, helped to identify human T-cell leukemia virus type 1 (HTLV-1), a bona fide leukemia-causing human retrovirus. Bob Gallo and his colleagues through their research on propagating human T cells in medium containing IL-2 also contributed to the identification of this human tumor virus. The 1980s subsequently brought the recognition of another pathogenic human retrovirus that would occupy Howard's interest and eventually some of his research efforts.

Acquired immunodeficiency syndrome (AIDS) was a disease entity identified in the early 1980s and found initially to be clustered in male homosexuals in the United States. The wasting that characterized AIDS was fatal, and suggestions for its cause varied widely and were often irrational. Luc Montagnier in the Institute Pasteur and Bob Gallo and his colleagues at the National Institutes of Health (NIH) identified a retrovirus linked to AIDS. Contentious claims of priority appeared for a while to cloud the importance of this discovery. Howard worked through an NIH committee to help name this virus and limit any contention—thus the neutrally named human immunodeficiency virus or HIV. Epidemiological studies provided increasingly robust data indicating that HIV causes AIDS, but a few virologists, such as Peter Duesberg, argued with this conclusion.[63] Some of Howard's colleagues suggested that such arguments be ignored, but he was very concerned that those arguments be addressed directly and refuted. In 1988 Howard joined Bill Blattner and Bob Gallo to publish an article entitled "HIV Causes AIDS" in *Science* (1988). Here he contributed not original research but rather his depth and breadth of reading as well as his scientific integrity to reason for the well-being of people. He repeated his reasoned address in a short article in *Policy Review* in 1990.[64] Howard willingly involved himself in national policy decisions to promote the best possible research on AIDS.

Between 1985 and 1994 Howard served on 12 national and international committees focused on multiple facets of HIV and AIDS. These included an oversight committee on AIDS activities of the Institute of Medicine from 1987 to 1990, chairing the HIV Genetic Variation Advisory Panel for the National Institute of Allergies and Infectious Diseases from 1988 to 1994, the Global Commission on AIDS from 1991 to 1992, and the World Health Organization Advisory Council on HIV and AIDS from 1993 to 1994. He devoted more of his efforts to guiding policies on AIDS and HIV than on any other public health problem faced during his professional life.

By 1992 Howard thought enough was known so that he could make experimental contributions toward the prevention of AIDS. HIV and HTLV-1 were known to be lentiviruses, a subtype of retroviruses that encoded several genes in addition to the *gag, pol,* and *env* of the simple retroviruses such as SNV. These additional genes were necessary for HIV's replication. No simple retrovirus had been isolated from people, and no lentiviruses had been isolated from chickens, mice, and cats, which harbor many simple retroviruses. Howard hypothesized that in this current niche of time, human beings have evolved to be resistant to simple retroviruses. A vaccine might be constructed by engineering the *gag, pol,* and *env* genes of HIV into a simple retroviral vector and be used to immunize people against infection by HIV (1993,1). Kathy Boris-Lawrie, a postdoctoral fellow, and he began testing this hypothesis by working with the animal lentiviruses, bovine leukemia viruses, and simian immunodeficiency virus, as models. Howard died of cancer in February 1994 before these preliminary experiments were completed.

This final project exemplified Howard's research. It grew out of a thorough appreciation of HIV as a retrovirus. It embodied a bold hypothesis. It will be a lasting sorrow that he did not live to test his hypothesis, to learn from the experiments he proposed, and to contribute his further insights to biology and human welfare.

NOTES

1. G.M.Cooper, R.G.Temin, and B.Sugden, eds. *The DNA Provirus: Howard Temin's Scientific Legacy.* ASM Press, 1995.
2. Dulbecco and Vogt. *J. Exp. Med.* 99(1954):167–82.
3. Mannaker and Groupé. *Virology* 2(1956):838–40.
4. Bather. *Brit. J. Cancer* 11 (1957):611–19.
5. Crawford and Crawford. *Virology* 13(1961):227–32.
6. Temin and Rubin. *Virology* 8(1959):209–22.
7. Brenner and others. *Nature* 190(1961):576–81.
8. Gros and others. *Nature* 190(1961):581–85.
9. Goldberg and others. *Proc. Natl. Acad. Sci. U. S. A.* 48(1963):2094– 2101.

10. Reich and others. *Proc. Natl. Acad. Sci. U. S. A*. 48(1962):1238–44.

11. Bader. *Virology* 22(1964):462–68. Vigier and Goldé. *Virology* 23(1964):511–19.

12. Temin. *J. Natl. Cancer Inst.* 37(1966):167–75.

13. Kates and McAuslan. *Proc. Natl. Acad. Sci. U. S. A*. 58(1967):134–41.

14. Shatkin and Sipe. *Proc. Natl. Acad. Sci. U. S. A*. 61(1968):1462–69.

15. Sambrook and others. *Proc. Natl. Acad. Sci. U. S. A*. 60(1968):1288–95.

16. Baltimore. *Nature* 226(1970):1209–11.

17. Baltimore, Huang, and Stampfer. *Proc. Natl. Acad. Sci. U. S. A*. 66(1970):572–76.

18. Temin. *J. Natl. Cancer Inst.* 37(1966):167–75.

19. Temin. *J. Cell. Physiol.* 69(1967):377–84.

20. Temin. *Wistar Inst. Symp. Monogr.* 7(1967):103–16.

21. Temin. *Int. J. Cancer* 3(1968):491–503.

22. Figure 11 in Temin. *Int. J. Cancer* 3(1968):771–87.

23. Temin. *J. Cell. Physiol.* 74(1969):9–16.

24. Temin. *J. Cell. Physiol.* 75(1970):107–20.

25. Pierson and Temin. *J. Cell. Physiol.* 79(1972):319–30.

26. Smith and Temin. *J. Cell. Physiol.* 84(1974):181–92.

27. Temin. *Perspect. Biol. Med.* 14(1970):11–26.

28. Temin. Pp. 176–87 in *The Biology of Oncogenic Viruses,* ed. L.G. Silvestri, vol. 2. North-Holland, 1971.

29. Huebner and Todaro. *Proc. Natl. Acad. Sci. U. S. A*. 64(1969):1087–94.

30. Stehelin and others. *Nature* 260(1976):170–73; Stehelin and others. *J. Mol. Biol.* 101 (1976):349–65.

31. Coffin and Temin. *J. Virol.* 7(1971):625–34; Coffin and Temin. *J. Virol.* 8(1971):630–42; Kang and Temin. *Proc. Natl. Acad. Sci. U.S. A.* 69(1972):1550–54; Kang and Temin. *Nature New Biol.* 242(1973):206– 208; Mizutani and Temin. *J. Virol.* 12(1973):440–48; Kang and Temin. *J. Virol.* 12 (1973):1314–24; Mizutani, Kang, and Temin. *Cold Spring Harbor Symp. Quant. Biol.* 38 (1974):289–94.

32. Temin, Kang, and Mizutani. Pp. 1–13 in *Possible Episomes in Eukaryotes,* ed. L.Silvestri. North-Holland, 1973.

33. Temin. *Natl. Cancer Inst. Monogr.* 52(1979):233–38.

34. Kelly and Smith. *J. Mol. Biol.* 51(1970):393–409.

35. Sharp and others. *Biochemistry* 12(1973):3055–63.

36. Kornberg and Baker. *DNA Replication.* Freeman, 1992.

37. Southern. *J. Mol. Biol.* 90(1975):503–17.

38. Maxam and Gilbert. *Proc. Natl. Acad. Sci. U. S. A.* 74(1977):560–64; Sanger and others. *Proc. Natl. Acad. Sci. U. S. A.* 74(1977):5463–67.

