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VOLUME 83

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*Any opinions expressed in this memoir are those of the authors
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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

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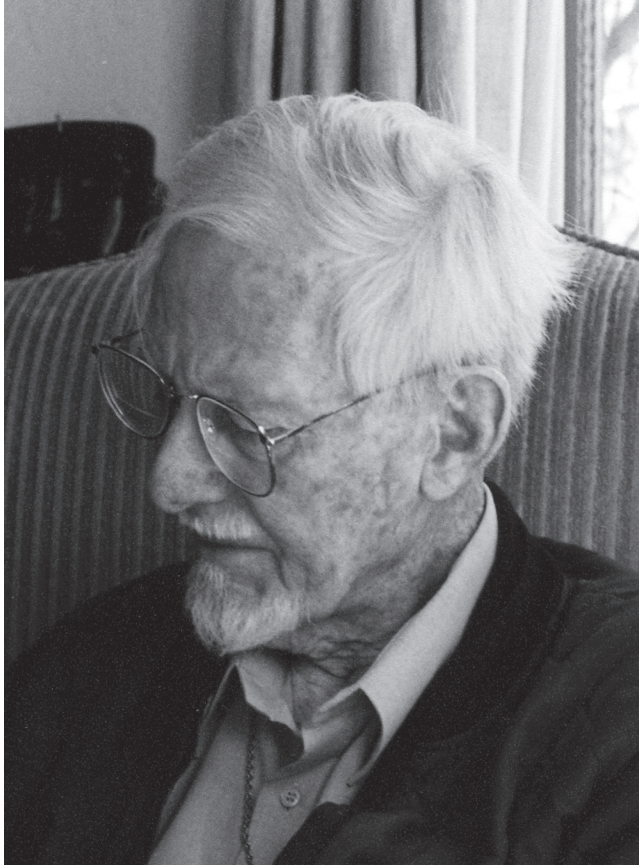
J. DESMOND CLARK

April 10, 1916–February 14, 2002

BY FRED WENDORF

B Y ANY MEASURE J. Desmond Clark was the most influential and productive archaeologist who ever worked in Africa. More than any other individual he shaped our understanding of African prehistory, and his interests and goals have structured almost all the prehistoric research now underway on that continent.

I first met Clark in the fall of 1960, when he came to Santa Fe to give a talk on his work in Northern Rhodesia. I was then working as an American Southwestern archaeologist, but Clark's talk stimulated my interest in the archaeology of Africa. It was only two years later, in 1962, and still knowing nothing about African prehistory, that I found myself leading the Combined Prehistoric Expedition in the salvage excavations at prehistoric sites in the Aswan reservoir in Egypt and Sudan. It was my very good fortune that Clark was the first person I turned to in my frantic scramble to learn enough about African prehistory to do my job and not embarrass myself totally. Clark responded quickly with a packet of reprints and a long list of readings that began my African education. On many occasions since then I turned to him for guidance, and I found Desmond always to be generous with his advice and encouragement. I have also

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learned that I was not alone in receiving help from Clark. In fact, there are very few archaeologists now working in Africa, including Africans, who have not benefited from his advice and support.

Clark was remarkably well informed about the archaeology and Pleistocene geology of almost every part of Africa, mostly because throughout his life he found opportunities to do field work in a wide variety of areas and over the whole chronological range of human experience in Africa, from the earliest human artifacts to an occasional ethnographic study of modern tribal groups. He was also an exceptionally gifted synthesizer, and he drew on his wide experience to write several summary books that remain the best available general texts on the archaeology of Africa (1954, 1959, 1970, 1982).

Desmond Clark was born in London into a fairly well-to-do merchant family. One of his grandfathers was a chemist who had developed a profitable business in cosmetics, traveled widely on the continent, and acquired a strong interest in antiquities. Clark always credited this grandfather with stimulating his own interest in prehistory. Clark's father was trained as an electrical engineer, but after he returned from service on the Western Front during World War I he took over the family cosmetic business and managed it until his death. When his father returned from service, Desmond and his family moved to the small village of Northend, in the Chiltern Hills, a beautiful wooded area about 40 miles west of London. It was here that Clark developed his interest in the natural environment. At age six he was sent away to boarding school, first to a school at Portishead, near Bristol, and then to Swanbourne House, a preparatory school in Buckinghamshire, where he studied for and passed his common entrance exams. From there he went to Monkton Combe School near Bath. Here his interests in archaeology

began to form, stimulated by his teachers, of which one was a local antiquarian.

In 1934 Clark was accepted by Christ's College, Cambridge, where he studied history for two years, then archaeology and anthropology under Miles Burkitt, who awakened in him an interest in artifacts and the history of the discipline, and Grahame Clark, who taught him the importance of the paleoenvironment to archaeology, primarily how changes in the environment might influence human behavior. Another significant influence on Desmond at this time was Sir Mortimer Wheeler, who instructed him in rigorous field techniques. Clark worked for Wheeler at Maiden Castle during the 1936 field season and part of the summer of 1937. Desmond was an excellent student, and in 1937 he received his bachelor of arts degree with first-class honors, as well as an honorary bachelor scholarship from Christ's College.

Despite his distinguished undergraduate academic record there were almost no positions in archaeology when Clark received his B.A. degree. In fact, there were only three permanent non-museum positions in archaeology in the entire country, and none of these were open. Clark applied unsuccessfully for several museum positions in England. Then in the late fall of 1937 he was offered a three-year appointment, with an option for a long-term contract, in Northern Rhodesia (now Zambia) as secretary of the Rhodes-Livingstone Institute and curator of the David Livingstone Memorial Museum. The position included a salary of £400, plus a house with basic furniture. Although not previously interested in African archaeology, Clark eagerly accepted the offer and in mid-December went by boat to Cape Town, arriving there the first week of January 1938. A few days later he traveled by train to Livingstone, a three-day journey. Although initially intending to stay only 3 years in North-

ern Rhodesia, he remained there and held the same two positions for 23 years, until 1961, when he accepted an appointment as professor of anthropology at the University of California, Berkeley. He stayed at Berkeley as professor, and from 1986 as professor emeritus, until his death.

While at Cambridge, Clark met a fellow student who was reading modern languages. Her name was Betty Baume, and she was from Yorkshire. Their friendship soon blossomed, and they became engaged during his final year. Shortly after his arrival in Livingstone, Clark sought and received permission to marry Betty from the governor (permission to marry was required of all first-tour staff). In late spring of 1938 Betty came to Livingstone, and a month later they were married. This began one of the great partnerships in archaeology. Betty went with Desmond on all his expeditions, she ran the field laboratory while he supervised the excavations, and she translated his notoriously terrible handwriting and typed many of his manuscripts. She even served as acting curator of the museum while he was away in service during World War II. They had two children, a son, John Wynne Desmond Clark, now living in England, and a daughter, Elizabeth Anne Cable Clark, who resides in Australia. Betty died two months after Desmond.

During the 1930s Clark was one of the three or four professional archaeologists in southern Africa, but when he arrived in Livingstone his first efforts were to do something about the Rhodes-Livingstone Museum. Clark found the museum to be a disorganized shambles, with collections, mostly ethnographic and historical materials, displayed on open tables, and housed in an old Palladian-style building that had previously served as the United Services Club. There was only one small display of archaeological artifacts, and these were from Gatti's 1929 excavations at Mumbwa caves. Most of the collections were still in boxes. There was no

technical staff and the collections were little more than
assemblages of artifacts and mineral specimens with few or
no records. He set about reorganizing the museum: creat-
ing thematic exhibits of both archaeological and ethnologi-
cal materials and writing an accompanying handbook. Clark
also directed an annual two-week winter field school in ar-
chaeology that was based at the museum. All these activities
and improvements at the museum were popular with the
local people and schoolchildren, and after World War II
this popularity made possible the construction of a new
museum with funding from several private companies and
the Northern Rhodesia government.

With the museum in reasonable shape Clark turned his
attention to research on the local archaeology. He began
his fieldwork with geologist Basil Cooke from Johannesburg,
and their study of the stone tools and fossils of the Old
Terrace gravels of the Zambezi River resulted is his first
publication, in 1939, with H. B. S. Cooke. He published two
other papers that same year, one a summary of the known
Stone Age sites in Northern Rhodesia (issued as the first
occasional paper of the Rhodes-Livingstone Museum), and
the other a discussion of the origin and aims of the David
Livingstone Memorial Museum, which appeared in the *Mu-
seums* Journal (London). Clark also obtained a research
grant to excavate the Mumbwa caves in Northern Rhodesia,
and his report on that work (1942) recorded a sequence of
Stillbay, Rhodesian Wilton, and Iron Age seasonal occupa-
tions in those caves.

From 1941 to 1946 Clark was in the British army, serv-
ing initially as a sergeant in the Seventh East African Field
Ambulance Corps in Ethiopia, Madagascar, and Somalia.
His unit took part in the retaking of Berbera in British
Somaliland, and several engagements on the plateau at
Hargeisa and Boroma, and finally, in late 1941, at Gondar,

the last battle in the Ethiopian campaign. After officer training he became a civil affairs officer in the British Military Administration in Somalia, where he was stationed in the southern part of the country. During this period he also traveled to Kenya and became close friends with Louis and Mary Leakey, visiting them frequently. While in Ethiopia and Somalia, in addition to his work as a soldier and later as a civil affairs officer, Clark also managed to do some archaeology, recording sites and even performing limited excavations. In 1944 and 1945 he published three short articles, all on Stone Age sites he found in Ethiopia. By 1946, when he took his discharge from the army, Clark had accumulated 22 petrol boxes of artifacts and quantities of field notes from his studies in Somalia and Ethiopia. With the help of the army he managed to get them all safely to Livingstone, and eventually to Cambridge. Later the sites he surveyed and the data he collected provided an important part of his Ph.D. dissertation and the basis of his highly respected book *The Prehistoric Cultures of the Horn of Africa* (1954).

On his release from the army and his return to Northern Rhodesia in 1946, the improvement of his museum was again Clark's first concern. One of his initial tasks was to begin planning a new Rhodes-Livingstone Museum, the drawings for which were published in 1947. This was followed in the same year by an article issued by the Rhodes-Livingstone Institute on the public service role of museums. Other publications during this period were limited to a few brief articles on a variety of topics, including the Bushmen, copper production in Central Africa, and the formation and chronology of the Victoria Falls. Clearly, there was a lack of focus, but this was to change shortly.

In 1947, less than a year after Clark returned to Northern Rhodesia, Louis Leakey organized and hosted the First Pan-African Congress on Prehistory. This congress brought

together for the first time almost everyone interested in African prehistory—archaeologists, Quaternary geologists, and paleontologists—who came from 26 countries and from all parts of Africa and abroad. It gave those who attended the opportunity to meet and learn what others were doing and to discuss mutual problems. It was a landmark event for African prehistory and for Clark. He gave a well-received paper on his research in the Somalilands, but his engaging personality, together with his scholarly competence and experience with the prehistory of southern and eastern Africa gave him considerable prominence beyond his presentation. Most important, however, the discussions at the congress stimulated Clark's commitment to archaeological research, and over the next decade following 1947 Clark conducted excavations in the upper Zambezi Valley, dug the Late Stone Age cave of Nachikufu, and reexamined the Broken Hill site (1959) where "Rhodesian man" had been discovered in 1921.

In 1948 Clark took a year's leave and returned to Cambridge to complete his residency requirement for a doctorate. He received his degree in 1951, writing his thesis on his work in the Zambezi Valley and the Horn of Africa. The previous year he published his first regional synthesis, issued as a monograph by the South African Archaeological Society (1950). In that year he also published several articles on a variety of archaeological topics, and served as president of the South African Archaeological Society. Clark was rapidly becoming a leader among African archaeologists, a position that was reinforced by a remarkable publication record that included 57 papers and six books published in the 10 years between 1950 and 1959. He also continued to be active in the museum field, and in 1955 he served as president of the South African Museums Associa-

tion, giving a presidential address on the role of museums in public education.

Clark was also interested in cultural preservation, and he realized that something needed to be done to protect the archaeological and historical sites in Northern Rhodesia. To provide this protection, in 1950 he founded and was secretary of the Northern Rhodesia National Monuments Commission, with authority to protect all monuments built before 1897. Clark served as secretary of the Commission until 1961, when he left to go to Berkeley. He was then elected an honorary member of the commission, a position he held until his death.

The Second Pan-African Congress was held in 1952 in Algeria, and Clark served as chairman of the prehistory section. Stimulated by the papers and the collections he saw while at the congress, Clark proposed a correlation of prehistoric cultures north and south of the Sahara that was published in the *South African Archaeological Bulletin* (1954). Although the model he proposed is now known to be incorrect, it was Clark's first attempt to view African prehistory as a whole.

The Third Pan-African Congress was held in Livingstone in 1955 with Clark as the organizing secretary and coeditor of the proceedings. Shortly after the congress in Livingstone, Clark was invited to do field work in Angola, where mining activities had exposed many archaeological horizons buried in fossil dunes. He spent four field seasons there (1959, 1960, 1963, and 1968) and he wrote four volumes on the results of his excavations. These were published by the Museu do Dundo in Lisbon (1963, 1966).

Although Clark moved to Berkeley in 1961, he continued his archaeological research in Northern Rhodesia (each year from 1962 through 1968 and again in 1972), as well as smaller projects in South Africa (in 1962, 1966, 1979, and

1985). He also found time to spend two field seasons in Syria (1964, 1965) and two more along the Nile in central Sudan (1972, 1973).

In 1953 Clark discovered the most important site of his career at Kalambo Falls in Northern Rhodesia. This was a deeply stratified, waterlogged Lower Paleolithic locality with superb preservation of wood, seeds, leaves, and pollen. Because of the acidity of the soil, however, almost no bone was preserved. It was here that Clark introduced the technique of "point plotting" each individual artifact. This resulted in the first record of African Acheulian activity areas. Because of his earlier training at Cambridge and his initial experience with Cooke and other geologists, the research at Kalambo Falls was organized as a multidisciplinary project with a focus on the reconstruction of the paleoenvironments of the site. A number of students and young scholars, including many who are now major figures in prehistoric studies in Africa and elsewhere, participated in the excavation and writing of the reports. The first two books on his work at Kalambo Falls (1969, 1974) established him as one of the two leading African prehistorians, the other being Louis Leakey. The third volume on Kalambo Falls (2001), an even more massive report than the first two, was delayed in part because of the enormous size of the effort and because Clark began to lose his eyesight while he was working on the manuscript. Fortunately he was able to finish the report and see it through the press. He was nearly blind when he died a few months later.

Shortly after Clark arrived in Berkeley in 1961 he and his colleagues in the Department of Anthropology began the development of a research and graduate training program in African prehistory and related disciplines that soon became the most distinguished center in the world for such studies. In addition to the outstanding faculty involved in

the program, a key feature was the active recruitment of students from Africa. By the time Clark retired from teaching in 1986, 10 Africans from 6 different countries had received their doctorates under his direction. These African graduates are now university teachers, museum directors, and heads of antiquities organizations in their own countries. Beginning in 1974 Clark began a long-term project in Ethiopia. Initially it was focused on the Arussi-Harar Plateau and the Gadeb Plain, on the eastern side of the Rift Valley in the southeastern section of Ethiopia. He worked there for four seasons, until 1978, and he published several interesting papers on the results of these investigations, which were mostly at Lower Paleolithic (Oldowan) and Acheulian sites. Then in 1981 and 1982 he shifted to the Afar Middle Awash Valley where he worked in the rich Lower and Middle Paleolithic localities in that area. Unfortunately only one paper based on this work was published, in part because the research was unfinished. The project was placed on hold when the Ethiopian government declared an eight-year moratorium on all paleoanthropological research in Ethiopia by foreign scholars while the Ethiopian Ministry of Culture established new rules and regulations. It was not until 1990 that Clark was able to return to the Middle Awash and the Afar Basin.