39. Hill and Hillova. *C. R. Acad. Sci. Paris D* 272 (1971):3094–97.

40. Kang and Temin. *J. Virol.* 14(1974):1179–88.

41. Duesberg and Vogt. *Proc. Natl. Acad. Sci. U. S. A.* 67(1970):1673–77.

42. Hirt. *J. Mol. Biol.* 26(1967):365–69.

43. Kates. *Cold Spring Harbor Symp. Quant. Biol.* XXXV(1970):743–52.

44. Keshet and others. *Cell* 16(1979):51–61.

45. Shank and others. *Cell* 15(1978):1383–95 and 1397–1410.

46. O'Rear and others. *Cell* 20(1980):423–30.

47. Williams and Blattner. *J. Virol.* 29(1979):555–75.

48. Shimotohno and Temin. *Proc. Natl. Acad. Sci. U. S. A.* 77(1980):7357–61.

49. Coffin. *J. Gen. Virol.* 42(1979):1–26.

50. Shimotohno and Temin. Figure 2 in *Proc. Natl. Acad. Sci. U. S. A.* 77(1980):7357–61.

51. Chen and others. *J. Virol.* 45(1983):104–13; Wilhelmsen and others. *J. Virol.* 52(1984):172–82.

52. Gilmore and Temin. *Cell* 44(1986):791–800; Gilmore and Temin. *J. Virol.* 62(1988):703–14; Ballard and others. *Cell* 63(1990):803–14.

53. Shimotohno and Temin. *Cell* 26(1981):67–77.

54. Watanabe and Temin. *Proc. Natl. Acad. Sci. U. S. A.* 79(1982):5986–90.

55. Mann and others. *Cell* 33(1983):153–59.

56. Panganiban and Temin. *Proc. Natl. Acad. Sci. U. S. A.* 81(1984):7885–89.

57. Drinkwater and Klinedinst. *Proc. Natl. Acad. Sci. U. S. A.* 83(1986):3402–06.

58. Coffin. *Science* 267(1995):483–88.

59. Wei and others. *Nature* 373(1995):117–22.

60. Hu and Temin. *Proc. Natl. Acad. Sci. U. S. A.* 87(1990):1556–60.

61. Temin. *Proc. Natl. Acad. Sci. U. S. A.* 90(1993):6900–6903.

62. Zhang and Temin. *J. Virol.* 67(1993):1747–51.

63. P.Duesberg. *Science* 241(1988):514.

64. Temin. *Policy Rev.* 54(1990):71–72.

SELECTED BIBLIOGRAPHY

1958 With H.Rubin. Characteristics of an assay for Rous sarcoma virus and Rous sarcoma cells in tissue culture. *Virology* 6:669–88.

1959 With H.Rubin. A radiological study of cell-virus interaction in the Rous sarcoma. *Virology* 7:75–91.

1960 The control of cellular morphology in embryonic cells infected with Rous sarcoma virus in vitro. *Virology* 10:182–97.

1963 Further evidence for a converted, non-virus-producing state of Rous sarcoma virus-infected cells. *Virology* 20:235–45.

The effects of actinomycin D on growth of Rous sarcoma virus in vitro. *Virology* 20:577–82.

1964 Homology between RNA from Rous sarcoma virus and DNA from Rous sarcoma virus-infected cells. *Proc. Natl. Acad. Sci. U. S. A.* 52:323–29.

1967 Studies on carcinogenesis by avian sarcoma viruses. V. Requirement for new DNA synthesis and for cell division. *J. Cell. Physiol.* 69:53–63.

1970 With S.Mizutani. RNA-dependent DNA polymerase in virions of Rous sarcoma virus. *Nature* 226:1211–13.

With D.Boettiger. Light inactivation of focus formation by chicken embryo fibroblasts infected with avian sarcoma virus in the presence of 5-bromodeoxyuridine. *Nature* 228:622–24.

1971 The protovirus hypothesis. *J. Natl. Cancer Inst.* 46:3–7.

With J.M.Coffin. Ribonuclease-sensitive deoxyribonucleic acid polymerase activity in uninfected rat cells and rat cells infected with Rous sarcoma virus. *J. Virol.* 8:630–42.

1973 With N.C.Dulak. A partially purified polypeptide fraction from rat liver cell conditioned medium with multiplication-stimulating activity for embryo fibroblasts. *J. Cell. Physiol.* 81:153–60.

1974 With G.M.Cooper. Infectious Rous sarcoma and reticuloendotheliosis virus DNAs. *J. Virol.* 14:1132–41.

1977 With E.Fritsch. Formation and structure of infectious DNA of spleen necrosis virus. *J. Virol* 21:119–30.

1979 With E.Keshet and J.O'Rear. DNA of noninfectious and infectious integrated spleen necrosis virus (SNV) is colinear with unintegrated SNV DNA and not grossly abnormal. *Cell* 16:51–61.

1980 With K.Shimotohno and S.Mizutani. Sequence of retrovirus provirus resembles that of bacterial transposable elements. *Nature* 285:550–54.

1981 With S.K.Weller. Cell killing by avian leukosis viruses. *J. Virol* 39:713–21.

1982 With K.Shimotohno. Loss of intervening sequences in genomic mouse α-globin DNA inserted in an infectious retrovirus vector. *Nature* 299:265–68.

1983 With S.Watanabe. Construction of a helper cell line for avian reticuloendotheliosis virus cloning vectors. *Mol. Cell. Biol.* 3:2241–49.

1988 With W.Blattner and R.C.Gallo. HIV causes AIDS. *Science* 241:515–16.

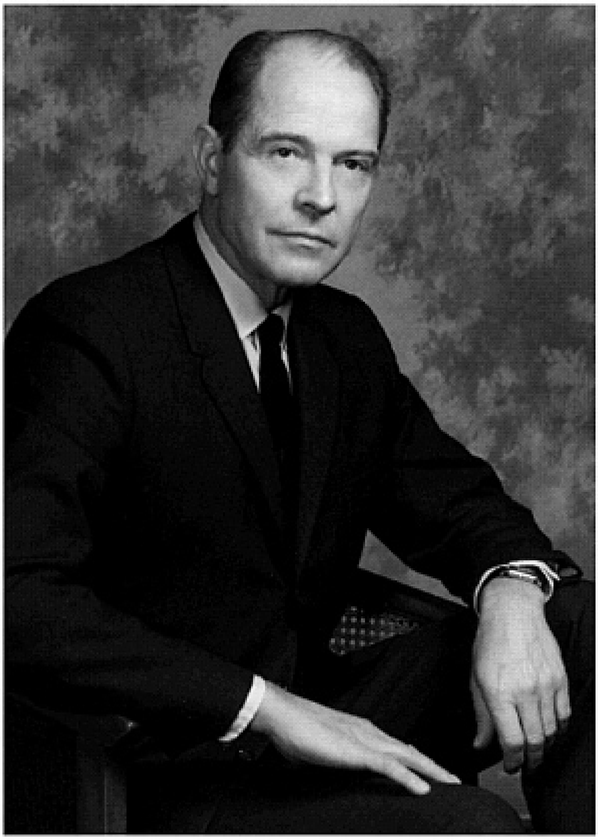
With J.P.Dougherty. Determination of the rate of base-pair substitution and insertion mutations in retrovirus replication. *J. Virol.* 62:2817–22.

With C.Gelinas. The v-*rel* oncogene encodes a cell-specific transcriptional activator of certain promoters. *Oncogene* 3:349–55.

1990 With W.-S.Hu. Retrovirus recombination and reverse transcription. *Science* 250:1227–33.

1993 A proposal for a new approach to a preventive vaccine against human immunodeficiency virus type 1. *Proc. Natl. Acad. Sci. U. S. A*. 90:4419–20.

With J.Zhang. Rate and mechanism of nonhomologous recombination during a single cycle of retroviral replication. *Science* 259:234–38.



BENTON J. UNDERWOOD

February 28, 1915–November 29, 1994

BY GEOFFREY KEPPEL

BENTON J.UNDERWOOD was one of the pre-eminent leaders in the post-World War II development of research on the acquisition and retention of verbal materials, frequently referred to at the time as the study of verbal learning and memory. Underwood is recognized for his extensive contributions to the experimental and theoretical analysis of this field and for a career as an innovator and a pacesetter in a rapidly growing and changing domain of research. Between 1941 and 1982, he amassed nearly 200 publications, including 10 books and 5 research monographs. Approximately 85 percent of his articles and monographs consisted of reports of experiments. His most ambitious research effort was his study of massed and distributed practice, which spanned over 17 years and included 26 empirical reports and theoretical articles.

Underwood was born on February 28, 1915, in Center Point, Iowa. He received his primary and secondary education in Albion, a small town serving the farming community in central Iowa, where his father owned and operated the local lumberyard. His mother was particularly supportive of her children's education, providing each with the opportunity to take special music lessons and expressing great ad miration for a new idea, a well-written theme, or a good set of grades. She was particularly proud when Underwood published a short piece in the local paper on the history of Albion.

Upon graduating from high school in 1932, Underwood hoped to become a high-school athletic coach—a position viewed locally, in Underwood's words, "as being little short of aristocratic." With the help of a scholarship, personal loans, and room-and-board jobs, Underwood attended Cornell College in Mount Vernon, Iowa, and graduated in 1936 with majors in education and psychology. After graduation, he found a temporary teaching job in the high school in Clarion, Iowa, and then, a year later, realized his long-term dream by serving for two years as a junior college athletic coach and a part-time academic teacher in Tipton, Iowa. He decided to further his education when he realized that "it was of much greater interest and challenge to teach an academic subject to reluctant minds than to try to teach a pivot shot to would-be athletes lacking in basic coordination." With his new bride, Louise Olson Underwood, the couple headed west, where he planned to enroll in the summer session of 1939 at the University of Oregon. Underwood was experiencing difficulty in choosing between graduate work in education or in psychology, which was resolved when he took a psychology course offered by John Dashiell, who was a visiting professor from the University of North Carolina. After a few weeks in this course, Underwood made the decision to dedicate himself to a career in psychology.

Late that summer, Underwood accepted a position as a research assistant to Arthur W.Melton, chairman of the Psychology Department at the University of Missouri. Under Melton's guidance, Underwood discovered the importance of applying experimental techniques to understand behavior and the excitement of research in Melton's field, verbal learning and memory, the study of which would occupy his entire professional life. After receiving a master's degree in the summer of 1940, Underwood moved to the State University of Iowa, where he became a research assistant to John A.McGeoch, who was then the head of the Psychology Department and a major figure in the field of verbal learning and memory. With the approval of a benevolent draft board, Underwood was permitted to complete his Ph.D. before being assigned to military duty. After McGeoch died in 1941, Kenneth W.Spence guided Underwood in his dissertation research, which was completed in late 1942.

By all accounts, Iowa was a stimulating environment for graduate students to grow and develop. There were theoretical battles being waged on a number of important fronts: hammering out positions in a philosophy of science appropriate to psychology, debating and arguing critical theoretical points in animal learning, and developing research based on Melton's recent proposal of the unlearning of associations. In Underwood's words, "Iowa was a very exciting place …and I consider myself to be most fortunate to have been able to participate in it. The interplay between theory and experiment which took place at that time was a very heady experience, one which too few graduate students have." This experience, particularly Spence's creative approach to solving problems in an analytical and experimentally rigorous manner, created a lasting impression on Underwood.

Underwood received a commission in the Naval Reserve in January 1943 and was assigned to the Naval Aviation Psychology Branch of the Bureau of Medicine and Surgery. After the war, he accepted a position in January 1946 as assistant professor at Northwestern University and advanced to associate professor in 1948 and to professor in 1952. In 1976 Northwestern University appointed him Stanley

G.Harris Professor of Social Science in recognition of his scholarly contributions to the discipline of psychology and of his service to the university, which included a term as chair of the Psychology Department. He retired from Northwestern in 1983. Except for a visiting year at Berkeley (1958– 59), where he collaborated with Leo Postman on a number of research projects, Underwood remained in residence at Northwestern. He respected the faculty of the Northwestern department and enjoyed the general atmosphere of the university. He particularly valued the critical research orientation of his departmental colleagues.

Benton J.Underwood died on November 29, 1994, following a long degenerative illness. He is survived by his wife, Louise, a retired high-school English teacher; his two children, Judith Maples, a librarian, and Kathleen Olson, an author; and six grandchildren.

While the remainder of this biographical note will emphasize Underwood's academic and professional contributions, I would be remiss not to mention some of his personal qualities that endeared him to others. One of these characteristics was his fondness for playful arguments in which he would take a strong position and later admit that he did not necessarily believe the position he had been arguing. He also thoroughly enjoyed hearing about new research findings. Neal F.Johnson, a speaker at Underwood's memorial service, poignantly described Underwood's reaction to a new empirical finding or theoretical analysis:

> When a clever experimental approach to an issue was outlined, he would show the quick flash of a radiating smile; then would come the look of intense concentration as you described the details of the methods and procedures that were used; but when you came in with that final bit of confirming data as the clincher, he would give an exclamation—slap his knee—and then his face would literally explode into his marvelous warm

> smile. To me, I think that smile was more rewarding than an editor's letter of acceptance."[1]

Another characteristic was his passionate enjoyment of musical comedies, particularly a professional production of *The Music Man,* in which his granddaughter Karen Olson Pierce performed a starring role. Still another was his broad interest in sports, undoubtedly stemming from his early experiences as a player and coach. At the annual departmental picnic, Underwood would always emerge as the "most valuable player" in the highly contested softball games held at these events. In addition to an interest in sports, he was also a devoted gardener and an avid reader of historical biographies.

Two remarkable publications provide summaries of Underwood's research contributions. The first is the chapter prepared by Leo Postman, his frequent collaborator on a number of important papers dealing with interference and forgetting, for the Festschrift held in 1971 to honor Underwood, who was completing his twenty-fifth year at Northwestern University. Postman's chapter, titled "The Experimental Analysis of Verbal Learning and Memory: Evolution and Innovation," concluded with the following statement:

> I have tried to touch upon some of the major landmarks in the continuous evolution of our field during the last quarter century. It has been a period of methodological advances, productive self-criticism, and theoretical growth. Before concluding, let me make explicit what you have undoubtedly known all along. In developing this account I have drawn, with a few scattered exceptions, on the work of only one man. So great is the debt of gratitude that we owe to Benton J.Underwood."[2]

The other publication is a 1982 book prepared by Underwood for the Praeger Centennial Psychology Series in which he presented a representative sampling of his re search papers and divided his work into the following categories: (a) research on the role of proactive interference in forgetting; (b) studies of the role of implicit associative responses in learning, recognition, and recall; (c) the development and testing of the frequency theory of memory; (d) investigations on the higher mental processes involved in concept learning and thinking; (e) research on the effects of massed versus distributed practice; and (f) an analysis of the structure of memory. In the first chapter, Underwood provided the theoretical background that guided the 15 papers that are reprinted in the volume. In the last chapter, he offered a fascinating glimpse at future directions he anticipated for this and related research. Here is Underwood at his speculative best.

Underwood's research exemplified the functionalist tradition in which global relationships between manipulated independent variables and response or dependent variables were analyzed into subcomponents through the use of new methodology and revised theoretical orientations. His work on interference and forgetting provides a good example. In a careful review of the literature, Underwood (1957) discovered that the forgetting reported in these studies was directly related to the number of lists of verbal material subjects had received before they learned and recalled a particular list. In fact, when he measured forgetting by testing subjects who learned and later recalled a single list of verbal materials, he found forgetting to be in the range of 20–25 percent, rather than the 75 percent usually reported in multi-list studies.

In subsequent research, Underwood examined characteristics of the learning materials that might be shown to influence this reduced amount of forgetting. Typically, he would manipulate independent variables that exert profound effects on acquisition, such as the meaningfulness and simi larity of the learning materials, and then determine whether these variables also affected the rate of forgetting. Such studies immediately presented a serious methodological problem, however, because subjects who learn at different rates are usually not matched in the degree to which they have learned the different sets of material. Underwood spent over a decade working on this problem, the result of which was to show that most independent variables that influence acquisition have little or no effect on forgetting. In fact, Underwood was led to the conclusion that there may be no individual differences in forgetting, once individuals are equated for differences in learning.