Unable to work in Ethiopia, Clark turned his attention to other areas, and for the first time he began to develop long-term projects outside Africa. It had long been known that Lower Paleolithic sites with lithic assemblages at least superficially similar to those in Africa occurred in central and western India. Clark was interested in these because they indicated possible contacts with Africa and might relate to the spread of early humans into Southeast Asia. In 1980 Clark, with several Indian colleagues, began a study of several Lower Paleolithic sites in the Madhya Pradesh of

north-central India. He spent four seasons there between 1980 and 1983; In 1983 Clark published a book with G. R. Sharma on the results of this research. In many respects, however, the results were disappointing. Preservation was poor, associated fauna was limited to nonexistent, and dating was insecure. In early 1987 Clark was invited to visit north China and see the Paleolithic sites there and study the collections from these sites. Later that year and continuing into 1988 he returned to visit the Paleolithic sites in south China. His interest in China continued in late 1989 and early 1990, when he did archaeological research at several very early Paleolithic sites in the Nihewan Basin in western China. Unfortunately the results of this research had not been published when he died.

Clark received many honors for his research and scholarship. His first was in 1960 when he became a commander of the Order of the British Empire. This was followed in 1967 by the Commandeur de l'Ordre National de Senegal; the Huxley Medal from the Royal Anthropological Institute, London, in 1974; and in 1985 the Gold Medal of the Society of Antiquaries in London. In 1985 he also received two honorary doctorates, one from the University of Witwatersrand in Johannesburg and the other from the University of Cape Town. He was elected a foreign associate member of the National Academy of Science in 1986 and a full member in 1993. Clark also received the Gold Medal of the Archaeological Institute of America in 1989.

The quality of Clark's research and his established record for publishing his results were widely admired by his colleagues, and for this reason his requests for funds were usually favorably received by the award panels at the National Science Foundation (10 grants between 1962 and 1984 for paleoanthropological research in Africa), the Smithsonian Institution (five grants between 1980 and 1985

for research in central India), and the Wenner Gren Foundation (with several grants to assist his research in Africa, to publish two books [*Atlas of African Prehistory* and *Background to Evolution in Africa*], to fund a movie on flaking stone artifacts, and to assist with data analysis for volume III of *The Kalambo Falls Prehistoric Site*).

Possibly one of Desmond's most treasured public honors, and certainly the most emotional, was the great party held at Berkeley for him when he retired in 1986. Nearly 200 of his old students, friends, and colleagues came from all over the world to celebrate his enormous professional achievements and to express their thanks for all that he had done for them. It was a measure of his contributions to archaeology as both teacher and scholar that they came from several countries in Africa, from Europe, from China, and from many universities and museums in the United States.

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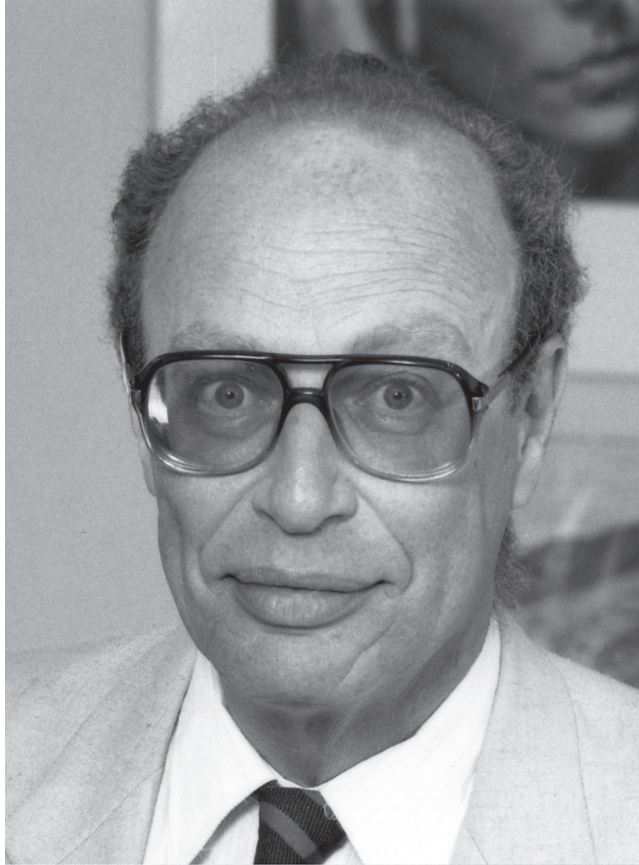
LEOPOLDO MÁXIMO FALICOV

June 24, 1933–January 24, 1995

BY MANUEL CARDONA, MARVIN L. COHEN, AND
STEVEN G. LOUIE

LEOPOLDO ("LEO") MÁXIMO Falicov died on January 24, 1995, after a short illness involving cancer of the esophagus. He was a professor of physics at the University of California, Berkeley, and a specialist in the theory of condensed matter physics. He was elected to membership in the National Academy of Sciences in 1983. He was also a member of the Academia Nacional de Ciencias Exactas, Fisicas y Naturales of Argentina, and the Royal Danish Academy of Sciences and Letters. He was a fellow of the American Physical Society, Britain's Institute of Physics, and the Third World Academy of Sciences. He received numerous fellowships, including the Sloan, Fulbright, and Guggenheim fellowships, and an honorary doctor of science degree from the University of Cambridge.

Falicov's early (postdoctoral) work, performed at the University of Cambridge (England, 1958-60) established and elucidated the complex nature of the electronic band structures of metals (such as magnesium, aluminum, zinc, cadmium) and the details of their Fermi surfaces (1962,1). At the University of Chicago (1960-69) he proposed the existence of magnetic breakdown in metals that possess small energy band gaps and coauthored an important paper on superconductive tunneling (1962,2). At Berkeley (1969-95)

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he was also responsible for a number of "firsts" in theoretical condensed matter physics, including the so-called Falicov-Kimball theory of semiconductor-metal transitions (1970), the theory of resonant photoemission (1977), resonant Raman scattering (1973), and many others. A book on group theory and its applications to solid-state physics (1966), based on a course he taught at the University of Chicago and now out of print, has been a standard textbook to a couple of generations of condensed-matter physicists. Falicov's theoretical work was complemented through strong interactions with experimentalists. Because of his talent for spatial visualization, Falicov's theories were often geometrical and very clearly defined. The intense experimental research on Fermi surfaces of metals and semimetals in the 1960s and 1970s resulted in data that could be viewed as parts of puzzles. Falicov's work on Fermi surface geometries allowed consistent interpretation of the data and brought the pieces of the puzzles together. Some of his drawings of Fermi surfaces were considered to be works of art, such as the "Falicov monster" model for magnesium and his "poisoned turnips" model for arsenic. These pictures have been reproduced in standard textbooks and on covers of conference proceedings. His great command of geometry and symmetries was reflected in the excellent text he wrote on group theory.

Leo Falicov was born in Buenos Aires, the federal capital of Argentina, on June 24, 1933. His parents were both of Eastern European Jewish origin. His father, Isaías Félix Falicov, was born in Argentina, whereas his mother, Dora Samoilovich, immigrated to Argentina with her parents at an early age. It seems that her father left southern Russia to avoid being drafted into the Russo-Japanese War. Those of us who knew Leo for many years were very aware of his Argentinean roots, which reflected themselves not only in

his speech (both in Spanish and in English) but also in his attitudes and his gentle, mild-mannered temperament.

Leo's parents both studied dental medicine at the University of Buenos Aires, where they probably met. While this may sound surprising given their recent immigrant Jewish background, one must keep in mind that Argentina was at the turn of the twentieth century one of the world's strongest economies and an immigrant's paradise. Compulsory and free lay public education had been established in the mid-1800s by D. F. Sarmiento, the first civilian president of Argentina. The quest for higher education and learning found fertile ground in Argentina at the turn of the twentieth century. In spite of the available opportunities the economic realities of early immigrants compelled Leo's parents to study dentistry, a professional course that was not only one of the shortest in those days but also provided financial independence at an early age. The Falicov-Samoilovich couple also had a son, Raúl, four years younger than Leo. Raúl studied medicine in Argentina and also immigrated to the United States (Argentina is often mentioned as one of the few countries in the world with a serious brain drain problem). Raúl lived in San Diego until he succumbed to cancer in 1989. Leo's parents also had a daughter, Estela, who was 10 years younger than Leo. Estela, a sociologist, now lives in Buenos Aires.

Like most Argentineans, Leo attended public grammar school (in Buenos Aires) and then a highly prestigious public high school, the Colegio Nacional de Buenos Aires. He graduated in all cases with the highest grades and honors. We have attempted, without success, to find out whether any specific person may have exercised a significant influence on his analytical and mathematical abilities and interests. His father seems to have had a general interest in mathematics and, even more so, in games that required considerable

intellectual effort, such as bridge. Leo inherited his father's interests and developed remarkable skills in such pastimes (he won a number of bridge championships). After graduating from the Colegio Nacional de Buenos Aires, Leo entered the state-owned School of Engineering and Natural Sciences at the University of Buenos Aires and remained in his parents' home during the ensuing studies. As with many other adolescents, this must have been a period of considerable soul searching for Leo, in particular concerning his professional interests and future. He hesitated between an engineering and a chemistry curriculum. He remained in Buenos Aires until 1955, when he moved to Bariloche, managing to obtain a *licenciado* degree (something between a bachelor and a master, common in Spanish-speaking countries) in chemistry from Buenos Aires in 1957, after only two years of residence in Bariloche and in spite of the heavy workload there.

We have learned that while a student at the University of Buenos Aires, Leo became a very close friend of two highly gifted young men, Enrique Bonacalza (who was murdered in 1997 near Bariloche) and Edgardo Slemenson. Early in 1955 they must have heard that a new graduate school of physics was about to open in San Carlos de Bariloche, a beautiful spot at the foot of the Patagonian Andes, located in splendid isolation 1,800 kilometers away from Buenos Aires, straight line, on the shore of Lake Nahuel Huapi. The new school was to be run by the Argentinean Atomic Energy Commission and not only would tuition be free but the students were all to receive a stipend to cover their living expenses. Correspondingly, admission requirements would be very strict (a policy, unusual in Latin America, that has been kept to the present day). Leo and his friend Bonacalza applied for admission to the new school and had no difficulty passing the entrance examination. They both moved to Bariloche in the spring (our fall) of 1955 and

graduated with the *licenciado* degree in physics in 1958, Leo with the highest honors and as the valedictorian of the first graduating class. Nearly simultaneously Leo wrote a doctoral dissertation on the Lennuier effect (1960), an intriguing phenomenon observed in Paris in 1947 by the doctoral student whose name it bears. The effect, as explained by Leo, involves quantum-mechanical frequency shifts in the resonance fluorescence of atomic vapors (e.g., mercury) at low pressure.

To gain perspective about Leo and his career we must now delve into the series of bizarre events that led to the creation of what is now called, after its first director, the Instituto de Física Balseiro, in a rather isolated but extremely beautiful spot of the Argentinean Patagonia. World War II left Argentina, a country rich in foodstuffs and raw materials, in very good financial shape. Its liberal immigration policies had attracted a considerable number of European professionals and intellectuals, among others, fugitives from Franco's dictatorship in Spain and from the anti-Semitism of other European dictators. They were joined at the end of the war by a few more escaping not only from the justice of the Allies but also from postwar devastation and penury. They gave a welcome boost to the budding Argentinean academic establishment. The physicists among them, however, soon felt the frustration of their isolation, compounded by the ubiquitous secrecy that accompanied the atomic research performed by the nuclear powers. Some of the Argentinean physicists were able to approach President Perón, a populist military dictator, concerning the necessity for Argentina to develop its own nuclear program. In 1948 a young Austrian-German chemist (born in the Czech Sudetenland) by the name of Ronald Richter managed to gain access to Perón and to offer him a scheme to achieve, with rather simple means, controlled nuclear fusion and

thus to obtain an inexhaustible source of inexpensive energy. The scientific basis of the scheme, if any, seems to have been the concept of the Boltzmann distribution: Among a large ensemble of atoms in thermal equilibrium there are always a few, at the top of the distribution, that possess the energy required to achieve fusion. The scheme falls into the category of what is nowadays called cold fusion. Richter's only credentials were an unpublished D.Sc. thesis from the German University in Prague, but Perón was fascinated by the scheme and approved its support without any peer review. Some German aeronautical engineers had just succeeded in building for Perón an aircraft factory. His decision to support Richter may have been based on the ensuing belief that any project undertaken by Germans is bound to be successful: After all, the airplanes flew.

After a brief start in his friend's aircraft factory Richter approached Perón with claims of espionage and sabotage and the need to move his labs to an isolated place protected by the utmost secrecy. After a search by plane of the most remote areas of the country, Richter decided to take his lab to Isla Huemul, a beautiful 1-square-kilometer island in the middle of Lake Nahuel Huapi. Perón agreed and gave Richter full executive powers, as his representative, to run civil and professional life on the island, and on some adjacent areas around Bariloche, whichever way he saw fit. He moved his lab to Bariloche early in July of 1949, designing labs and "reactors" that led to civil engineering works of Pharaonic proportions. In March 1951 Perón set up a press conference in Buenos Aires at which he and Richter announced what they claimed to be the first observations of controlled fusion at Huemul, details being cloaked in secrecy. The details of the conference, as described in a fascinating book by Mariscotti (Mario A. J. Mariscotti, *El Secreto Atomico de Huemul,* Estudio Sigma, Buenos Aires,

1996), are strikingly similar to those of the press confer-
ence held at the University of Utah in 1980s to announce
the discovery of cold fusion (Gary Taubes, *Bad Science, the
Short Life and Weird Times of Cold Fusion,* Random House,
New York, 1993). As in the latter case the report of Richter's
achievement received wide international coverage and seri-
ous and concerned study from organizations such as the
Atomic Energy Commission in the United States, which rec-
ommended (according to the declassified minutes of a meet-
ing held on July 26, 1951) to grant Professor Lyman Spitzer
of Princeton $50,000 to perform "research in the area in
which Dr. Richter had claimed success."

As in the case of the Utah cold fusion 40 years later,
once the initial announcement was made public, demands
for details and more visible results grew from day to day.
Lack of new results, Richter's mismanagement of engineering
contracts, and Peron's rising difficulties with the military
forced the president, adamant to admit the possibility of a
fiasco for which he would have been responsible, to send a
commission to Bariloche to investigate the facts. The few
competent physicists available in Argentina were not to his
liking, so he appointed as members a priest, a naval officer,
two engineers (one of them a Berkeley alumnus), and a
young physicist by the name of José A. Balseiro, who was
doing postdoctoral work in England and was asked to return
immediately to Argentina. The report of the commission
was devastating: It recommended immediate closure of
Richter's laboratories. After several bizarre incidents Perón
reluctantly agreed to send a landing squad to Huemul and
to close the labs. This happened on November 22, 1952, a
few months after the dramatic death of Evita. The total cost
of the project has been estimated at U.S.$300 million (today's
value). Huemul Island and its buildings became the prop-
erty of the military and were used occasionally for target

practice. They were privatized a few years ago, and are now in the hands of a company that offers excellent guided tours of Richter's installations. It will probably never be known whether Richter was a misguided visionary or a fraudulent crook (or a combination thereof).