In addition to the 1982 retrospective book, the flavor of Underwood's approach to research is also reflected in his research books and monographs. In these more generous formats, he was able to describe the development of ideas and to detail the careful analyses of individual research protocols that were a hallmark of his empirical work. One cannot help but be impressed with the multitude of interrelated studies relentlessly chipping away at various puzzles revealed by earlier experiments, while still moving closer to a satisfactory resolution of some sort. Underwood's theoretical ideas were never too far removed from the data, reflecting a healthy respect for a fruitful interplay between fact and explanation. The first of his three research books, *Meaningfulness and Verbal Learning,* was coauthored with Rudolph W.Schulz and published in 1961. As some students have described, the book reads like a detective novel, with its false leads, red herrings, and careful "plot" development. His other two books were published within five years of his retirement, *Temporal Codes for Memories: Issues and Problems* (1977) and *Attributes of Memory* (1982), both representing new ways of conceptualizing memory storage and retrieval. A colleague of mine at Berkeley, Arthur P.

Shimamura, viewed his treatise on temporal codes as "a testament to Underwood's scientific acumen" and a topic that is "important for our understanding of autobiographical memory, episodic retrieval, and source recollection."[3]

Another facet of Underwood's career was that of research methodologist, both in his research field of verbal learning and memory and in the more general arena of psychological research. Underwood was a master at designing simple, clean, and analytical studies. His development of methods permitting the study of forgetting as a function of independent variables that influence learning, which I described earlier, represents a major methodological contribution to the field.

Underwood produced two textbooks that dealt exclusively with issues of research design. One of these was his 1957 book intended for graduate students, *Psychological Research,* which conveyed the art and logic of experimental design in a clear and exquisite manner. Without question, this book helped to set the standards of research design in psychology in general—not just within the confines of experimental psychology. The other book, *Experimentation in Psychology,*[4] published with John J.Shaughnessy in 1975, was addressed to the undergraduate student majoring in psychology, providing detailed discussions of the issues that confront a researcher in the design of common experimental designs employed in psychology and in the interpretation of the results of these experiments.

Underwood also wrote two other textbooks with the undergraduate in mind. One of these is his influential and successful *Experimental Psychology* (1949, 1966), which helped to define the field in the early years after the Second World War and continued to have an important influence on undergraduate courses in experimental psychology through the 1970s. The other textbook,[5] which was coau thored with several faculty colleagues at Northwestern, offered a pragmatic and clear introduction to statistical procedures of relevance to undergraduate majors in psychology.

A third aspect of Underwood's career was his impact as a teacher and a research mentor. His major undergraduate teaching assignment at Northwestern was a required two-quarter laboratory course in experimental psychology. A faculty colleague recalls that "when [Underwood] taught his section of experimental psychology, a rigorous lab course with multiple papers always held at eight in the morning, so many students were eager to take it that he interviewed each of them in order to keep the section from getting too large."[6] Underwood found ways to engage and to motivate even the most recalcitrant student. From his students he excelled at eliciting energetic discussions on matters of experimental design and interpretation of results. I observed him on numerous occasions in this undergraduate course generating a productive class discussion with different examples of research problems and designs—bogus experiments in which critical design flaws were cleverly embedded. He was brilliant at encouraging students to stretch their newly acquired knowledge to the next step in the design process, by drawing out an incorrect answer to the point that the student and the class would recognize the mistake and then helping a student with a promising answer to gloriously reach the desired goal.

Underwood devoted a great deal of attention to his teaching. John J.Shaughnessy recalled an incident:

> When I worked with Ben as his teaching assistant he worked at home on Wednesdays. When I saw him one Thursday I asked him what he had done the day before. He said he had worked on the upcoming test in his experimental psychology class. Knowing how much Ben could get done in a day I asked him what else he had worked on. Ben gave me that wonderful quizzi

> cal look of his and said that he had spent the whole day making up the test. He commented that he typically spent an entire day to make up a test like that. I doubt that Ben's students knew or cared that they were taking a test that was made 'fresh' for them. I know that Ben cared about his students so much that he wanted to make a test that would best teach them.[7]

His graduate students remember him best not only as an unflagging critic of their research designs, data analyses, and theoretical interpretations but also as an infectiously enthusiastic connoisseur of research. In 1959 my wife, Sheila, and I reversed the migratory flow to California by moving from Berkeley to the Chicago area so that I could attend graduate school at Northwestern University and work with Underwood as his research assistant. While I was attracted to his approach to the study of verbal learning and memory, I was unprepared to be smitten by his talents as a teacher. His lectures were typewritten, reflecting close attention to fact, clarity, organization, and a great deal of time spent at preparation. He began his lectures by reading from his typescript, but quickly deviated from the printed page and breathed life into the myriad topics under study.

During his years at Northwestern, Underwood directed over 30 Ph.D. dissertations and an even greater number of master's theses. Perhaps his greatest contribution to teaching occurred when he was guiding graduate students through these major research projects. He was involved at all stages of the study, from debating the initial premise, to designing a thorough and compelling design, through the detailed analyses and final draft—he was an active and willing participant. His policy with master's students is particularly revealing. He viewed the thesis project as a training exercise, where the second-year student would learn how to conduct research. He often began the process by suggesting a research topic if the student needed help—a topic was drawn from his thick notebook of researchable ideas—and then he coached and debated the implementation of the eventual study with fervor and good humor. Assistance and guidance in the fine-grain analysis of the response protocols were next, followed by an intense process of constructive criticism and endless drafts. But Underwood's responsibility did not end with the filing of the thesis with the graduate division. He offered to prepare the thesis for publication and to accept a "junior" authorship for his efforts. His students were grateful for his offer and for his intimate involvement in their development as researchers. As one student put it, "He stands above all others as the inspiration and benevolent guide to my academic, intellectual, and professional life. I shall always be grateful to him, and for him." And another student wrote, "His spirit is joyously intertwined with so many others—for the betterment of all."

Underwood's treatment of his research assistants is also revealing. He would appoint one individual as his assistant, a position that was held for four years, which coincided with the length of time typically required to complete a Ph.D. degree at Northwestern. As one of Underwood's research assistants, I was centrally involved in the crafting of experiments. Although the direction and thrust of the research was his, Underwood used me as a sounding board for his ideas and proposed research designs. I was responsible for translating a design into a set of experimental procedures that undergraduate assistants, who actually performed experiments, could follow. I supervised the data collection and the beginnings of the data summary. Summers at Northwestern were devoted to the heavy-duty analysis of the data we had collected during the school year. Since this was a joint effort, I could observe how Underwood would extract information from a response protocol; he was continually on the lookout for unique patterns of responses, which often suggested a new analysis or line of investiga tion. Finally, Underwood usually prepared the first draft of the research report, but expected his assistants to offer the same sort of critical comments he provided his students when they prepared drafts of their own research. This research apprenticeship provided me with a unique and valuable research experience that I would draw upon throughout my academic career.

Finally, there is Underwood's service to his profession, reflected in his leadership in professional organizations and his participation in the deliberation of government boards and panels. He was president of the Midwestern Psychological Association (1956–57), president of two divisions of the American Psychological Association, (Experimental Psychology, 1959–60, and General Psychology, 1969–70), and chair of the Psychology Section of the American Association for the Advancement of Science (1964). As for government boards and panels, he served on the Psychobiology Review Panel for the National Institute of Mental Health, the Department of Defense's Advisory Panel on Personnel and Training, the National Research Council's Committee on Naval Medical Education and panel for screening fellowship applications for the National Science Foundation, and the Illinois State Certification Board for Psychology. Underwood also contributed to scientific psychology through his service as an editor of the *American Journal of Psychology* and a member of the editorial boards of three other journals. With Leo Postman, Underwood participated in the founding of the *Journal of Verbal Learning and Verbal Behavior,* serving as a consulting editor for nearly two decades.