Mounting political unrest from the death of Evita until Perón's ouster by the military in 1955 made the pursuit of scientific activities all but impossible, especially in Buenos Aires. Hence, a few visionary academics conceived the idea of setting up an elite school of physics in Bariloche, making use of the abandoned equipment and of the empty buildings on the lakeshore. It was argued that talented young men graduating from this school would be able to prevent the occurrence of a mishap similar to that of Richter. The negotiations with possible sponsors were long and difficult. Finally classes started in the Argentinean spring of 1955 at about the time of Perón's ouster. Leo joined the first entering class. The first director of the new physics school was José A. Balseiro. Bariloche remained indeed insulated from the ensuing political turmoil, as had been hoped by its founding fathers. (A biography of Balseiro written by two friends of Leo from his Bariloche days has recently appeared: A. López Dávalos and N. Baldino, *J. A. Balseiro: Crónica de una Ilusión,* Fondo de Cultura Económica, Buenos Aires, 1999).

Balseiro, a gifted physicist with limited research experience, had already proved, as chairman of the Huemul commission, to be an excellent administrator. He was able to recruit a competent and dedicated faculty, including Spanish mathematicians, German and Austrian physicists, Italians, and some of the best Argentinean scientists at hand. To them Leo owed, by his own admission in the correspondence available to us, a great deal of his theoretical training. He graduated in 1958, having obtained the maximum

grade of *sobresaliente* (outstanding) in the 39 courses he took (a record number for three years!). He must have attracted Balseiro's attention as the brightest of his students and a relationship of mutual admiration, respect, and friendship developed between them. The Instituto Balseiro kindly made available to us copies of six of the long letters written regularly by Leo to Balseiro in the period from October 1958 (from Cambridge) until April 1961 (from Chicago). They are mostly written in Leo's beautiful handwriting in elegant, flowery Spanish, never forgetting to apologize for the "long silence" since writing his last letter. We also have a copy of one of the answering letters from Balseiro written in June 1961, shortly before his premature death in March 1962 at the age of 43 (from leukemia). He is buried in a simple grave in front of the institute's library, which now bears the name of Leopoldo M. Falicov.

In his first letters to his mentor, written after his arrival in Cambridge, Leo points out that hardly any courses were offered there whose contents he was not thoroughly familiar with (thanks to Bariloche). As an exception he mentions Volker Heine's lectures on group theory, which no doubt must have been an important source for the book Leo wrote in Chicago (1966). He also describes the many seminars he attended on current research topics and adds, "The rest lacks any interest" (this statement should lead to an exercise in humility when read by faculty members of the famous English university). He mentions, however, being very impressed by the "hands on" attitude of his English classmates who got involved in current research projects in spite of their insufficient background. He adds that they were also very impressed by the depth of his knowledge and the education he had received in Bariloche. This and some of the letters that followed expressed his firm desire to return to Bariloche. Later on he begins to wean himself from his

alma mater and in his last letter, written from Chicago, he is saddened by the fact that "to the *muchachos* who now work in Bariloche I must almost be a stranger."

Leo's rise through the academic ranks from postdoctoral researcher to full professor at the University of Chicago was rapid. His outstanding scientific achievements during this period were matched by his teaching. His lectures were extremely clear and he was accessible to students who were all impressed by his extraordinary handwriting. His blackboards were works of art filled with equations involving Arabic, Greek, and German script lettering together with diagrams that were drawn as if rulers were used.

While on sabbatical leave from Chicago at Cambridge University in 1966, Leo was first approached to consider joining the Berkeley faculty, which he did in 1969 as professor of physics. He served concurrently as a faculty senior scientist and principal investigator in the Materials Sciences Division of the Lawrence Berkeley National Laboratory. At Berkeley he continued to produce outstanding research and Ph.D. students and was a highly regarded instructor. In addition Leo attracted outstanding postdoctoral researchers. Many who were from South America and other Spanish-speaking countries returned home and greatly influenced the development of physics in their countries.

Leo's international connections were vast. He and his wife, Marta, immensely enjoyed their stays in Denmark. He often traveled to Europe and Asia and served on a large number of external evaluation committees. Leo held visiting positions at more than 20 universities around the world.

At Berkeley it was quickly realized that Leo's organizational skills, his rapid handling of paperwork, and his ability to make good decisions made him an ideal candidate for committee chairs and faculty administration. When he was chair of the Physics Department (1981-83), he claimed

responsibility for hiring nine new faculty members and per-
formed his duties with unusual speed. During this period
he managed his research group without any decrease in
activity. He was almost quantum mechanical—seeming to
be in "his chairman's office" and "his own office" at the
same time. When he retired in 1994, he was awarded the
Berkeley Citation to acknowledge his high level of service
to the university.

Leo met his wife, Marta Puebla, on the boat from Buenos
Aires to England. She was going to study painting in London,
under the auspices of the British Council. On the boat they
both met César Milstein, a fellow Argentinean and British
Council scholarship holder, who received the Nobel Prize
for medicine in 1984. Leo and Marta were married in August
1959. There is one short reference to that event in his cor-
respondence with Balseiro. "I have very important private
news: Next Thursday, and coinciding with the beginning of
vacations at the lab, I am getting married and shall go for a
month to get to know the Continent. My (by now no longer
so) future wife has spent a year learning painting in London
. . . she is now in Cambridge preparing herself for her
change in civil status." In 1968 Marta gave birth to twin
boys, Alexis and Ian. Ian's difficulties in starting to talk led
to the realization that he was hearing and speaking impaired.
This handicap received utmost attention from Marta and
Leo. Their colleagues and friends were (and still are) most
moved by the admirable way they managed this handicap
and how they succeeded in communicating with Ian and
giving him the same type of education Alexis received, avoid-
ing special schools and colleges. They both attended public
schools in Berkeley; any kind of private schools would have
meant for Leo and Marta betraying their Argentinean prin-
ciples of free and lay public education. Both sons attended
the University of California at Berkeley, Alexis graduating

with a major in physics and Ian in computer science. Ian went on to obtain a master's degree in computer science at the University of California, Santa Cruz, while Alexis obtained a Ph.D. in theoretical physics at MIT. Instead of carrying on Leo's torch Alexis then went to medical school at Harvard, graduating as an M.D. in 1999. Both sons are married and have one (Alexis) and two (Ian) children. Alex is an orthopedic surgeon working at several hospitals associated with the University of Washington, while Ian works as a computer expert for a private company, Surety, in Reston, Virginia.

The label "renaissance man" is overused these days, but it is an apt description of this unusual man who is sorely missed. He was a highly skilled rug weaver, an activity he pursued on old-fashioned looms as a form of relaxation. Leo Falicov's life was rich with art, music, literature, and hobbies. Leo courted his Marta by reciting from Pablo Neruda and Garcia Lorca, while sitting by a river in Cambridge, England. He loved the opera. He could recite poetry and quote literature in three languages. He collected art and played the piano. His sense of humor and wry stories made him a favorite dinner companion. He is fondly remembered as a vibrant individual and brilliant scholar from whom his family, friends, colleagues, and students derived love and support.

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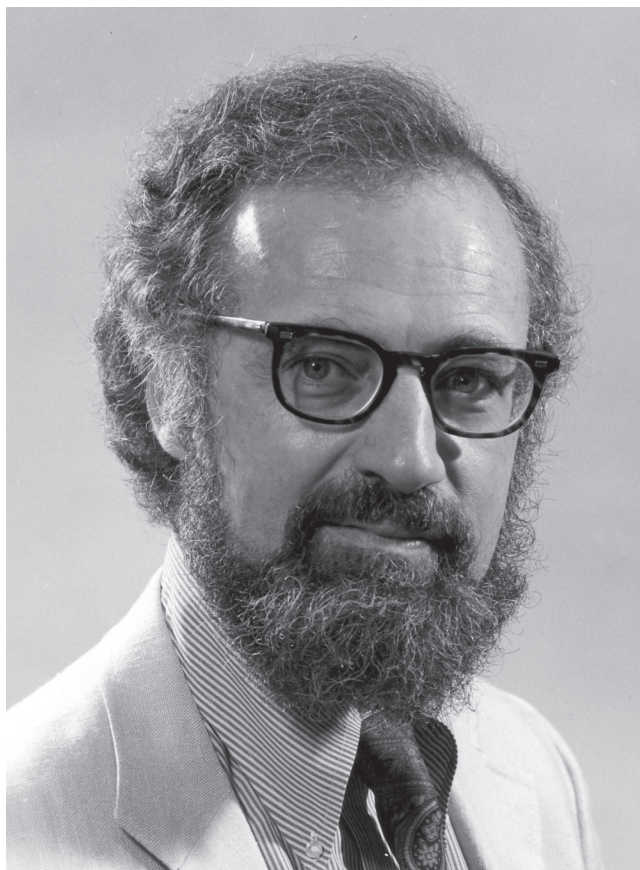
HAROLD P. FURTH

January 13, 1930–February 21, 2002

BY T. KENNETH FOWLER

H AROLD FURTH, AN AMERICAN giant in the world of fusion
research, died of heart failure in Philadelphia on
February 21, 2002. He is buried in Princeton, where he
spent most of his career at the Princeton University Plasma
Physics Laboratory. Harold and I were collaborators in the
pursuit of fusion energy, at Princeton in his case, at Livermore
in mine. I am deeply saddened by his death and honored
to be the one to record his career for the National Academy
of Sciences.

Harold was elected to the Academy in 1976 for his many
achievements in plasma physics, the underlying discipline
for the magnetic confinement approach to harness nuclear
fusion energy. From graduate school days Harold's forte
was a deep understanding of magnetic fields, one of the
areas in which plasma physics has enriched other disciplines,
especially astrophysics. This served him well in his fusion
career, in inventing new concepts and in understanding
the ultimately successful tokamak involving in part currents
created by the plasma itself. ("Tokamak" is a Russian acronym
for a nuclear fusion device in which a plasma is confined in
a toroidal tube by a magnetic field.)

Harold's main contribution to magnetic fusion research

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was the tokamak fusion test reactor (TFTR), which he proposed in 1973, and which provided the first definitive demonstration of controlled fusion energy in 1993-94, producing 10 megawatts of fusion power for about one second in a plasma of equal parts deuterium and tritium, the DT fuel of future fusion reactors. It was Harold who conceived the design concept that won the project for Princeton, and it was he who led the project to success, first as chief scientist and finally as director of the Princeton Plasma Physics Laboratory from 1981 until he stepped down for medical reasons in 1990.

The TFTR is far and away the most important accomplishment in the 50-year history of magnetic fusion research in the United States. The origin of TFTR in 1973, finally approved for construction in 1976, was a milestone in Harold's career. At the time, magnetic fusion was an emerging research program following early success with tokamaks in the Soviet Union and a sequel at Princeton. New management at the Atomic Energy Commission, seeing an opportunity for funding in the wake of the oil crisis of that time, was determined to embark on a tokamak experiment with actual DT fusion reactions, not just a simulation with ordinary hydrogen plasmas as in all past experiments, the nearer to a power reactor the better. Young physicists at the Oak Ridge National Laboratory rose to the challenge, while Princeton worried whether a facility with radioactive tritium was compatible with the campus environment, and all of us were concerned that the Oak Ridge proposal was too much to tackle.

Things came to a head at a meeting I attended in Washington in late 1973. By then Harold was prepared. One issue was leakage of heat through electrons, most mysterious of the many mysteries plasmas hold, and something Harold had hoped to end run—a theme he continued to pursue in

his defense of TFTR in the late 1990s as the place to study direct heating of DT ions by the energetic alpha particles produced by fusion reactions without recourse to electrons as the intermediary. Along this line in 1971 Harold, John Dawson, and Fred Tenney published a paper about a concept, called the two-component torus, whereby fusion energy would be produced directly by fusion reactions of energetic neutral beams with ions in a plasma, again without the need to heat electrons to fusion-reaction temperatures. At a crucial point in the meeting after the attendees had begun to accept something less than ignition as the goal, Harold went to the board, saying, "If that's all you want." He then outlined the TFTR proposal that led in 1986 to a new record temperature of 200 million degrees Celsius, and in December 1993 to more than 6 megawatts of fusion power for a second or so, and the design goal of 10 megawatts a few months later.

Harold Furth was born in Vienna, Austria, on January 13, 1930. After studying at the Ecole Internationale in Geneva he immigrated in 1941 with his parents to the United States, where he graduated at the head of his class from the Hill School in 1947. He then entered Harvard University, where he completed graduate studies in 1956, with an intervening year at Cornell. His introduction to physics came through his experiments identifying cosmic rays in photographic emulsions permeated by high magnetic fields.

After Harvard Harold worked at the University of California Radiation Laboratory at Berkeley and Livermore from 1956 to 1967. There he soon began the fruitful collaboration with Stirling Colgate that led to Harold's first experimental work on plasma confinement devices that might eventually serve as fusion reactors, initially in a linear pinch in which the mutual attraction of parallel currents in a plasma applies a constricting force that confines the plasma column. Instability of the pinch had inspired an improved version with

an externally applied magnetic field parallel to the current. When this too exhibited unstable turbulence, probably due to plasma resistivity omitted in the theory, Furth and Colgate proceeded in a totally different direction with the invention of the levitron, a large conducting ring levitated in space and charged with a current that provided confinement for a plasma surrounding the ring, without resort to the internal force of plasma currents used in the pinch device. Harold later constructed a levitron called FM-1 at Princeton.

Meanwhile, the importance of resistivity not lost on him, Harold provided the conceptual basis for a theory of resistive instabilities in magnetically confined plasmas, published jointly with John Killeen and Marshall Rosenbluth in 1963. Characteristically Harold had been able to visualize what happens when twisting plasma columns in turn twist magnetic field lines embedded in them, causing localized sheet currents needed to prevent the tearing and reconnection of the field lines. Resistivity destroys these sheet currents, allowing tearing to happen, at a rate enhanced by the thinness of the sheet currents. Resistive instability turned out to play an important role in natural phenomena, such as the Earth's magnetotail and other aspects of solar physics and cosmology. Applying resistive instability theory in this way was an early example of cross-fertilization of plasma physics learned from fusion research with other fields of science.

During a year-long workshop at Trieste in 1965-66, Harold joined Soviet colleagues Roald Sagdeev and Alex Galeev in showing how Coulomb collisions among plasma particles could transport them across the magnetic field of devices like the Soviet tokamak much faster than they could in idealized models, by virtue of complicated particle orbits in the twisted magnetic field of the tokamak. It was Furth who dubbed these distorted orbits "bananas," as he had pictured them in thinking through the transport process, now called

neoclassical transport. While neoclassical transport degrades heat confinement of the ions, it also later became the basis for others to predict and then measure the self-generated "bootstrap" current in tokamaks that greatly diminished the requirement for external power to maintain the current in a steady-state tokamak.

After arriving at Princeton in 1967 as professor of astrophysical sciences and co-head of the Experimental Division at the Princeton Plasma Physics Laboratory, Harold assumed leadership in planning new experiments, shortly before the breakthrough announcement in 1968 that the Soviets had achieved a record temperature of 10 million degrees Celsius in one of the tokamak devices called T-3. Harold first did not believe the Soviet claims, blaming the results on runaway electrons that did eventually prove to be the explanation of another device touted by the Soviets, called TM-3.

Once convinced Harold quickly led the Princeton laboratory toward proposals for three tokamaks, one by converting their largest stellerator into a tokamak and two new devices—the adiabatic toroidal compressor that would provide additional heating by squeezing the plasma, and the Princeton large torus (PLT) in which the plasma would be heated by neutral beams created by accelerating ions to the energies required for fusion and then neutralizing them in flight, to be captured in the plasma when they become ionized again by collisions with plasma electrons and ions. All three proposals were funded by the government, leading to a quick confirmation of the Soviet results at Princeton in 1970 and record tokamak temperatures exceeding 60 million degrees Celsius—sufficient for fusion ignition—in the PLT in 1978.

Harold never stopped inventing improved magnetic configurations, such as the bean-shaped tokamak with improved stability properties (PBX-M) in 1985, and the spheromak that is totally self-generated by currents inside the plasma.

After TFTR began experiments with real deuterium and tritium (DT) fuel, Harold also pursued new ways to enhance fusion power production without relying solely on thermal reactions in a DT plasma with equilibrated temperatures among all particle constituents.

Even before becoming the director of the Princeton Plasma Physics Laboratory, Harold had emerged as the intellectual leader of magnetic fusion research in the United States and a tireless advocate for fusion energy. The esteem accorded him by colleagues is evident in remarks at a memorial service at Princeton a few months after his death. "Harold Furth was a special person, in a special place, at a special time," noted Anne Davies, current director of the Office of Fusion Energy Sciences at the Department of Energy. "Scintillating" is the word Marshall Rosenbluth chose to describe Harold. "When he came into a room or joined a discussion, the air fairly crackled with wit, logic, scientific insight, and forceful leadership. Everybody's creativity level went up in an effort to keep up with Harold."

Harold's protégé and currently director of the Princeton laboratory, Rob Goldston, spoke for most of us. "Harold was a giant of fusion science, a person of untiring energy and boundless optimism. He buoyed all of us. Harold led the U.S. fusion program to tremendous growth in the 1970's and 1980's. Indeed, many of the scientific accomplishments even in the 1990's are the result of his leadership. We will all miss him."

As in everything else he touched, Harold was a brilliantly successful laboratory director and an influential, respected leader in the international fusion community. Perhaps his greatest disappointment as director was a failure to procure funding for the compact ignition tokamak (CIT) as a follow-on to TFTR and, as the name implies, the first demonstration of a plasma that burned by itself. Harold

had garnered strong support from the U.S. fusion community, but as Washington and the public lost interest in energy in the 1980s, CIT was not to be, despite strong recommendations for a revival of the idea by the Fusion Policy Advisory Committee of 1990, chaired by Guy Stever. That committee did recommend immediate funding for DT operation in TFTR, long delayed, and that was done, as related above.

Harold was a revered mentor and colleague of young scientists, including experimentalist Rob Goldston, theorist Nathaniel Fisch, and many others. He held some 20 patents, primarily in the areas of controlled magnetic fusion technology and metal forming with pulsed magnetic fields. He published over 190 technical papers.

Harold served on numerous government committees over the years and on scientific advisory committees at other laboratories, including the Max Planck Gesellschaft. He served on the Board of Editors for the following journals: *Nuclear Fusion, Plasma Physics and Controlled Fusion, Journal of Fusion Energy, Reviews of Modern Physics,* and *Physics of Fluids.* At the National Academy of Sciences' National Research Council he was a member of the Board on Physics and Astronomy of the Division on Engineering and Physical Sciences.

Harold was a fellow of the American Physical Society, the American Association for the Advancement of Science, and the American Academy of Arts and Sciences. He received the E. O. Lawrence Memorial Award from the U.S. Atomic Energy Commission in 1974; the James Clerk Maxwell Award from the American Physical Society in 1983; the Joseph Priestly Award from Dickinson College in 1985; and the Delmer S. Fahrney Medal from the Committee on Science and the Arts of the Franklin Institute in 1992.

On a personal level Harold will long be remembered

for his engaging wit, always kind if a little irreverent. It is fitting to conclude with an example, written in his twenties when he first came to Livermore prior to his later move to Princeton. This was his poem about Edward Teller that was published in *The New Yorker* magazine in 1956, reprinted in Teller's *Memoirs*:

Perils of Modern Living

Well up beyond the tropostrata
There is a region stark and stellar
Where, on a streak of anti-matter,
Lived Dr. Edward Anti-Teller.

Remote from Fusion's origin,
He lived unguessed and unawares
With all his anti-kith and kin,
And kept macassars on his chairs.

One morning, idling by the sea,
He spied a tin of monstrous girth
That bore three letters: A.E.C.
Out stepped a visitor from Earth.

Then, shouting gladly o'er the sands,
Met two who in their alien ways
Were like as lentils. Their right hands
Clasped, and the rest was gamma rays.

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HOMER DUPRE HAGSTRUM

March 11, 1915–September 7, 1994

BY PHILIP W. ANDERSON AND
THEODORE H. GEBALLE

HOMER HAGSTRUM WAS BORN in St. Paul, Minnesota. His father, Andrew, had emigrated there from Värmland, Sweden, as a 22-year-old with his older brother, Nels, in 1889. His mother, Sadie Gertrude Fryckberg, was born in St. Paul in 1883, the youngest daughter of a family that had also migrated from Sweden. Homer was the second of four boys who reached maturity. The home environment was built upon strict Swedish Covenant practices, with a strong emphasis on education. Drinking, dancing, card playing, and movies were considered sinful.

Homer continued to live at home throughout his graduate years at the University of Minnesota, and did not see a movie until he was 25 years old and ready to go forth into the world. His going to see "Captains Courageous" actually caused his mother to break down and weep. She had gone from high school to work when her father died and was determined that her sons should obtain as much education as they could absorb. His father, with only an elementary school experience in Sweden, became the owner with his brother of a successful men's clothing store, Hagstrum Brothers, in St. Paul. The oldest son, Jean, although groomed to become a minister, later became a distinguished professor of English at Northwestern University in Evanston, Illinois,

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and sometime head of the National Endowment for the Humanities. The youngest two brothers, Vincent and Paul, became executives in the mercantile world. Homer and Jean had the unusual distinction of being awarded honorary degrees together from their alma mater, the University of Minnesota, during the commencement day of 1986.

Homer roller-skated to a local elementary school, where he attended an alpha class that covered two years' work in one year. In middle school he skipped half of his eighth-grade class. Homer later felt that being much younger than his classmates was a distinct social handicap. At home he showed a strong mechanical aptitude, with a workshop and darkroom in the basement and a crystal radio set in the attic. The high school Homer attended, Minnehaha Academy, was a private religious school in Minneapolis. He had begun questioning his family's religious doctrine early on, and in high school became engaged in science. He was fortunate to have an excellent science teacher, Henry Schoultz, who profoundly influenced his life. Even as a freshman Homer stayed after school and worked in Henry's laboratory.

In his senior year Homer and Henry built a 6-inch reflecting telescope, which remained at the school for many years. At home Homer built an "observatory," a portable wooden structure, to perch on the apex of the roof of his house. Homer sat up observing with star charts and flashlight for years afterwards. A photograph shows Homer sitting on the steep roof with one of his telescopes in hand. His early interest in science, astronomy, and mathematics, and in working with his hands, never diminished and gave him great pleasure for the rest of his life. In later years he arranged vacations so he could observe solar eclipses even when they were in faraway places, such as Africa—where he

camped in the desert with his son, Jonathan—and South America.

Homer entered the University of Minnesota as an electrical engineering student, obtaining his B.S.E.E. in 1935 summa cum laude and also his B.A. in 1936. While at the university he developed a lifelong love of classical music and delighted later on in relating how he had learned about music while "ushering under Ormandy and Metropolis." Homer found physics to be his natural home and went on to graduate school, completing his M.S. in 1939 and his Ph.D. in physics and mathematics in 1940. He became the last graduate student of John Tate, who is well known, in addition to his own scientific achievements, for being the longtime editor of *Physical Review.* Tate was the second major influence in Homer's scientific life. His first two papers, published with Tate in 1941, were concerned with the ionization and dissociation of molecules by electron impact, and with the thermal activation of the oxygen molecule.

Homer left Minnesota in 1940 to join Bell Telephone Laboratories where he remained for 45 years, his entire professional career. Bell Labs was then at its West Street location in downtown Manhattan, and Homer found an apartment nearby. He had time after work to go out with friends, discovering opera, ballet, ballroom dancing—which he took up with enthusiasm—and skiing. It was at a ski resort on the slopes of the Berkshires in Massachusetts that he met Bonnie Cairns from Woodstock, Illinois, who was interested in art and sculpture. In contrast with the 25 years it took him to leave his first home, it took only six months before he and Bonnie were married in 1948. On a trip to Europe in 1955 Homer found a decrepit armillary sphere on the floor of an antique shop in Florence, Italy. Bonnie pitched in her half of the travel funds to produce the 60 dollars

needed to buy it. Homer undertook the study of armillaries upon returning home and repaired and reconstructed the instrument, which dated from the sixteenth century. It became one of his and the family's most prized possessions.

After the war Homer and Bonnie moved to Summit, New Jersey, near Murray Hill, where the research effort of Bell Labs was relocated. They had two children, Melissa and Jonathan, and raised them in a comfortable suburban setting. The children completed graduate school, each obtaining a Ph.D.: Jonathan's in geology and Melissa's in anthropology.

A large number of physicists and other scientists had come from all over the world to join Bell Labs. Because of far-flung origins and the absence of local family and old friends, strong new ties were cemented. The Hagstrums' close friends included Joyce and Phil Anderson, John and Maggie Galt, Ted and Sissy Geballe, Bruce and Joan Hannay, David and June Thomas, Peter and Cathy Wolff, and of course, many others. The group met throughout the year, celebrating major holidays, going on outings with children, and on forays to Manhattan for symphonies and plays—off and on Broadway. After a few drinks Homer loved to recite German poetry and sing Swedish hymns. He enjoyed a good winter hike in the Great Swamp, and ice-skating with his and other children. Later in life he especially loved hiking in high alpine terrains with beautiful nighttime skies. He became a pillar of the Unitarian Church, whose minister Jake Trapp was the father of Bernd Matthias's wife, Joan.

Homer was devoted to his family. He actively encouraged Bonnie to develop her own talent as a sculptor and to travel to northern Italy to study and work in the local marble. Bonnie's work in stone is highly regarded. Some was shown in an exhibition at the National Academy of Sciences in the spring of 1991. In contrast to the Bible camp where Homer

spent his youthful summers, his children went to camps
with an outdoor orientation. Upon returning one summer
from a camp in New Mexico, Jonathan brought home a
wild bull snake for a pet. Initially the snake escaped regu-
larly from its terrarium and roamed the house at will. Homer,
in particular, was fascinated by the snake's mode of loco-
motion and would bring it out to show guests, usually to
their great dismay. Jonathan later flew the snake back to its
natural habitat.

Homer's professional life was spent at only two institu-
tions—the University of Minnesota, where he was educated,
and Bell Labs, where he did his pioneering research. His
thesis was a characteristically careful and definitive investi-
gation of the ionization and dissociation of molecules by
electron impact and on the thermal activation of the oxy-
gen molecule. His first two publications resulting from this
work were published (naturally in *Physical Review*) with
Tate in 1941. Homer went straight to Bell Labs in 1940 and
joined the physical electronics group under Jim Fisk. That
group was responsible for developing and, at first, manu-
facturing the "strapped" microwave magnetron that became
the core element in the Allies' radar superiority during the
war. One of the first dozen the English made was delivered
to the United States by the famous Tizard mission of Sep-
tember 1940, and within a month Bell Labs had under-
taken the responsibility of producing them. In the whole
battle of the black boxes this and the early warning radar
were most responsible for turning back the Germans in the
crucial early battles on which England's survival depended—
in the case of the magnetron the Battle of the Atlantic of
1941. Fisk, Hagstrum, and Paul Hartman described the work
in a postwar paper in the *Bell System Technical Journal*
(1946). Others who were involved include J. R. Pierce, J. C.
Slater, J. P. Molnar, and A. H. White. In later years Homer

enjoyed telling stories about his trip to England with John Pierce during the war in connection with this work and about the games with "fly-powered airplanes" the group invented to relieve the pressure of their work. He remained close friends with Ad White and Julius Molnar.

In 1946, with wartime priorities no longer dictating research, Homer returned to the study of dissociation by electron impact measuring the dissociation energies of important molecules such as nitrogen, oxygen, carbon dioxide, and nitric oxide (1951). The success of the experiments required ever improving the advanced vacuum techniques. Homer and H. W. Weinhart published a calibrated leak made from a porcelain rod (1950), but in fact his real contribution was in setting, and then breaking again and again in the course of the years, records for vacuum pressure and other measures of cleanliness (1976,1).

In the early 1950s Homer turned his attention to the interaction of ions with metal surfaces (1960). His first paper was on electron ejection from Mo by He^+, He^{++}, and He_2^{++} (1956). Homer recognized that this process could be turned into a new kind of spectroscopy: ionization neutralization spectroscopy (INS). This required new instrumentation, new experimental protocols, and new theory, all of which Homer took on and succeeded in arriving at workable solutions. This led to his first paper, in 1953, on the instrumentation and experimental procedure. The theory of the neutralization process at the solid surface turns out to be a complicated two-electron quantum problem. As the slow ion approaches the surface some of the large neutralization energy (i.e., the negative of the ionization energy of the atom) goes to emitting an electron from the surface while the second electron falls into the ion. The spectroscopic information is contained in the kinetic energy distribution of the electron emitted from the surface. Homer

considered two related paths (1954, 1961), the first being a direct Auger following the theory of S. S. Shekhter (*J. Exp. Theor. Phys.* [U.S.S.R.] 7[1937]:750) and the second being more complex, involving resonance neutralization followed by Auger de-excitation (H. S. W. Massey, *Proc. Camb. Philos. Soc.* 26[1930]:386).

Many of Homer's wartime associates who were still at Bell had been tapped for higher administration, mostly on the technical side. During the immediate postwar years he continued to work in the physical electronics group, which did research mostly related to vacuum tubes. But this group was also mined for administrative talent, in view of the expectation that heated cathodes and vacuum technology would soon be superseded by solid-state devices. From this group came, for instance, Molnar, K. G. McKay, John Hornbeck, and its head, Addison White, as higher-level managers; several eventually went on to have very distinguished careers in management.

Homer, along with Conyers Herring, represented to the next generation such as ourselves the possibility of a second fruitful track within the expanding Bell Labs, a career staying within the cutting edge of fundamental science without succumbing either to the blandishments of academia or the technical management route. But in 1954 the Bell administrators recognized that surface physics was becoming an ever more important frontier in science and in technology. New and improved methods for characterizing surfaces were needed in semiconductor physics and technology, as well as in heterogeneous catalysis and biology. One of the first interdisciplinary research departments with expertise in physics, chemistry, and metallurgy—but focused on a single subfield, surface physics—was organized with Homer as department head. Sidney Millman, his perceptive laboratory director, undertook to relieve Homer of the most bur-

densome administrative duties in order to free his research time. Within a few years there were other interdisciplinary departments such as biophysics.