Underwood received all the honors that his profession can bestow on an experimental psychologist. He was presented the prestigious Warren Medal given by the Society of Experimental Psychologists in 1964. He received an honorary doctor of science and an honorary membership in

Phi Beta Kappa from Cornell College in 1966. He was elected to the National Academy of Sciences in 1970 and subsequently served as the presiding officer of its psychology section between 1974 and 1977. He was awarded the Distinguished Scientific Contribution Award from the American Psychological Association in 1973, the Distinguished Teaching Award in Psychology from the American Psychological Foundation in 1987, and was named a distinguished graduate by the University of Iowa in 1989.

The citation accompanying the Distinguished Scientific Contribution Award, which he received at the peak of his career, reads as follows:

> For his massive contributions to the experimental and theoretical analysis of verbal learning and memory. A master of experimental design, he has been a recognized leader in the development of a modern and sophisticated methodology in his field of research. For more than a quarter of a century his wide-ranging investigations have focused on the fundamental processes of acquisition and retention. The substantive areas in which his work has yielded new theoretical insights and basic empirical findings are too numerous to list. Among the highlights are his systematic explorations of the effects of distribution of practice, the principles of transfer, the mechanisms of interference in retention, and the role of discriminative processes in recognition. While firmly rooted in the traditions of his discipline, he has throughout his career been an innovator and a pacesetter in a rapidly growing and changing domain of research."[8]

Underwood's papers, monographs, and books continue to influence contemporary research on learning and memory. To illustrate, memory researcher Arthur P.Shimamura provided the following assessment of these lasting contributions, and included some recent applications of his work:

> During the rise of cognitive psychology in the 70s and 80s, Underwood's empirical and theoretical contributions were influential in a variety of domains, including issues of semantic release from proactive interference, part-list cueing, the fan effect, encoding specificity, and the effect of misleading information in eyewitness testimony.

> During the 90s, one could argue that Underwood's contributions have become, if anything, more influential. Interference effects in studies of learning and memory are again discussed as prominent issues in a variety of domains, including retrieval-induced forgetting, implicit versus explicit memory, and source recollection. Indeed, two volumes have been published that are specifically devoted to interference effects in memory. In terms of aging research, Lynn Hasher and Rose Zacks's inhibition theory is one of the most prominent views of age-related effects on memory and cognition. In cognitive neuroscience, inhibitory control (i.e., reducing interference) plays a significant role in our understanding of working memory and frontal lobe function. In computational models of memory, it is important to establish basic properties studied by Underwood, including effects of proactive interference and the distinction between massed and distributed practice."[3]

In short, Underwood's influence on research in the field of human learning and memory continues to be felt through the citation of his formal publications and through the research and teaching of those who were fortunate to be either his students or research colleagues and by their students as well. He will also be remembered for his goodness and kindness as a person.

THE BIOGRAPHICAL FACTS I have cited were drawn from a number of sources, including materials submitted by Underwood to the National Academy of Sciences, autobiographical notes published in the Praeger Centennial Psychology Series (1982) and in the announcement of the Distinguished Scientific Contribution Award presented by the American Psychological Association, and comments provided by his wife, Louise Olson Underwood.

NOTES

1. N.F.Johnson. My memories of Benton J.Underwood. Comments presented at the memorial service for Benton J.Underwood, December 16, 1994, held in the Alice S.Millar Chapel, Northwestern University, Evanston, Ill.

2. L.Postman. The experimental analysis of verbal learning and memory: Evolution and innovation. In *Human Memory: Festschrift*

in Honor of Benton J.Underwood, eds. C.P.Duncan, L.Sechrest, and A.W.Melton, p. 21. New York: Appleton-Century-Crofts, 1972.

3. A.P.Shimamura. Personal communication, 1998.

4. B.J.Underwood and J.J.Shaughnessy. *Experimentation in Psychology.* New York: John Wiley and Sons, 1975.

5. B.J.Underwood et al. *Elementary Statistics.* New York: Appleton-Century-Crofts, 1954.

6. W.F.Hill. Testimonial to Ben Underwood at his memorial service. Comments presented at the memorial service for Benton J. Underwood, December 16, 1994, held in the Alice S.Millar Chapel, Northwestern University, Evanston, Ill.

7. J.J.Shaughnessy. Ben, the teacher. Comments presented at the memorial service for Benton J.Underwood, December 16, 1994, held in the Alice S.Millar Chapel, Northwestern University, Evanston, Ill.

8. Citation. *Am. Psychol.* 29(1974):38–39.

SELECTED BIBLIOGRAPHY

1945 The effect of successive interpolations on retroactive and proactive inhibition. *Psychol. Monogr.* 59 (3, Whole No. 273).

1949 *Experimental Psychology*. New York: Appleton-Century-Crofts.

1952 An orientation for research on thinking. *Psychol. Rev.* 59:209–20.

1957 Interference and forgetting. *Psychol. Rev.* 64:49–60.

Psychological Research. New York: Appleton-Century-Crofts.

1959 With J.M.Barnes. “Fate” of first-list associations in transfer theory. *J. Exp. Psychol.* 58:97–105.

1960 With L.Postman. Extraexperimental sources of interference in forgetting. *Psychol. Rev.* 67:73–95.

With R.W.Schulz. *Meaningfulness and Verbal Learning*. Philadelphia: Lippincott.

1961 Ten years of massed practice on distributed practice. *Psychol. Rev.* 68:229–47.

1962 With G.Keppel. Proactive inhibition in short-term retention of single items. *J. Verbal Learn. Verbal Behav.* 1:153–61.

1964 Degree of learning and the measurement of forgetting. *J. Verbal Learn. Verbal Behav.* 3:112–29.

With W.P.Wallace. Implicit responses and the role of intralist similarity in verbal learning by normal and retarded subjects. *J. Educ. Psychol.* 55:362–70.

1965 False recognition produced by implicit verbal responses. *J. Exp. Psychol.* 70:122–29.

1966 With B.R.Ekstrand and W.P.Wallace. A frequency theory of verbal-discrimination learning. *Psychol. Rev.* 73:566–78.

1967 With B.R.Ekstrand. Effect of distributed practice on paired-associate learning. *J. Exp. Psychol.* (Monograph Supplement No. 1.) 73(4):1–21.

With G.Wood. Implicit responses and conceptual similarity. *J. Verbal Learn. Verbal Behav.* 6:1–10.

1969 Attributes of memory. *Psychol. Rev.* 76:559–73.

With J.S.Freund. Verbal-discrimination learning with varying numbers of right and wrong terms. *Am. J. Psychol.* 82:198–202.

1970 With J.S.Freund. Testing effects in the recognition of words. *J. Verbal Learn. Verbal Behav.* 9:117–25.

1972 With M.Patterson and J.S.Freund. Recognition and number of incorrect alternatives presented during learning. *J. Educ. Psychol.* 63:1–7.

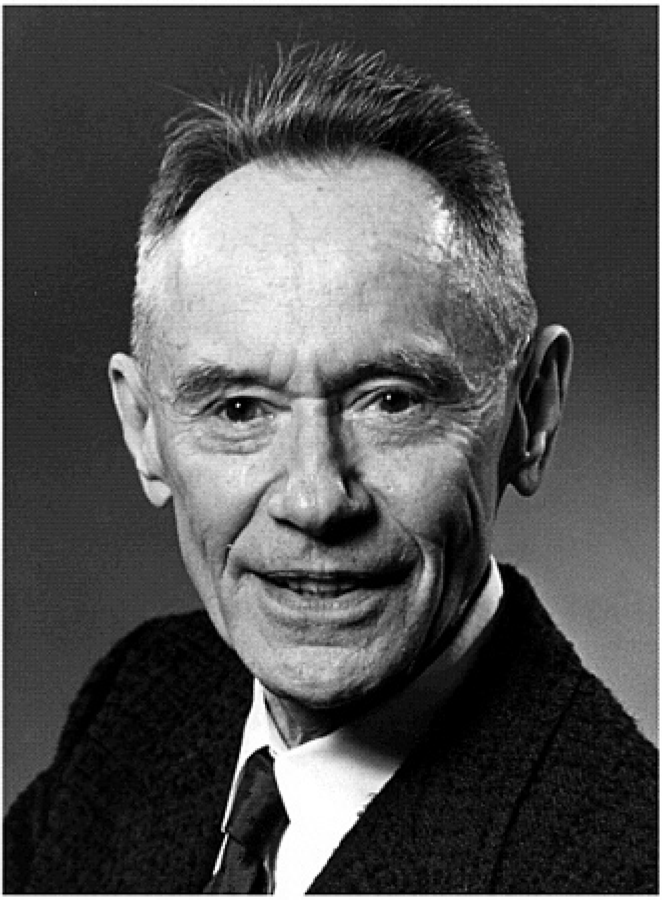
1973 With J.Zimmerman. The syllable as a source of error in multisyllable word recognition. *J. Verbal Learn. Verbal Behav.* 12:701–706.