Homer recognized that INS had potentially more surface sensitivity than the more widely used sensitive soft X-ray scattering (SXS) and photoemission spectroscopies (PES). But more accurate INS data were required. It took Homer five years of sustained research to design and construct a new apparatus that pioneered by incorporating a low-energy electron-diffraction insert for being able to investigate the surface symmetry and reconstruction. In the course of this work he introduced the concept of a turret within which the sample could be maneuvered to allow a number of different probes or coatings to be applied to the same surface, a methodology that was widely applied. The apparatus for INS and the procedures for the data analysis are described by Homer in a comprehensive article (1966,1). He was awarded the Medard W. Welch Award by the American Vacuum Society in 1974. In 1976 he was elected to the National Academy of Sciences and was awarded the Davisson-Germer Prize by the American Physical Society.

With a minimum number of assumptions the relative probability that an electron at a given band energy in the solid will be involved in the neutralization process—the transition probability—is calculated. It depends upon the initial and final state densities and upon the transition matrix elements and final state interactions much as in PES. It depends upon wave functions outside the surface and is thus more surface sensitive than the other spectroscopies. It is also amenable to studies of surfaces containing foreign atoms. In a series of investigations with Y. Takeishi (1965), G. E. Becker (1966, 1973), E. G. McRae (1976), and T. Sakurai (1976, 1979) that continued until his last working day at Bell, Homer kept taking data. He and his collabora-

tors studied pure well-characterized surfaces of the metals
Fe, Co. Ni, Ag, Cu, W, and Mo and the semiconductors Si,
Ge, and GaAs. The studies of these surfaces with adsorbed
oxide, sulfides and other chalcogenides, and hydrides were
made, as well as with alkali metals. Among many other re-
sults of interest was the observation of band narrowing at
the surface for Cu and Ni, the first observation of surface
resonances in adsorbed atoms and of the kinetics of ad-
sorption. At the time of his retirement he was making the
first measurements of magnetic resonant states in adsorbed
atoms, though this work was not completed.

Homer was that rare type of scientist who enjoyed work-
ing on all aspects of a carefully thought out research pro-
gram, from his initial idea to the design and construction
of the needed apparatus, to the taking of data and then
modifying the theory when necessary to obtain a detailed
understanding. In the golden age of research at Bell Labs
at that time it was possible for Homer to take five years
from his research to build the apparatus. Even though he
succeeded in establishing INS as a valued spectroscopy, it
has not become a standard laboratory practice. The con-
fluence of new developments rendered INS of less value
than Homer had envisioned. In particular, a spectacular
array of new scanning tunneling probes has come into be-
ing following Hans Rohrer and Gerd Binnig's revolutionary
demonstration of scanning tunneling microscopy in 1984.
There the electron tunneling is by means of wave functions
that extend from the surface much as in INS. In all other
respects the tunneling tip, which can be accurately con-
trolled in all three dimensions, is much superior to the
moving ion. INS has been made obsolete after only two
short decades of existence. If there is a lesson to be learned,
it is that science moves ahead on many fronts and the most

admirable achievements are not necessarily the most en-
during.

Homer kept taking data right up until the day he re-
tired from Bell. He planned to be engaged in analysis in
the years ahead. Unfortunately, about that time Homer suf-
fered a series of small strokes that damaged his short-term
memory and impaired his ability to concentrate. Nothing
that has transpired detracts from Homer's achievements.
While INS will not be remembered as a milestone of twenti-
eth-century physics, Homer Hagstrum will be remembered
as a pioneer who created many of the ideas and techniques
of modern surface physics.

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SEYMOUR S. KETY

August 25, 1915–May 25, 2000

BY LOUIS SOKOLOFF

S EYMOUR SOLOMON KETY, a member of the National Acad-
emy of Sciences since 1962, died on May 25, 2000. He
was an outstanding scientific statesman, but more signifi-
cantly an eminent neuroscientist and pillar of biological
psychiatry. He will long be remembered for his legendary
scientific achievements, outstanding statesmanship, and mag-
nanimity of spirit. I was fortunate to have known Seymour
for approximately 56 years as a teacher, preceptor, collabo-
rator, colleague, and friend, and in every one of these roles
he earned an unmatched level of esteem, not just from me
but also from almost everyone with whom he interacted.
He graced every field in which he worked and those with
whom he worked, and I know of no scientist who was so
universally respected, admired, and even loved. Neuroscience
and psychiatry have suffered a great loss.

Seymour was born in Philadelphia on August 25, 1915.
He was raised there in rather humble but intellectually stimu-
lating surroundings. In his childhood he suffered an auto-
mobile-inflicted injury to one foot that, though not serious,
resulted in residual physical limitations that deprived him
of participation in the usual athletic activities of childhood
and directed him further toward intellectual pursuits. One

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of his greatest interests was in chemistry, and he spent many hours carrying out chemical experiments in a laboratory he created in his home. Seymour received all his primary and secondary school education in Philadelphia, where he attended the prestigious Central High School, the city's premier high school. There he was able not only to pursue his interests in the physical sciences but also to receive a fairly broad education in the classics, including both Greek and Latin, and to be inspired by an erudite and nourishing faculty.

After graduation from high school he attended the college and then the medical school of the University of Pennsylvania, from which he graduated in 1940. He then married Josephine Gross, whom he had known from childhood, and entered into a rotating internship at the Philadelphia General Hospital. Josephine was also a medical student and eventually a physician who was particularly interested in pediatrics. It may well have been her influence that led Seymour to choose an area of research while still in medical school and to pursue further during his internship. This research led to the first of his many major contributions to medical science.

Pediatricians were at that time concerned about the many children they saw with lead poisoning, probably due to their chewing on the lead-containing paint on their cribs. Marshaling his long-time interest in and knowledge of chemistry, Seymour conceived of the idea of using citrate to treat lead poisoning, because citrate forms a soluble chelate of lead that is relatively rapidly excreted in the urine. Better and more effective chelating agents are now in use, but this was the first proof of principle that chelating agents can be used in the treatment of heavy metal intoxication.

To pursue further his interest in lead poisoning after completion of his internship, Seymour obtained a National

Research Council postdoctoral fellowship to work with Jo-
seph Aub, a well-known researcher on lead poisoning at the
Massachusetts General Hospital in Boston. The fellowship
began in 1942, but by then the United States was at war,
and when Seymour arrived, he found that Aub had aban-
doned his work on lead poisoning and switched to a more
pressing problem during wartime: traumatic and hemor-
rhagic shock. Seymour joined the group working on that
problem, and it was the research on shock that led him to
develop an interest in circulatory physiology. He became
particularly intrigued by the cerebral circulation that ap-
peared to be relatively preserved in cardiovascular shock by
regulatory mechanisms that adjusted the distribution of the
reduced cardiac output to favor the brain, heart, and lungs
at the expense of less vital circulatory beds. To pursue this
new interest he elected to forego the opportunity to re-
main at Harvard and in 1943 returned to the University of
Pennsylvania to work with Carl Schmidt, then a leading
figure in the field of the cerebral circulation; Schmidt had
just published his bubble-flow-meter technique for the quan-
titative determination of cerebral blood flow (CBF) and
metabolism in anesthetized monkeys. Both Seymour and
Josephine had been born, raised, and educated in Philadel-
phia, and their desire to return to their roots may also have
been a factor in this decision.

Seymour was an instructor in Schmidt's Department of
Pharmacology when I first met him in 1944 as a student in
his first class in pharmacology. He was an excellent teacher
who presented lucid, stimulating lectures that emphasized
the experimental procedures and results underlying the
conclusions that were to be drawn. I still remember how he
made even a lecture on analgesics exciting. He was popular
with the students and readily accessible to them. As he was
not much older than we were, he often joined some of the

members of our class on the patio of Houston Hall, the university's Student Union, where we usually congregated after lunch. It was in casual conversations on those occasions that we first learned of his interest in the cerebral circulation. He was in the process of formulating ideas about a method for measuring cerebral blood flow in human subjects that would require the sampling of cerebral venous blood from the internal jugular vein. I suspect that he might have been trying to get us to volunteer for the procedure, but if so, it was without success.

At the 1944 annual meeting of the Federation of American Societies for Experimental Biology there was a symposium on the cerebral circulation that dealt mainly with the methods of its measurement. The dominant theme was the need for a method for measuring CBF quantitatively, and preferably one applicable to unanesthetized man. There were at the time nonquantitative methods for studying CBF in man. One was the thermoelectric flow recorder, a thermocouple in the form of a needle that could be inserted into the jugular vein to detect changes in flow within the vein by recording changes in the temperature of its blood content. This technique could indicate only blood flow changes within the vein but could not measure perfusion rates within the brain tissue. Another popular method at the time was the measurement of cerebral arteriovenous O_2 differences, which should vary inversely with changes in CBF if cerebral O_2 consumption ($CMRO_2$) remained constant, but it did not actually measure CBF and could not distinguish between changes in CBF and $CMRO_2$. The only method that quantitatively determined both CBF and $CMRO_2$ was the bubble-flow technique of Dumke and Schmidt, but this method required not only anesthesia but also such extensive surgery that its use was restricted to monkeys.

Seymour attended this symposium and accepted the chal-

lenge with a unique and conceptually brilliant approach. He was aware of Cournand's application of the direct Fick principle to the determination of cardiac output in man by measuring the rate of O_2 uptake into the lungs and the difference in O_2 concentrations between blood going to and coming from the lungs. Seymour reasoned that he could apply the Fick principle indirectly by introducing into the blood a foreign, chemically inert tracer that diffused freely across the blood-brain barrier and measuring the cerebral arteriovenous difference (i.e., difference in tracer concentrations in the arterial blood going to the brain and in representative cerebral venous blood coming from the brain). He initially chose the freely diffusible gas nitrous oxide (N_2O) as the tracer and administered it in low concentrations in the inspired air.

Arterial blood is the same in all arteries, but was usually sampled in the femoral artery. Venous blood varies from vein to vein, but representative cerebral venous blood was sampled from the superior bulb of the internal jugular vein. It was necessary also to know the amount of tracer taken up by the brain. In cleverly designed experiments he showed that after about 10 minutes the concentrations in the brain and cerebral venous blood were close enough to equilibrium to allow calculation of brain N_2O concentration from the measured cerebral venous concentration at that time and the relative solubilities (i.e., partition coefficient) of N_2O in brain and blood. The same principle applied equally well to other chemically inert tracers, such as [79]krypton and [133]xenon, and these were later used sometimes instead of N_2O, because it was more convenient to measure their concentrations in blood. Another particularly valuable feature of the N_2O method was that because it required the sampling of both arterial and cerebral venous blood to determine CBF, it became relatively simple also to determine the

brain's rates of utilization or production of oxygen, glucose, carbon dioxide, and lactate by measuring their cerebral arteriovenous differences and multiplying them by the value obtained for CBF.

This ingenious conceptual approach resulted in the Kety-Schmidt method for the quantitative determination of cerebral blood flow and metabolism in unanesthetized man. The experimental work that led to its development was supported by a grant from the Scottish Rite and carried out on conscientious objectors who had volunteered to be used as subjects in medical research rather than to be inducted into the armed forces during the war. The N_2O method and five of its applications in various physiological and disease states were published in a single issue of the *Journal of Clinical Investigation* in 1948. Its impact was like a thunderclap that revolutionized research on the human brain. Numerous applications in neurology, psychiatry, and medicine led to much of our knowledge of the normal physiology, pathophysiology, and pharmacology of the circulation and metabolism of the human brain in health and disease. Carl Schmidt, in whose department Seymour developed the method, wrote,

Now, for the first time, the clinical physiologist is no longer at a disadvantage in studying the circulation in the human brain. As a matter of fact he is now able to learn more about this, and its relation to the metabolic functions of the organ supplied, than about any other organ of the body. The change is one of the small profits of the research activities of the war years and is one more example of the benefits to be expected from giving brilliant young men opportunities to develop and test out original ideas.

These papers were published while I was serving in the U.S. Army as a neuropsychiatrist and undecided about what to do when I was discharged. The idea of studying directly the circulation and energy metabolism of the human brain in normal and mentally ill subjects attracted me, and shortly

after leaving the Army in 1949 I joined Seymour as a postdoctoral fellow in Julius Comroe's Department of Physiology and Pharmacology in the Graduate School of Medicine of the University of Pennsylvania, where Seymour had been appointed a full professor.

It was a fantastic experience. Seymour was an inspiring leader. Despite his towering intellect, he never allowed it to overwhelm us. He was always humble and unpretentious and listened to everything we had to say. Often he would raise questions and patiently consider our comments even though, as we would later learn, he already knew the answers. His attitude stimulated us to think critically and deeply. A frequent comment of his was, "Well, think about it." He valued conceptualization, originality, and uniqueness above all. In my very first project as a research fellow, which was on the effects of hyperthyroidism on cerebral O_2 consumption in man, we were scooped in the publication of the entirely unexpected finding that the oxygen consumption of the brain remained normal despite very large increases in total body O_2 consumption. He consoled me with the comment, "Don't feel bad. It must not have been such a great idea. Someone else thought of it too"—a sentiment typical of his attitude.

Seymour's office in the department had two doors. One opened into the corridor and the other into the large room where the research fellows had their desks. The latter door was almost always open, and we constantly interrupted his work, which at that time was mainly on the preparation of his now classical and seminal *Pharmacological Reviews* article "The Theory and Applications of the Exchange of Inert Gas at the Lungs and Tissues." One day late in the summer of 1950 the door was closed all day while Seymour was meeting with two U. S. Public Health Service officers in their white uniforms.

All of us were curious, of course, because we suspected that whatever this meeting involved it would impact us. Therefore, as soon as the officers left we queried him about the purpose of their visit. It turned out that they were Robert Felix and Joseph Bobbitt, the director and the executive officer of the National Institute of Mental Health (NIMH), one of the newly formed institutes in the National Institutes of Health in Bethesda, Maryland. They had come to offer him the position of scientific director of the intramural research programs of both the NIMH and the National Institute of Neurological Diseases and Blindness (then NINDB, now National Institute of Neurological Disorders and Stroke). When we asked him if he would seriously consider leaving Penn for such an offer, he replied that would indeed, because he had always been interested in mental disease and that this offer presented a challenging opportunity to study it. We then asked why they would choose him, a physiologist and neither a psychiatrist nor a neurologist, to direct a program of research on mental and neurological diseases. His reply was that he had had the same question and had raised it with Felix and Bobbitt. They explained that it was exactly for that reason that they wanted him; they thought that the scientific director of a research program on mental and nervous diseases should be a basic scientist and not a psychiatrist or neurologist in order to ensure rigorous and scientifically sound research. Seymour did not, however, rush to a decision. After several months of agonizing rumination and frequent consultations with friends, colleagues, and undoubtedly Josephine, he accepted the appointment, and in 1951 left Penn to undertake the organization of the intramural research programs of the NIMH and NINDB.