1975 Individual differences as a crucible in theory construction. *Am. Psychol.* 30:128–34.

1977 *Temporal Codes for Memories: Issues and Problems.* Mahwah, N.J.: Lawrence Erlbaum Associates.

1982 *Attributes of Memory.* Chicago: Scott, Foreman.

Studies in Human Learning and Memory: Selected Papers. New York: Praeger.



Courtesy of the Archives, California Institute of Technology

Oliver R. Wulf

OLIVER REYNOLDS WULF

April 22, 1897–January 11, 1987

BY HAROLD S. JOHNSTON

OLIVER REYNOLDS WULF was a chemist, physicist, and meteorologist. He was an expert in the chemistry of ozone and the oxides of nitrogen in the laboratory and in the atmosphere; infrared spectra of molecules as related to their molecular structure; photochemistry and physics of the atmosphere; and the relation of solar activity and geomagnetism to large-scale circulation of the atmosphere. He was elected to the National Academy of Sciences in 1949.

Oliver Wulf was born in Norwich, Connecticut, on April 22, 1897. He was the son of Otto Ernest Wulf and Grace Reynolds Wulf; he had an older sister and a younger sister. His father, a businessman, co-managed the largest department store in Norwich.

The family home at 120 Laurel Hill Avenue in Norwich had a basement with a cement floor. The basement was kept quite livable by a coal-burning furnace for heating the house. His father had installed a long workbench of 2-inch-thick plank along one side of the basement, and the workbench played an important role in Oliver's scientific development. Excited by early radio and wireless telegraphy, Oliver, in the third grade, built a 1-inch induction coil and a simple galvanometer. Noting his interest in the subject, his father bought him a book entitled *How Two Boys Made Their Own Electrical Apparatus*. While still in grammar school, he built a spark radio station with a crystal detector and using Morse code, he played chess with a man who lived on the other side of town. He cleaned used photographic glass plates, stacked them with tin foil between, and obtained a large condenser. His father bought him a 15,000-volt Thordarson half-kilowatt transformer. With this and other equipment, Oliver built a large Tesla coil and a two-electrode spark gap for his wireless transmitter. His system operated at high frequencies. He studied glow discharges, and he attained heavy brush discharges with a Geisler tube, which he made from a discarded light bulb.

Oliver found greatly increased opportunity upon going from grammar school to high school, the Norwich Free Academy. He found and read serious scientific books in the library on subjects related to electricity and magnetism. From the start, the high-school chemistry and physics teacher took an interest in him. This allowed him free access to the science stockroom, which had originally been well stocked but not used a great deal. He especially enjoyed using a large induction coil, which had been used for an X-ray tube. In his home laboratory, he constructed a high-temperature electric-arc furnace, with which he melted zinc, brass, and iron. Occasionally he blew out the 35-ampere master fuse in his home. The Tesla coils he built produced the distinctive odor of ozone. He read about ozone in chemistry books in the library, and he developed a method specifically to detect ozone in his laboratory.

Oliver graduated from Norwich Free Academy in 1915 and received the science award. In his home basement laboratory, from the third grade through high school, Oliver did experimental work in chemistry and physics, largely concerned with the effects of high-frequency, high-voltage electrical discharges.

After high school, Oliver went to Worcester Polytechnic Institute. He had a good time taking freshman chemistry and physics courses, but his grades were neither good nor bad. Professor Farrington Daniels, who became one of the foremost physical chemists of the time, took a good deal of interest in him to the point of great kindness. Daniels was studying the fixation of nitrogen by the discharge produced by a large Tesla coil. The apparatus was similar to what Oliver had used in high school, but it was much bigger than those he had before. The research that Daniels was doing could equally well have been carried out in either a physics department or a chemistry department. Oliver's past interest and experience had been more physics than chemistry, but because Daniels was doing research in his favorite field, Oliver became a chemist.

There was on campus a small stone structure, a geophysical and geomagnetic laboratory. Robert H.Goddard, the Goddard of rocket fame, was carrying out some experiments. Oliver's physics instructor was working with Goddard in that building, and he explained the research to Oliver, who found it extremely interesting. (Oliver Wulf received the Robert H.Goddard Award from Worcester Polytechnic Institute in 1962.)

Oliver entered Worcester in 1915 and would have graduated in the class of 1919, but he went into the Navy in June of 1918 and was at the officer school at Harvard when the war ended in late 1918. He received an honorable discharge from the Navy in April 1919. He returned to finish schooling at Worcester Polytechnic Institute, and he received his B.S. degree in chemistry in 1920. He filed his undergraduate thesis on "The Action of High Frequency Silent Discharge on Gases." It was unusual for an undergraduate student to do research to the extent that Oliver did with Farrington Daniels at Worcester.

During World War I, Farrington Daniels left Worcester to become director of the Fixed Nitrogen Research Laboratory in Washington, D.C. After Oliver graduated, Daniels invited him to join that laboratory, where he worked as a junior chemist at the U.S. Department of Agriculture (1920–22). Oliver worked with Daniels in parallel with another student who was studying a famous chemical reaction, the first-order decomposition of nitrogen pentoxide, the first clear-cut case of a first-order reaction.

Accepting an offer from the University of Wisconsin, Daniels left the Fixed Nitrogen Research Laboratory. A staff member of the laboratory, Richard Chace Tolman, was appointed the new director. Later Tolman was professor of theoretical chemistry at Caltech, and he achieved great distinction, for example, writing the heavy, thick book entitled *Relativity, Thermodynamics, and Cosmology,* which graduate students at Caltech fondly called "The Three Little Words Book."

Tolman assigned Oliver Wulf to work under Sebastian Karrer, a physicist. Wulf's work then became the production of ozone, and determining for sure, if possible, the molecular weight of ozone, which is the work he did up to the time he left the Fixed Nitrogen Research Laboratory. In those days, no one was quite sure that what one called ozone was all O_3. Some had proposed an N ozone and an O_4 ozone. In view of these uncertainties, Wulf's question was: "What is the molecular weight of what WE call ozone?" Wulf concentrated on preparing pure ozone, and he weighed bulbs of that gaseous material on a sensitive balance. He found the molecular weight of ozone to be indeed 48, establishing that it was O_3. This procedure sounds simple, but it had difficulties. He flowed oxygen from a commercial tank through a high-temperature furnace to burn up any methane and other hydrocarbons; passed the stream through chemical traps to remove water, carbon dioxide, and nitrogen oxides; sent the pure dry oxygen between two concentric glass cylinders; and applied a silent electric discharge, which broke oxygen (O_2) apart to give two oxygen atoms (O). Each oxygen atom added to an oxygen molecule to form ozone (O_3). Wulf passed the gaseous mixture of oxygen and ozone through a liquid-air cold trap to condense the ozone. He slowly removed the liquid air container to let the oxygen boil off and leave behind deeply purple liquid ozone. He let the ozone evaporate into an evacuated glass bulb of about 1/2 liter volume and at a pressure of about 1/20 atmosphere. Such a bulb would weigh about 200 grams. If ozone were O_4, the mass of the bulb and gas would be 200.07143 grams; if ozone were O_3, the mass of the bulb and gas would be 200.05357 grams. The difference is 0.0089 percent of the total weight. A good chemical analytical balance can be used to make such measurements, but it requires great attention to details to achieve the necessary precision.

One may ask, "To increase precision, why not go to higher pressures of ozone?" The answer is that pure ozone gas at room temperature readily explodes at pressures above about 1/20 atmosphere. Pure liquid ozone readily detonates, shattering glass apparatus and throwing off pieces of glass at high velocities.[1] If ozone is prepared from gaseous oxygen containing traces of hydrocarbons, the probability of explosion greatly increases. If ozone is prepared from gaseous oxygen containing traces of nitrogen, the final product is contaminated by oxides of nitrogen. If the reactor contains traces of water vapor, the yield of ozone is greatly decreased.

Early in 1922 Tolman left the Fixed Nitrogen Research Laboratory in Washington, D.C., to be a full professor at the California Institute of Technology. The next 12 months were eventful for Wulf. He became engaged to be married.

He decided that his salary as a junior chemist was not enough to support a family. In the summer of 1922 he obtained a job from the Bristol Company in Waterbury, Connecticut, makers of recording instruments. Shortly afterward, he received a letter from Professor A.A.Noyes inviting him to accept a scholarship and be a graduate student at Caltech. Noyes was chairman of the chemistry department at Caltech, in fact, he was one of the main founders who converted the provincial Throop Institute of Pasadena into the California Institute of Technology. Undoubtedly, Tolman had recommended to Noyes that he make this offer.

His fiancée, Beatrice (Bea) Jones, urged Wulf to go to Caltech. His father and all the men in Wulf's family were businessmen of some kind, and he was obsessed with the idea of becoming a good businessman. He wrote to Noyes, thanking him but declined, saying he felt he ought to go to work full time to support a family. In the summer and early fall of 1922 he was alone, a bachelor in Waterbury, going daily to work on a long trip by trolley car to the Bristol Company. He was an apprentice working under a very excellent machinist in the heavy-machinery brass works.

Oliver Reynolds Wulf and Beatrice Mae Jones were married on October 21, 1922. They lived in an apartment in Waterbury. By January 1923 Wulf recognized that the work in the Bristol brass works was not suitable for him. At Bea's strong recommendation, he wrote to Professor Noyes, asking if his offer still held. Noyes warmly renewed the offer. Mr. and Mrs. Wulf crossed the country by train and arrived at Caltech in March 1923.

Professor Noyes met the Wulfs at the Pasadena station and introduced them to advanced graduate student Richard Bozorth, later famous at Bell Labs. On Bellevue Drive between Euclid and Marengo they found living quarters on the second floor of a rather large garage, where they lived until Wulf obtained his Ph.D. degree in 1926. Fellow graduate students in 1924 were Linus Pauling, Ernest White, Reinhardt Schuhmann, Bill Houghton, Joseph Mayer, Paul Emmet, and Merle Kirkpatrick.

Wulf spoke of a feeling of excitement around Caltech at that time. Professor Hendryk Anton Lorentz was present in the physics department. Wulf recalled a lecture by Professor Ehrenfest in which he placed an imaginary ensemble on the laboratory bench, and as he walked across the speaking area he very carefully went around the imaginary ensemble he had left there. Professor Raman, a tall figure with arms frequently folded, was an excellent lecturer. There was the Astronomy-Physics Club with participation by Hubble and his staff, and Wulf was fascinated by the unfolding of Hubble's famous work. In a visit there, Professor Michelson gave a very interesting seminar concerning the Michelson-Morley experiment.

Wulf took a kinetic theory course given by Professor Robert Millikan, president of Caltech. Other chemists in the course were Linus Pauling, Rudolph Langer, and Don Loughridge. Hearing that the Nobel Prize had been awarded to Millikan, Wulf and the other students gave him a standing ovation when he came into the classroom on the third floor of East Bridge Hall.

When Wulf took up graduate work at Caltech under Professor Richard Tolman, he studied the kinetics of the thermal decomposition of ozone by two methods: (1) a static method with manometric determination of the rate of decomposition and (2) a flowing method with chemical analysis of ozone. He flowed ozone through a coil of glass tubing where ozone decomposed at a rate depending on the concentration of ozone in the tubing and the temperature of the glass. His Ph.D. thesis and the three articles he co-authored with Tolman were based on the thermal decom position of ozone as measured by the flow method. Wulf started his research in the spring of 1923 and continued through half of 1926.

At the end of his graduate studies at Caltech, Wulf received a National Research Fellowship, one of the few sources of support for postdoctoral research at that time. During his last year as a graduate student at Caltech, he started some work on the photochemistry of ozone. He was interested in the structure of the ozone molecule with respect to its absorption of light, and that interest led him to the general question of the absorption of light by molecules. Professor Raymond Birge in the physics department at Berkeley had an active program in spectroscopy, including infrared spectroscopy of molecules as related to their shapes, ultraviolet spectroscopy of diatomic molecules, and hydrogen atom emission. During 1926–27 Wulf took his NRC fellowship to the University of California to work in collaboration with Birge. He extended his study of ozone to include its molecular spectroscopy. Later, he made significant contributions to molecular spectroscopy by studying the infrared and ultraviolet spectra of other molecules, simple and complex.

The Fixed Nitrogen Research Laboratory in Washington, D.C., where Wulf had worked as a junior chemist (1920–22), had become the Bureau of Chemistry and Soils, a laboratory for fertilizer investigations in nitrogen, phosphorous, and potassium, and he was offered a position there. After Wulf completed his fellowship at Berkeley, he and Bea spent three weeks driving their model-T Ford from Berkeley to Washington. Wulf progressed from associate chemist to senior physicist at the Bureau of Chemistry and Soils in the U.S. Department of Agriculture (1928–39).

Frederick Gardner Cartrell, inventor of the electronic smoke precipitator, was head of the Bureau of Chemistry and Soils, and he strongly supported Wulf and his work.

Wulf carried out further studies of the oxides of nitrogen, and he retained a strong interest in ozone. He studied photochemical destruction of ozone and photochemical production; the combination of these two processes gives the ozone photochemical steady state. He set up a simple laboratory experiment to illustrate that the photochemical steady state depended on movement of the gas relative to the source. In his words,

> Flow away from the source may bring ozone formed where radiation is being strongly absorbed to regions where photochemically it is dark, the ozone is stable and thus stored, while flow toward the source, any such stored ozone would be erased in the region of strong absorption of radiation. It was thus apparent that the winds of the upper atmosphere could affect its ozone content.

Wulf did substantial work on the vertical distribution of ozone in the atmosphere, as set up by photochemistry and air motions.

In 1932, while in Washington, Wulf received a Guggenheim Fellowship. He spent the first half-year in Berlin, where he said he “received a tremendous education,” including an inspiring association with Professor Michael Polanyi. He and Bea were in Berlin when they heard that the bank in which they had deposited almost all their money had failed and gone into bankruptcy, a widespread event during the depression. During their second half-year, they went to Göttingen to associate with James Franck at the second institute of physics at the university; Max Born had the first institute of physics upstairs in the same building. They later did additional travel in Europe, Mexico, and the Caribbean.

In 1935, Wulf received the Hillebrand Prize sponsored by the American Chemical Society.

Solar radiation at shorter wavelengths (and thus higher energy) than the wavelengths that form ozone is absorbed by air at much higher altitudes to photo-ionize air to form the ionosphere, which was responsible for long distance radio communication.

Wulf's interest in how air motions move ozone in and out of the ozone formation region in the stratosphere, the temperature structure of the atmosphere, and how solar radiation produces ions in the upper atmosphere led him into the study of meteorology and atmospheric dynamics. In 1939, at the recommendation by Carl Rossby, famous meteorologist and atmospheric dynamicist, Wulf was appointed senior meteorologist in the U.S. Weather Bureau. He remained a member of the Weather Bureau from 1939 until he retired in 1967, even though the Weather Bureau assigned him to do independent work at places other than Washington, D.C. Again at the recommendation by Carl Rossby, the Weather Bureau assigned him in 1941 to the Institute of Meteorology at the University of Chicago to teach meteorology to Air Force cadets, which he did until the end of the war.