The Clinical Center of NIH was under construction when he arrived, and Seymour, as scientific director, had what he

considered almost unlimited resources in space, budget, and positions to organize the intramural research programs of the NIMH and NINDB. He approached this responsibility in characteristic Kety fashion: cautiously, deliberately, systematically, studiously, and with great humility. He had no preconceived notions about how best to study mental and neurological diseases but had faith that more basic, fundamental knowledge of the structure and functions of the nervous system would be needed. He therefore emphasized the basic sciences and relegated most of his resources to laboratories organized along more or less traditional disciplinary lines.

Seymour then exhaustively consulted leaders in these disciplines to identify outstanding candidates and succeeded in recruiting a truly impressive array of laboratory chiefs. Some of these were Wade Marshall, chief of the Laboratory of Neurophysiology; William Windle, chief of the Laboratory of Neuroanatomical Sciences; Giulio Cantoni, chief of the Laboratory of Cellular Pharmacology; Kenneth Cole, chief of the Laboratory of Biophysics; David Shakow, chief of Psychology; and John Clausen, chief of the Laboratory of Socio-Environmental Sciences. He retained for himself the position of acting chief of the Laboratory of Neurochemistry while he was trying to recruit an outstanding biochemist with interest in the nervous system; he also reserved for himself within that laboratory the Section on Cerebral Metabolism in which he could carry out his own research.

Seymour did not pretend to be expert in all these disciplines in the program. Once these laboratory chiefs were appointed he gave them full authority and support to direct their own laboratories as they chose, but provided them with his advice, counsel, and assistance in recruiting their staffs. The laboratory chiefs were selected not because they had been working in the latest most fashionable, so-called

"hot" research areas but because they had demonstrated originality and conceptual ability in their choice, design, and execution of their previous research. He was unimpressed by mere descriptive research or research driven more by ambitious, wish-fulfilling (though unrealistic) goals than by insight. His acumen in his selection of laboratory chiefs, as well as some members of their staffs that he had helped to recruit for them, was eventually confirmed; one won a Nobel Prize, at least three received Lasker awards, and at least a dozen, if not more, were eventually elected to the National Academy of Sciences.

While engaged in the organization of the intramural research programs of the NIMH and NINDB, Seymour collaborated with several biochemists in Europe and the United States (e.g., Heinrich Waelsch, Paul Mandel, Derek Richter, Henry McIlwain) in efforts to bring greater recognition and respect to and interest in the field of neurochemistry. Their efforts resulted in the initiation in 1954 of biennial neurochemical symposia, later transformed into the International Society for Neurochemistry, the founding of the *Journal of Neurochemistry* in 1956, and the establishment of the International Brain Research Organization (IBRO) in 1960.

Seymour allocated to his own Section on Cerebral Metabolism a modest amount of laboratory space in which to conduct his own research. Because his nitrous oxide method measured only average blood flow and metabolic rates in the brain as whole, it could not localize changes in these functions in discrete regions of the brain. He therefore undertook the development of a method to measure local cerebral blood flow based on his theory of inert gas exchange between blood and tissues that he had previously developed and published in 1951. With the help of several research fellows (i.e., William Landau, Walter Freygang, Lewis

Rowland, and myself) he ingeniously translated his theories into an operational method for measuring local CBF. The method could be used with any chemically inert tracer that could diffuse freely across the blood-brain barrier, but they selected ^{131}I-labeled trifluoroiodomethane ($[^{131}I]CF_3I$), a gas with the requisite properties. Localization within the brain was achieved by a unique quantitative autoradiographic technique that limited its use to animals. The method and its use to determine local CBF in individual structural and functional units of the brain in conscious and anesthetized cats was first reported in 1955. When used to examine the effects of visual stimulation, the autoradiograms clearly visualized the increases in CBF in the various structures of the visual pathways and led to the very first published demonstration of functional brain imaging, a field now enjoying enormous popularity.

Because the trifluoroiodomethane method was designed for use with autoradiography, it could be used only during uptake of tracer by the tissues. The underlying principles on which it was based were, however, equally applicable to clearance of the tracer from tissues after they had been pre-loaded with the tracer. Seymour had in fact used the clearance approach to determine blood flow in muscle of human subjects. He had injected ^{14}NaCl directly into the muscle and measured its clearance from its site of injection with a Geiger counter. The publication in 1949 that described these experiments included a detailed description of the theory and procedure for calculating local blood flow from the rate of clearance of the tracer. The ^{24}NaCl clearance method could not, however, be used in brain because ^{24}NaCl is not freely diffusible in either direction across the blood-brain barrier, but Niels Lassen, David Ingvar, and colleagues later adapted it by using radioactive gases, first radioactive krypton (^{85}Kr) and subsequently ^{133}xenon.

The ^{133}Xe method has been extensively and very effectively used as a clinical and research tool for several decades. More recently the trifluoroiodomethane method has been resurrected for human use, but with ^{15}O-labeled water as the tracer and PET scanning in place of autoradiography, and is now widely used in the functional brain imaging of cognitive processes in humans. All these fantastic new developments in neurobiology were derived from Seymour's pioneering work.

In 1956 Seymour stepped down from the position of scientific director to become the chief of the Laboratory of Clinical Science. Having completed organization of the basic research components of the intramural research programs of NIMH and NINDB and being too humble to feel that he should or could direct or interfere with the research of the outstanding and diverse cadre of laboratory chiefs that he had assembled, he no longer found the position of scientific director sufficiently challenging. As he put it, he no longer enjoyed the role of "deciding where to put the broom closets." There were also other reasons; he was anxious to become more immersed in his own research in new areas in which he had become interested. He had been impressed by developments in psychopharmacology, particularly those involving the monamine neurotransmitters and the actions of psychotomimetic drugs, such as LSD, mescaline, indole derivatives, and the like. There were suggestions at the time that abnormal metabolites of amino acids or of epinephrine might be involved in schizophrenia. There were also a few published studies, which though flawed and inconclusive suggested genetic influences in schizophrenia. All this reinforced Seymour's suspicion that schizophrenia might be a biochemical disorder that was at least partly inherited. He therefore established in the Laboratory of Clinical Science a program of research on the

biology of schizophrenia. One of his projects was to examine the hypothesis that abnormal disposition of epinephrine might be involved in schizophrenia, and to facilitate this study he contracted for the first commercial synthesis of radioactive epinephrine and norepinephrine. The labeled compounds later proved to be of immense value to Julius Axelrod, a member of the laboratory, in his Nobel Prize-winning research. Although no definitive evidence of a biochemical defect linked to schizophrenia was derived from these studies, they did serve to organize Seymour's thinking about the subject and led to his publication of several critical and heuristic papers in *Science* that almost certainly laid the foundation for modern biological psychiatry. He was quite amused by my quip that he had transmuted psychiatry from psychoanalysis to urinalysis.

His research at NIMH was interrupted in 1961, when he accepted the position of chairman of the Department of Psychiatry at Johns Hopkins University. He had, however, never received formal training in clinical psychiatry, and he felt very uncomfortable being in the position of psychiatrist in chief at Johns Hopkins University Hospital. Therefore, after one year he resigned and returned to his position as chief of the Laboratory of Clinical Science at NIMH and resumed his research on schizophrenia, this time focused on the question of genetic contributions to the disease.

Previous studies of siblings and monozygotic and dizygotic twins had suggested a genetic influence, but they had failed to disentangle convincingly the roles of "nature and nurture." He conceived the brilliant idea of studying the adoptive and biological family lines of schizophrenics who had been adopted at birth. The necessary data were available in the Danish Case Registry, and he in collaboration with colleagues, mainly David Rosenthal and Paul Wender at NIMH and Fini Schulsinger in Denmark, initiated such

studies. In 1967 he left NIMH for Harvard University, where he first became director of psychiatric research at the Massachusetts General Hospital, then director of the Laboratories for Psychiatric Research, Mailman Research Center, McLean Hospital, and finally professor of neuroscience in the Department of Psychiatry. In 1983 he retired from Harvard and returned to NIMH from which he retired once again in 1996.

Throughout all these decades and all his moves he continued his studies on adopted schizophrenics. The results demonstrated far greater incidence of the disease in the biological than in the adoptive family lines and thus provided unequivocal evidence of a major genetic component in the etiology of schizophrenia. The conclusions were not readily accepted by many committed to a social and/or environmental basis for the disease. Seymour acknowledged that schizophrenia was not a purely genetic disease, like phenylketonuria or Huntington's disease, only that there was an inherited susceptibility in a group of patients that fell within what he called a "schizophrenia spectrum." He responded to sometimes severe criticism with his characteristic wit and wisdom. For example, in response to the statement "Schizophrenia is a myth," he wrote, "If schizophrenia is a myth, it is a myth with a strong genetic component." The adoption studies contributed not only to our understanding of schizophrenia but also their underlying strategy and design provided a research model that has been and continues to be followed in studies of a number of other psychiatric disorders.

Seymour Kety's legacy encompasses at least three different areas of endeavor. As a physiologist he made extraordinary contributions mainly to the field of cerebral circulation and metabolism but also to general circulatory and respiratory physiology. As a wise and adroit statesman he

developed at NIMH and NINDB outstanding research pro-
grams in neuroscience, contributed substantially to the rec-
ognition of neurochemistry as a respectable and important
field of neuroscience, was a powerful force for the develop-
ment of biological psychiatry, and was a sage counselor on
countless advisory boards and committees. As a psychiatric
geneticist he conceptualized and developed a methodologi-
cal approach for separating the contributions of nature and
nurture in the etiology of mental disease and used it to
prove the existence of a strong genetically determined vul-
nerability to schizophrenia.

There is, in addition, Seymour Kety the man. His pro-
fessional achievements gained him enormous international
recognition and acclaim. He received many awards, honor-
ary degrees, and honorary titles and was elected into some
of the most honorific societies, such as the National Acad-
emy of Sciences, the American Academy of Arts and Sci-
ences, and the American Philosophical Society. In 1999 he
received his last award, the Lasker Award for Special Achieve-
ment in Medical Science, which touched him deeply. None
of these honors changed him. He remained the same humble,
modest, self-effacing, unselfish, considerate, kind, generous,
and warm human being that he was when I first met him 56
years earlier. He always remained readily accessible to all
and never used his razor-sharp intellect to overwhelm or
intimidate. He was intensely loyal and supportive of his col-
leagues and truly relished their successes whenever they
occurred. Perhaps his wife, Josephine, a master of one-liner
repartee, kept him humble. For example, Seymour once
expressed to her his surprise that a newly arrived research
fellow from India did not appear to be very impressed when
Seymour had proudly escorted him through NIH's newly
opened Clinical Center, the world's largest all-brick build-
ing furnished with the most modern hospital facilities. Her

response was, "Did you ever hear of the Taj Mahal?" When Seymour was scientific director of NIMH, psychoanalysis was a powerful influence in psychiatry, and the NIH administration felt that the director of its research program should undergo a personal psychoanalysis. Seymour resisted, but finally, when they offered to pay for it, he was inclined to accept. Josephine's comment was, "Suppose they offered you a free appendectomy. Would you take it?"

The Ketys were generous and genial hosts and would often entertain at their home. These were always delightful experiences full of scintillating conversation and humor from guests with a wide variety of backgrounds. Seymour had an enormous reservoir of jokes and amusing anecdotes that he enjoyed telling and occasionally using to make a point. The Ketys were also great art lovers, and Seymour was enamored of good food and wine. Seymour Kaufman and I, both of us in the intramural program of NIMH, were present at what was probably the zenith of his experience with the French cuisine. In the summer of 1958 the three of us attended in sequence an International Neurochemical Symposium in Strasbourg, France, an International Biochemical Congress in Vienna, Austria, and finally the inaugural meeting of the Collegium Internationale Neuro-Psychopharmacologicum (CINP) in Rome, Italy. During the meeting in Strasbourg Kety inquired from Kaufman and me whether, if he bought a car, we would be willing to ride with him to these meetings and then onto Paris, France. We, of course, gratefully accepted, but it was not until we reached France on the leg from Rome to Paris that we learned his intentions. He had longed to but had never previously eaten at any of the three-star restaurants in the almost biblical *Guide Michelin*. He had, therefore, planned a route that led us to four of only twelve such restaurants in all of France so honored at that time by the guide. Because

of time constraints we ate in four consecutive days at
Baumanière in Les Baux, Provence; De La Pyramide in
Vienne, Burgundy; Hostellerie de la Poste in Avallon, Bur-
gundy; and La Tour d'Argent in Paris. Kaufman and I were
thoroughly saturated with food but not iron-man Kety, who
attributed our weakness to lack of stamina due to our youth.
Those restaurants probably represented the epitome of the
traditional French haute cuisine with its rich, flavorful sauces
that he had come to admire so much. He later lamented
the subversion of the classical French sauces by the advent
of the nouvelle cuisine and cuisine minceur.

Seymour is survived by his wife, Josephine; daughter,
Roberta Kety; son, Lawrence Kety; and two grandchildren.
He will be greatly missed not only by them but also by his
many colleagues and friends whose lives he so greatly influ-
enced and enriched.

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E. F. Knipling

EDWARD F. KNIPLING

March 20, 1909–March 17, 2000

BY PERRY ADKISSON AND JAMES TUMLINSON

EDWARD F. KNIPLING, RETIRED U.S. Department of Agricul
ture entomologist and administrator died on March 17,
2000, in Arlington, Virginia, at the age of 91. He was best
known for developing the sterile insect technique, which
was the principal technology used to eradicate the screw-
worm fly from North America.

Often called "Knip" by his friends and colleagues, he
was born in Port Lavaca, Texas, on March 20, 1909, and
grew up on his parents' small farm. His dad assigned many
chores to him on the farm, one being the odious task of
doctoring baby calves that had screwworms burrowing in
their navels and wounds. Another was picking cotton by
hand in boll-weevil-ravaged fields. From this experience young
Knipling developed an interest in entomology and later said
that he decided at an early age he wanted to make a greater
contribution to agriculture than treating screwworm-infested
calves or pulling a sack down a cotton row. Thus, after
leaving the insect-laden farming area of the Texas gulf coast
he decided that entomology was the logical field for him to
enter.

After graduating from high school Knip enrolled at Texas
A&M College (now Texas A&M University), where he was

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awarded bachelor and master of science degrees in ento-
mology in 1930 and 1932, respectively. In 1947 he was awarded
a Ph.D. in entomology from Iowa State University.

Knip's career with the U.S. Department of Agriculture
(USDA) began in 1930 as a field aid in the former Bureau
of Entomology and Plant Quarantine, where he assisted in
field studies in Mexico on the pink bollworm. In 1931 he
was appointed a junior entomologist to conduct research at
Menard, Texas, on the biology and control of the screw-
worm. The screwworm is a subtropical fly that lays its eggs
in the open wounds of warm-blooded animals. The flesh-
eating larvae or maggots cause suffering, death, and untold
economic losses in cattle, other livestock, wildlife, and even
humans. In his screwworm research assignment Knipling's
talents as a scientist became obvious, as did his keen intel-
lect for looking at old problems in a new way. By 1937 he
had teamed with a young colleague, R. C. Bushland, to
study the mating habits of screwworm flies. Observing that
male flies mated repeatedly while female flies mated only
once in their lifetime, Knip believed they had found a weak
link in the screwworm's life cycle that might be exploited
for control. The question was: "How?" This was a question
Knip pondered for several years before finding the answer.

Knip's research in Texas on screwworms was interrupted
intermittently when he was assigned to conduct research
on other pest problems of livestock in Illinois, Iowa, and
Georgia. In 1940 he was placed in charge of research on
mosquitoes of the northwestern states with headquarters in
Portland, Oregon.

During World War II Knip was given the important as-
signment of devising better ways for controlling the arthro-
pod vectors (flies, mosquitoes, lice, and other biting in-
sects) of human diseases affecting our troops. He was made
director of the USDA research laboratory at Orlando, Florida,

where he led the development of DDT and other insecti-
cides and repellents for use by our armed forces and allies
to control the vectors of malaria, typhus, plague, and other
arthropod-vectored diseases that had exacted a tremendous
toll on troops in previous wars. The laboratory was success-
ful in its mission to develop effective control measures of
the disease vectors, thus preventing infection, illness, and
death of thousands of service personnel across the world.
The research conducted at the Orlando laboratory received
national and international recognition. Many of the repel-
lents and methods of control for the arthropod vectors of
some of the most serious human diseases are still being
used throughout the world today.

During this period Knip continued to think about the
screwworm problem. With imagination and innovation he
conceived the idea of using sterile insects for population
suppression and eradication. He reasoned that if male flies
could be produced in large numbers, sterilized, and re-
leased into the environment they might out-compete, on a
simple probability basis, the wild fertile males in breeding
with females. Because female screwworms mate only once,
those that were bred with sterile males would lay infertile
eggs and thus not produce any progeny. Knip reasoned
that if a sufficient number of sterile males could be re-
leased into the wild population they would essentially over-
whelm and breed the screwworm population into extinc-
tion. Knip was consumed by this idea and soon began
developing simple mathematical models of the population
dynamics of the screwworm fly. These models convinced
him that the sterile insect concept should work according
to laws of probability if methods could be developed for
sterilizing the males and mass rearing the flies in sufficient
numbers to out-compete the fertile males when released
into the field.

In 1946 Knip was placed in charge of all USDA research on insects affecting livestock, man, households, and stored products and was transferred to headquarters in Washington, D.C. From this position he encouraged Bushland who was still in Texas to pursue this line of research with the screwworm fly. They maintained frequent communication to exchange ideas and discuss new research approaches to the problem.

In the January 1950 issue of *American Scientist* Professor H. J. Muller of Indiana University in Bloomington reported that fruit flies could be sterilized by exposure to X rays. This report excited Knipling and Bushland and they decided to try this procedure on screwworm flies; however, Bushland's laboratory did not have the needed equipment, and funds were not available to purchase what was needed. Not being one to give up, Bushland smuggled insects into the X-ray laboratory of an army hospital in San Antonio, where he was a friend with some of the staff members. There he was able to use their equipment on days when the unit was not busy. He tested various dosages of X rays on the adult, larval, and pupal stages of the screwworm. He discovered that screwworm flies subjected to an appropriate dosage of X rays in the pupal stage not only survived but also emerged into healthy adults that were sexually sterile. Cage studies using both sterile and normal flies in various ratios confirmed the theory that reproduction of the screwworm could be inhibited at levels consistent with the mathematical probability models.

Part of the problem was solved. There was a way to sexually sterilize the screwworm without any serious adverse affect on their health or their ability to compete with wild males in mating with females. The other parts of the problem were: "How do you mass rear large numbers of screwworm flies and how many will be needed to suppress a field

population over a large area?" Bushland was given the prob-
lem of developing methods for mass rearing the insects and
improving the sterilization technology, while Knipling con-
tinued working on mathematical models to answer the ques-
tion of how many flies would be needed to obtain success
with sterile male releases.

In 1954 Knip was given the opportunity to test his theo-
ries when the Dutch government asked the USDA for help
in controlling screwworms that were decimating the goat
and dairy calf populations on the island of Curacao off the
coast of Venezuela. From a rearing facility in Florida 170,000
flies a week were produced, sterilized with a gamma radia-
tion source, and transported to and released across the is-
land. Very soon the number of wild flies in the population
was reduced; after several months and about three fly gen-
erations the population was eradicated from the island, which
has remained free of infestation since 1954.

This successful demonstration that the sterile insect re-
lease method could be used to eradicate insect pest popula-
tions not only excited Knipling and Bushland but also gave
their work great impetus as it excited the livestock produc-
ers in screwworm-infested areas of the United States.

During the late 1950s a much larger and more difficult
test of the sterile insect release technique was made. Live-
stock producers in Florida gained support of federal and
state agencies to conduct an eradication program in their
state. By 1959 the screwworm was eradicated from Florida
and all of the southeastern United States.

This success led livestock producers in Texas and Okla-
homa to organize and gain support for a similar program.
The producers raised a substantial amount of money for
the program and were assisted by two prominent Texas ranch-
ers, President Lyndon Johnson and Governor Dolph Briscoe
of Texas, in obtaining federal and state funds and technical

assistance. By 1966 the screwworm was eradicated from the United States. In 1972 the program was expanded to Mexico, where eradication was achieved in 1991. The program has since moved through all of Central America and a barrier zone is now being maintained at the Panama-Colombia border.

The eradication of the screwworm from North America was truly a remarkable achievement, both technically and economically. The benefits to livestock producers throughout the eradication zone are well over $1 billion per year. The cumulative benefits over more than 50 years, including all the economic multipliers, environmental quality, and avoidance of animal and human suffering, are too large and staggering to even estimate.

The success of the sterile insect release technique for eradicating the screwworm fly was the first successful demonstration that a pest species can be eliminated from large geographical areas with appropriate technology. Furthermore, the sterile insect technique is credited as being one of the most significant peaceful applications of nuclear radiation for the benefit of mankind. This technique has since been used to eradicate and control other pests, such as the Mediterranean and other fruit flies in California, Florida, and other parts of the world. In 1988 it was also discovered that the screwworm had been accidentally introduced into Libya and soon thousands of animals were infested. The greater threat was that the screwworm fly might infest most of Africa, causing severe losses to food animals and wildlife. The sterile insect release technique was employed, and the fly was successfully eradicated from Africa.

From 1953 to 1971 Knip was director of the USDA's Entomology Research Division, where he was in charge of all arthropod research conducted by the Agricultural Research Service. During this period great advances were made

in the field of entomology and pest management, attrib-
uted to his vision and leadership in developing and pro-
moting principles and strategies for suppressing insect pests
by such techniques as sterile insect releases, pheromone
traps, biological control agents, and cultural practices, with
a minimal use of insecticides.

During the latter part of his career Knip became con-
vinced that it was also possible to eradicate the boll weevil,
the second scourge of his youth, from the United States.
He was able to gain support for his ideas within the USDA
and with cotton producer groups. A large research project
was mounted in the early 1960s to develop the technology
needed to eradicate the weevil, or at least eliminate it as an
economic pest of cotton in the United States. During the
1960s and 1970s Knipling developed a conceptual frame-
work for an eradication program, using a variety of tech-
niques. His concepts were field tested in Mississippi and
later fine tuned in the cotton fields of Virginia and North
Carolina, where the boll weevil was successfully eradicated
in 1987. Following this, eradication programs were conducted
throughout the southeastern United States. The program
has moved westward across the Cotton Belt, with eradica-
tion efforts currently underway in the mid-south, Texas,
and Oklahoma. Eradication of the boll weevil from the United
States should be accomplished relatively soon. When this is
done, the use of chemical pesticides on cotton, and the
consequential environmental impact, will be greatly reduced.

After retirement in 1973 and until his death Knipling
remained professionally active, including serving as an un-
paid consultant to the USDA's Agricultural Research Ser-
vice and the Animal and Plant Health Inspection Service,
where he advised on pest management programs. Through-
out his 28 retirement years he continued to publish exten-
sively, and was considered a leading authority on insect

population dynamics and control. In 1979 he wrote a book on the basic principles of insect population suppression. In 1992 he wrote another book on insect parasitism from new perspectives. In these and many other publications, as well as in seminars and lectures on insect pest management, Knipling constructively questioned and challenged many conventional insect control strategies that are based on small areas, farm-to-farm applications, continued heavy reliance on insecticides, and reactive treatments after pest populations reach high levels and damage occurs. He was a strong proponent of the area-wide management of pest populations by a variety of proactive technologies. His primary theme was to prevent insect pests from reaching damaging levels by using biological and other nonpesticidal suppression methods that would not adversely impact the environment and nontarget organisms—over large geographic areas.

In addition to his many professional achievements Knipling was the patriarch of a large and active family that shared many common interests and bonds. His wife of 66 years, Phoebe, was also an Iowa State University Ph.D. graduate and was an accomplished educator in the Arlington County, Virginia, public school system. Together they had 5 children, 14 grandchildren, and 9 great-grandchildren.

Knip's professional interest in entomology and nature in general greatly influenced day-to-day life and activities of the family. For example, all of their pets were named after insects, either their common or scientific names: Siamese cats Anthonomus and Culex were named after the cotton boll weevil and a type of mosquito, respectively.

Knip was an avid outdoorsman and naturalist with a strong conservation ethic. The family owned several large properties in the mountain regions of Virginia, West Virginia, and Vermont. These properties were managed for recreation

and timber production. Knip was an accomplished archer, hunter, and fisherman. He almost always caught more fish than anybody else, often self-attributed to being able to "think like a fish" and outsmart them. He even carved and painted his own fishing lures, making them look like insects, of course. His favorite was a lure that looked like a cicada; he called it "Humbug" and caught lots of fish with it.

In summary, Knipling had three main themes in his life: his family, his profession, and his great reverence for nature and love of the outdoors. In his roles as a distinguished scientist and administrator Knip significantly advanced the world's knowledge of insect pest management and alleviated some of the most important insect pest problems of agriculture across the world, in an environmentally sound manner. The scientific principles and strategies he promoted and documented are sure to continue to guide new developments in insect population management well into the future.

SIGNIFICANT HONORS AND DISTINCTIONS

1947 Presidential Medal for Merit
1948 King's Medal for Service in the Cause of Freedom, Great Britain
1952 President, Entomological Society of America
1966 Membership, National Academy of Sciences
Rockefeller Public Service Award
1967 National Medal of Science
Honorary doctorate, North Dakota State University

1970 Membership, American Academy of Arts and Sciences
      Honorary doctorate, Clemson University
1971 President's Award for Distinguished Federal Service
1975 Honorary doctorate, University of Florida
1986 Agricultural Research Service Science Hall of Fame
1991 FAO Medal for Agricultural Science
1992 World Food Prize
1995 Japan Prize
1996 Honorary doctorate, Texas A&M University

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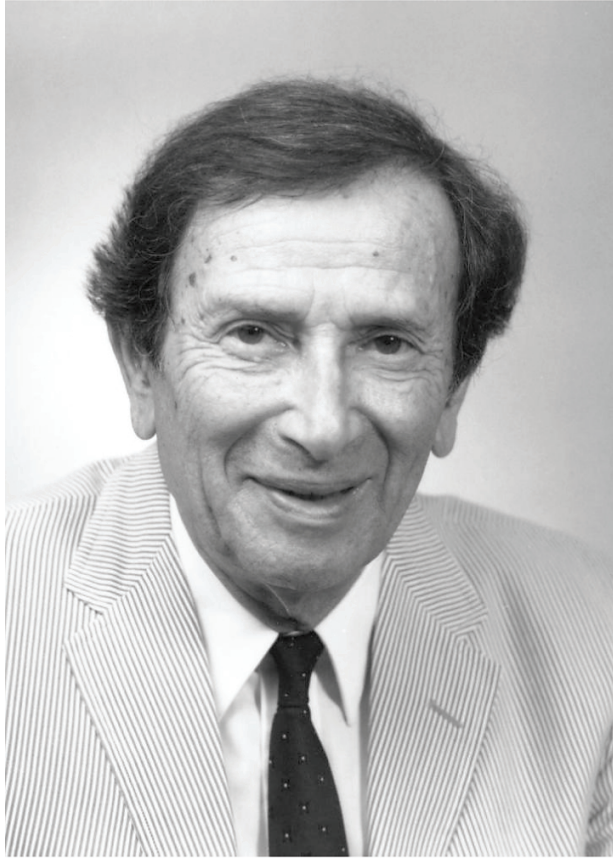
HEINZ ADOLF LOWENSTAM

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BY JOSEPH L. KIRSCHVINK

HEINZ LOWENSTAM DESCRIBED himself as a professional beach comber, but in fact he was among the twentieth century's most superb natural scientists. Building upon an early interest in minerals and fossils gained during his childhood playing on mining dumps in Germany, he was the first to blend biological and paleontological analyses to unravel the ecological associations of fossil communities. After being denied his Ph.D. from Nazi-controlled universities for the crime of being Jewish, he fled with his wife to the United States and managed to complete his degree at the University of Chicago just prior to the start of World War II. Classified as an enemy alien, he contributed to the U.S. war effort by developing paleoecological techniques to locate oil-bearing coral reefs in the sub-surface of the greater Chicago area. Rather than profiting personally from his work, Heinz published it freely in the open literature.

In the postwar isotope frenzy at the University of Chicago Heinz was drafted as the "atomic paleontologist" for Harold Urey's research group. His initial role was to provide pristine fossil materials for isotopic paleotemperature determinations, but his involvement grew rapidly to include that of identifying the most important scientific questions

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about Earth's past biosphere that could be addressed for the growing field of stable isotope geochemistry. In the process of finding unaltered fossil materials Heinz also began to wonder about the process of biomineralization itself: How do animals make minerals under biological control? How do they control the mineral composition, crystallinity, and particle size? Using his talents as a naturalist and exploiting advances in analytical techniques, Heinz nearly doubled the known diversity of minerals produced by organisms. One of his discoveries—the biomineralization of magnetite (Fe_3O_4) in the teeth of Polyplacophoran mollusks (the chitons)—has been crucial for understanding topics as diverse as the geophysics of marine sediment magnetization and the biophysical basis of magnetoreception in animals.

Heinz was born in 1912 in Upper Silesia, in what was then southeastern Germany but is now south-central Poland, in the town of Siemjanowicz. This was a suburb of Laurahutte, a mining district with a steel mill. In his oral history recorded for the Caltech archives Heinz described his birthplace as

a horrible region. . . . It was like Dante's Inferno. Across the whole horizon, you saw belching chimneys spewing out fumes from lead smelters, and steel mills. There were coal mines and iron foundries. The air was so poor that our plants in the house had to be specially tended so they didn't die from the fumes. . . . As a kid, I played on a mine dump—you know, the stuff that goes out from a lead and zinc mine. I wasn't supposed to go there, but I went with some miners' kids, and we played. We normally picked up a rock to throw, and one day the one that I picked up was awfully heavy. I knew it couldn't be an ordinary rock, so I broke it. It looked like silver. It was galena—lead ore. And that's what started me initially to collect minerals.

Many of Heinz's interests in nature clearly stem from his parents (Frieda and Kurt Lowenstam), although neither

of them had a university education. Before World War I his mother was the art editor of a newspaper and wrote poetry. She encouraged Heinz's interest in nature by taking him around and showing him things, and getting semi-popular publications on natural history. Heinz notes that she "was interested, among other things, in ancient Egypt, and she taught herself to read hieroglyphics. We would go to museums, like in Berlin, and she would read the inscriptions just like that and translate them." His father was similarly educated, in the sense that he was a classicist. "He went to the *Gymnasium*—the German academic high school. He always had pockets full of books. He was more interested in history and literature." His grandfather wrote a six-volume history of the Jewish people, and most members of his family studied languages and literature. Later in life Heinz would often comment on this peculiar background with statements like, "Ha, ha, ha, . . . you know I'm the black sheep of the family; I don't shpeak any lankvages."