In 1945 the Weather Bureau assigned Wulf to Caltech as a research associate with rank of full professor in the Division of Chemistry and Chemical Engineering, a position he held until he retired in 1967.[2]

Wulf found it especially interesting that ionized air, set in motion by winds in the upper atmosphere, moved across lines of force in Earth's magnetic field to produce small but observable magnetic signals at the surface of Earth. Wulf's major research at Caltech after he returned in 1945 was collaboration with Seth Nicholson, a solar astronomer and leading authority concerning sunspots. They worked together with the solar telescope and other equipment at the Mount Wilson observatory, and they published several articles together, studying the relation between solar activity, geomagnetic activity, and Earth's magnetic field. They also examined the effects of the Moon in perturbing recurrent Sun-induced geomagnetic activity. One interesting project was their study of global atmospheric tides as induced by the Sun and the Moon.

In a short speech at his retirement dinner in 1967 Wulf summed up his recent and future research.

> The realization that the movement of this photochemical ionized air reacted on the earth's magnetic field, in very small degree it is true, led to very great interest in the circumstance that probably this reaction to air motion in the lower ionosphere was being measured daily and not at one point occasionally, but at many magnetic observatories over the surface of the earth. Thus the realization that information concerning winds in the upper mesosphere and lower thermosphere, that is the lower ionosphere, was probably contained in the daily continuous records of the earth's magnetic field, led to a strong feeling that here was a field in the atmospheric sciences holding great promise, and it is in the midst of work in this field that we are at present and planning to continue.

To summarize, Oliver Wulf in his childhood carried out serious self-educational construction of devices and experiments with high-frequency, high-voltage electrical discharges. Later, this experience led his research, step by step, to nitrogen fixation by electric arcs, ozone chemistry, ozone photochemistry, ozone in the atmosphere as affected by photochemistry and air motions, atmospheric dynamics, meteorology, and ions and winds in the ionosphere, causing induced magnetic signals at the ground. His childhood fascination with electricity and magnetism at his basement workbench grew to become major contributions toward understanding electricity and magnetism in the global atmosphere.

THIS BRIEF REVIEW of Oliver Wulf's personal and professional life is based in part on my recollection of a pleasant and profitable association with him from 1946, but in large measure it is based on material from the Archives of the California Institute of Technology: (1) an interview with Oliver Reynolds Wulf by Tom Apostol, Oral History Project, Pasadena, California, copyright 1987; (2) an inter

view with Mrs. Oliver Reynolds Wulf by Harriet Lyle, Oral History Project, Pasadena, California, copyright 1982; (3) a four-page summary and list of items in the Wulf archives; and (4) a five-page transcript of an address Wulf made at his retirement dinner at the Pasadena Huntington Hotel on April 29, 1967. Statements I make in this memoir concerning his feelings and opinions are based on his words in the oral history and his talk at the retirement dinner.

NOTES

1. When I (H.S.J.) was a graduate student at Caltech in 1945–47, Professor Don Yost and I wanted to study the rate of reaction between ozone and nitrogen dioxide. Oliver Wulf instructed me how to prepare pure ozone, including the safety warnings. Later in my laboratory at Stanford, my graduate students and I made and used ozone for several studies. We had only one explosion. Fortunately, following Wulf's advice, we carried out the experiment inside a hood and behind heavy steel plates, and no one was hurt, but all adjacent apparatus was demolished.

2. It was at this time (1946–47) that Wulf taught me (H.S.J.) how to make and handle ozone in the laboratory. He also taught me about Sydney Chapman's mechanism for ozone formation and destruction in the upper atmosphere; about G.M.B.Dobson's measurement of ozone and its vertical distribution in the atmosphere by means of ground-based spectroscopy of scattered sunlight during sunset or sunrise; and about ions and winds in the ionosphere.

SELECTED BIBLIOGRAPHY

1922 With S.Farrar. Preparation of pure ozone and determination of its molecular weight. *J. Am. Chem. Soc.* 44:2391–97.

1927 With R.C.Tolman. The thermal decomposition of ozone: I. The homogeneity, order, specific rate and dependence of rate on total pressure. *J. Am. Chem. Soc.* 49:1183–1202.

With R.C.Tolman. The thermal decomposition of ozone: II. The effect of oxygen and accidental catalysts on the rate. *J. Am. Chem. Soc.* 49:1202–18.

With R.C.Tolman. The thermal decomposition of ozone: III. The temperature coefficients of reaction rate. *J. Am. Chem. Soc.* 49:1659–64.

The magnetic behavior of ozone. *Proc. Natl. Acad. Sci. U. S. A.* 13:744–48.

1928 A progression relation in the molecular spectrum of oxygen occurring in the liquid and in the gas at high pressure. *Proc. Natl. Acad. Sci. U. S. A.* 14:609–13.

The heat of dissociation of oxygen as estimated from photochemical ozonization *Proc. Natl. Acad. Sci. U. S. A.* 14:614–17.

1930 The band spectrum of ozone in the visible and photographic infrared. *Proc. Natl. Acad. Sci. U. S. A.* 16:507–11.

1931 With E.H.Melvin. Effect of temperature upon the ultraviolet band spectrum of ozone and the structure of this spectrum. *Phys. Rev.* 38:330–37.

1932 The dissociation of ozone and the mechanism of its thermal decomposition. *J. Am. Chem. Soc.* 54:156–60.

1934 Steady states produced by radiation with application to the distribution of atmospheric ozone. *Phil. Mag.* 17:251–63.

1936 With I.S.Deming. The absorption of solar radiation in the atmosphere and its relation to atmospheric temperature and ozone content. Oxford Conference on Solar Radiation.

With U.Liddel and S.B.Hendricks. The effect of ortho substitution on the absorption of the OH group of phenol in the infrared. *J. Am. Chem. Soc.* 58:2287–93.

1937 With I.S.Deming. The distribution of atmospheric ozone in equilibrium with solar radiation and the rate of maintenance of the distribution. *Terr. Mag.* 42:195–202.

1938 With I.S.Deming. On the production of the ionospheric regions E and F and the lower altitude ionization causing radio fade-outs. *Terr. Mag.* 43:283–98.

1939 With E.H.Melvin. Band spectra in nitrogen at atmospheric pressure. A source of band spectra excitation. *Phys. Rev.* 55:687–91.

1940 With E.J.Jones and I.S.Deming. Combination frequencies associated with the first and second overtone and fundamental OH absorption in phenol and its halogen derivatives. *J. Chem. Phys.* 8:753–65.

1942 The distribution of atmospheric ozone. *Proc. 8th Am. Sci. Congr.* 7:439–46.

1944 With S.J.Obley. The utilization of the entire course of radiosonde flights in weather diagnosis. Publication of the Institute of Meteorology, University of Chicago. Misc. Rep. No. 10.

1945 On the relation between geomagnetism and the circulatory motions of the air in the atmosphere. *Terr. Mag.* 50:185–97.

A preliminary study of the relation between geomagnetism and the circulatory motions of the air in the atmosphere. *Terr. Mag.* 50:259–78.

1946 A possible atmospheric solar effect in both geomagnetism and atmospheric electricity. *Terr. Mag.* 51:85–87.

1947 With S.B.Nicholson. Terrestrial influences in the lunar and solar tidal motions of the air. *Terr. Mag.* 52:175–82.

1948 With S.B.Nicholson. On the identification of solar M-regions associated with terrestrial magnetic activity. *Publ. Astron. Soc. Pac.* 60:37–53.

With S.B.Nicholson. A possible influence of the Moon on recurrent geomagnetic activity. *Phys. Rev.* 73:1204–1205.

With S.B.Nicholson. Recurrent geomagnetic activity and lunar declination. *Publ. Astron. Soc. Pac.* 60:259–62.