Upper Silesia was also politically unstable, caught up in the ravages of the First World War. At one birthday party he remembered machine-gun fire strafing his grandparent's home while everyone hugged the floor in panic. This was the first of many "I've almost been killed" episodes that were to punctuate Heinz's life. The Lowenstam family was hit hard by the German economic depression in the 1920s and the hyperinflation that followed. Due to his interest in the natural sciences and with the encouragement and support of his maternal grandfather, Heinz entered what was then an experimental *Höchschule* focused on math, physics, and chemistry as major subjects (in contrast to the *Gymnasium*, which provided a more academic education focused on the classics). Heinz found his new school area more conducive to collecting fossils than minerals, so he swapped collections with one of his teachers who wanted to become

a mineralogist; that's when he started his first systematic fossil collection and gained the desire to be a paleontologist. A seminar in his town given by Alfred Wegener, who first proposed the continental drift theory, expanded his interest to include geology, not just paleontology.

With continued support from his grandfather, Heinz was able to enroll in the vertebrate paleontology program at the University of Frankfurt. However, its leading paleontologist died suddenly just prior to his arrival, and the entire program collapsed. The students scattered to other universities, and in the fall of 1933 Heinz chose to continue at the University of Munich, which had the strongest German program in paleontology with the most international outlook. Shortly thereafter Adolf Hitler was named chancellor and the situation for German Jews became increasingly more precarious. Unfortunately, some of the professors at Munich were influenced strongly by Nazi propaganda. Others, such as Heinz's mentors Prof. Broili, Edgar Dacqué, and the biologist Karl von Frisch, were willing and able to ignore the rhetoric to some extent. Von Frisch even went so far as to give Heinz a desk to work at in his laboratory suite immediately after the first anti-Jewish edicts were announced. About this time Heinz met his future first wife, Elsa Weil, a student in the Ludwig-Maximillan University Medical School, at a vegetarian restaurant.

This Nazi influence resulted in a most unusual twist in Heinz's choice for a Ph.D. thesis topic. During a student field trip early in 1935 Heinz recalled one of the Nazi-influenced professors (Kölbl) pounding the table and saying, "German things must be done by Germans." A few minutes later he had the tenacity to ask Heinz what he was planning to do for his Ph.D. dissertation. In a fit of sheer impulsive rebellion Heinz announced that he was going to work on the geology of Palestine, despite the fact that he

had absolutely no personal resources to do so. Depressed at having shot his mouth off, he mentioned this to his friend and landlord later that evening, who said, "Don't worry. I have friends in New York. They will take care of it." Unbeknownst to Heinz, these friends were financed by the Iraq petroleum company, which was very interested in the geology of the Middle East and were eager to have good geological and paleontological studies done in the area.

So Heinz went to Palestine for 18 months. Although the area was still a British protectorate, Heinz realized that he would need to cooperate with the Bedouins to have full access to his field area. With a proper introduction from the British district commissioner he was able to live with the family of the number one Sheik for several months, learning Bedouin Arabic in the process. During the introduction, however, Heinz was forced to smoke for his first time; refusal would have been a deadly insult to the sheik and his family. (That led unfortunately to a 45-year tobacco addiction and his ultimate demise from lung cancer.) During his 18 months in Palestine Heinz was able to complete the first geological and paleontological analysis of the eastern Nazareth Mountains, which turned out to be one of the critical areas for understanding the geology of the entire Dead Sea rift system. During this time geologists from the Iraq petroleum company used his geological and paleontological skills, as Heinz was invited repeatedly to participate in field excursions throughout the entire Middle East. All they asked in exchange for these trips was to have copies of his field notes. At the time Heinz did not know that this was also the ultimate source of his field support in Palestine.

Upon completion of his dissertation research in the middle of 1936, Heinz returned to Munich and spent about a year finishing his thesis. After it was accepted and the

date for his exam was scheduled he and his fiancée, Elsa, were married. One week before his thesis defense, however, the Nazi government issued an edict that no more Jews would be allowed to receive their doctorates at German universities. Elsa had already received her medical degree the previous week, but Heinz was out in the cold, with nothing to show for his many years of university education, not even a bachelor's degree (the German Ph.D. was an all-or-nothing affair). They had no options but to leave. Several of the geology faculty at Munich then did an extraordinarily risky thing, as noted by Heinz.

So Dacqué wrote a letter on official university stationery, with the Nazi university seal on it, saying I had fulfilled the qualifications of the Ph.D., but due to political circumstances, they couldn't give me the diploma. He went over with me to Broili, who was the head of the paleontology department to have Broili sign where he had typed out his name. Broili sat down and signed. Within 10 minutes Kölbl [the Nazi professor] asked me to see him. I came in and [he] said, "I would like to see the letter which you just got from Broili and Dacqué." I said, "What Letter?" He said, "Don't be silly." He went over to my pockets and he knew in which pocket I had it. He pulled it out, read it; his eyes popped out, he got mad. He gave it back to me and said, "Nice letter, isn't it." He knew I was going to leave within a week or two. I said, "Yes." He said, " I want to give you a letter of recommendation, too. But you must not show it to the *Chicago Tribune*, because you know what would happen to me if you did that." I said, "I don't want your recommendation." He didn't listen. He sat down and wrote the letter—I was a good student, in general terms—and gave it to me. As I went out the door he said to me, "You cannot go to America and say that we mistreated you, can you?"

Fortunately Heinz and his wife had managed to get visas to immigrate to the United States, being sponsored by his wife's uncle in Chicago. The major problem was that the U.S. government considered Heinz to be a Polish citizen, given that his birthplace, Upper Silesia, was then part of Poland. (Heinz was a German citizen and had never been

in Poland, yet they told him he was Polish.) The visa queue for Polish citizens seeking to immigrate to the United States had been hopelessly overdrawn for 15 years. However, the U.S. consul in Stuttgart—the closest one—gave him one of three emergency visas. Heinz later came to suspect that this arrangement was made possible by the silent efforts of the oil company that had financed his studies in the Middle East. Heinz's parents and sister also managed to escape to Brazil, but most of his other relatives later perished in the Holocaust. His grandfather, who was not a Jew but had married one, chose to commit joint suicide with his wife by fire in their home rather than denounce their children and relatives to the Nazis.

Upon their penniless arrival in Chicago in June of 1937, Heinz discussed his situation with several of the geology faculty at the university. At first they simply looked through his grade sheets with little apparent interest until someone noticed the letter from Broili and Dacqué. As Heinz recalled in his oral history transcripts,

I hadn't thought of it. The letter happened to be in my pile of papers. They saw that letter and said, "Could we open it?" They read it, and—I'll never forget—their eyes got big. "Broili, Dacqué, they recommended?" After that the whole atmosphere changed dramatically. I immediately got a scholarship, in the middle of the year. I was told I would have to take a few courses, translate my thesis, and within a year or two I could get my degree. That's when I realized how important that letter was. It was a miracle that Broili and Dacqué had done it, too, because without it, I don't know.

After only a minor setback for failing his German language test (because he didn't understand the English instructions), Heinz finally received his Ph.D. from the University of Chicago in 1939.

In one aspect Heinz was frustrated with his experience in Chicago. Having fled from persecution in Germany amid the destruction of his friends and family, he wanted to en-

list in the U.S. Army so that he could go and fight the Nazis. When America finally joined the war, he was listed initially as an enemy alien and was subjected to severe travel restrictions, even to the extent of having his camera confiscated. When the Arctic and Desert Division of the Army realized that they could use Heinz's ability to speak Bedouin Arabic for their campaign in Egypt, they lifted his enemy status and rushed his citizenship papers through in record time, but before he could go, the battle in Egypt was over. At that time the German U-boats were sinking oil tankers going from Texas to the east coast, and the military argued correctly that he would be of more use to them as a civilian working on the coal and oil reserves for the Illinois Geological Survey. Still, Heinz managed to help the war effort by interpreting aerial photographs of the Rhur district coal mines for the Army Air Corps, and recognized that modifications to the coking ovens were designed to extract high-octane aviation fuel. The Allies bombed the plants, putting them out of business and giving Heinz some measure of revenge.

For a short while after graduation Heinz worked for a small oil company and then moved to the Illinois State Museum as a curator of invertebrate paleontology. Having no funds for field research, Heinz discovered that he could take the Chicago streetcar system to the end of the Stony Island line to reach an area rich with fossil coral reefs. His rationale for launching his studies on the paleoecology of the coral reef environments (which led eventually to the recovery of enormous quantities of oil) is best expressed in his own words from the Caltech archives.

It was called Stony Island because there were fossil reefs cropping out— coral reefs. I went over there, and it was in terrible shape. Then I discovered next to it long dump piles that had been made when drainage canals were built to connect the Illinois River with the Great Lakes to get barges

through. In digging the canals the work crews had dumped all this stuff on the side. I started to walk over those old dump piles, and I found very nice fossils, all marine, and I knew they were from the Silurian period—about 400 million years ago. Some people from the Field Museum had already catalogued some of these fossils—the black shale type . . . but nobody had looked at the skeletal remains in dolomite. I made a big collection of the material over a period of time and then tried to identify it. I couldn't. I researched the local literature, and none of the fossil groups that had been described from the Chicago area fit what I had found at all.

As Heinz expended his attempts to identify the fossils he eventually discovered that they matched almost precisely Silurian fossils in Tennessee. Previous paleontologists who had studied the fossils from museum drawers had assumed that the two populations were from two geographically separate areas, one in the South and the other in the North, but Heinz had found them in the same area. The northern population was in fact composed of organisms that lived in the reef environment, in the active wave zone. The southern fauna simply lived in deeper waters and was composed of smaller forms adapted to a darker, less active environment. Upon further study Heinz discovered that he could identify changes in the ecological communities surrounding the reef environments that varied systematically with distance from the reef complex, and was even able to determine the direction of the prevailing winds 400 million years ago from the horseshoe-shape atoll structures. By examining subsurface cores from several localities he was able to use these distance estimates to determine the location of buried fossil reefs. Ultimately, Heinz discovered a massive system of Silurian reefs that stretched from the edge of the Ozark Mountains to Greenland; it had been larger and more magnificent in Silurian time than the Great Barrier Reef of Australia is today.

Heinz also realized that the porous structure of a buried reef complex was an ideal trap for oil and gas. Several

major companies had discovered oil in the Chicago area almost by random drilling, and Heinz's ability to pinpoint the locations by simply examining the cores seemed nearly miraculous. Two of the companies even went so far as to break into Heinz's office, looking for information on where to drill; Heinz was able to identify the bandits by marking fake locations on his office map and watching which company started drilling there. Despite financial offers of up to 1 percent of the profits for the proprietary use of his technique (which would have made him a very wealthy man) and to the later dismay of his children, Heinz instead chose to publish his findings in the open scientific literature for the benefit of all. His only compensation was the gift of a binocular dissecting microscope from one of the companies. However, the title of his 1948 book on the topic (*Biostratigraphic Studies of the Niagaran Inter-Reef Formations in Northeastern Illinois,* Illinois State Museum Society) was so obtuse that it triggered a local columnist for the *Chicago Tribune* to complain in print about the waste of state funds on such useless studies. This triggered a heated public response from the presidents of several major oil companies, who noted that the work was leading to the recovery of enormous volumes of oil. His monograph was republished many times by the oil industry.

Immediately after the war the University of Chicago was a hotbed of isotopic research and was in particular the birthplace of isotope geochemistry. Harold Urey had recognized the importance of isotopic measurements for interpreting the past history of the Earth and had assembled a team focused on using deviations in stable isotope ratios to measure the temperature of ancient oceans. Urey had obtained fossils of Mississippian age (about 300 million years old), extracted the calcite from the shells, and had determined a temperature of about 60°C, higher than any known animal

was able to tolerate. One of Urey's colleagues recommended that he consult with Heinz about the plausibility of this result. After looking at thin sections of the fossil materials, and comparing them to living relatives, Heinz pointed out that the shells had been recrystallized completely. They had measured the temperature of the hydrothermal fluids that had altered the fossils, rather than the temperature of the oceans in which the animals had lived.

In his studies of the ecology of fossil reefs Heinz had been interested particularly in the variability of fossil preservation and had started a special collection of fossils that had been unusually well preserved. These provided much better materials for isotopic study and gave much more reasonable paleotemperature results. Urey was ecstatic. Heinz was a gold mine of materials and ideas, and his expertise was needed urgently by their paleotemperature research project. Two months after his first meeting with Urey, and after much arm twisting, Heinz left the Illinois Geological Survey and accepted a position as a research associate in geochemistry at the University of Chicago. The title was rather peculiar for those days, and he was often referred to informally as Urey's atomic paleontologist. After another year, and with much more arm twisting, Urey convinced Heinz (and the Chicago administration) that he should teach as well as do research, as it was the best method to attract the best, most skilled students. Heinz at first thought that his horrible blend of Milwaukee-German/English would preclude effective teaching, but in fact it enhanced his rapport with the students.

At his position with the Urey group Heinz was able to continue his research on Silurian reefs, as well as to extend his search for pristine fossil shell materials, an interest that later paved the way for his studies on biomineralization. One of the most exciting geochemical results ever derived

came from their study of upper Cretaceous cuttlefish, which had annual growth rings preserved in an unaltered carbonate matrix. Isotope paleotemperatures clearly showed the amplitude of the seasonal warming and cooling cycles experienced by animals that lived in the oceans 80 million years ago (Urey, Epstein et al. 1951). It was an intellectual milestone, the first direct and quantitative measurement of an ancient climate signal.

One of the amusing legends of the Chicago years was the progressive change in Heinz's office over the four-year period (related by his colleague Sam Epstein). There was initially a straight, uncluttered path from the door to Heinz's desk. Gradually with time this evolved into a more winding path, as piles of wooden drawers with fossils, maps, journals, notes, and glass sample vials filled with mysterious powders accumulated along the route. Eventually his desk disappeared from view, and one had to tread carefully through the maze to avoid upsetting things. Finally one day Sam noticed a small note on the outside of the door, stating that Heinz had moved his desk to the empty room next door.

Between 1950 and 1952 members of the Urey geochemistry group migrated largely to California, both to Caltech and the University of California, forming the core of new isotope geochemistry programs. Initially Heinz was hesitant to leave Chicago, but it was clear that most of the young, exciting geochemists of the Chicago "mafia" were departing; and even Urey eventually moved to California. Harrison Brown, Sam Epstein, and Clair Patterson came initially to Caltech and founded a new program in geochemistry; with support from the AEC this group was able to attract a superb engineer (Charles McKinney) to build the mass spectrometers. Heinz himself was not an instrument person, but he knew intuitively which measurements were signifi-

cant and which analytical standards were important (such as his Pee Dee Formation belemnite sample, now known as the PDB standard for carbon isotopic analyses). It was clear that Caltech was on the right track, and with encouragement from his principal collaborators he eventually agreed to move west. When the chairman, Bob Sharp, asked him what his professorial title should be, Heinz replied, "a paleoecologist." When asked what that discipline involved, Heinz would usually state that it was professional beachcombing, or whatever he happened to be interested in at the time. Although he continued his collaborations with former members of the Urey group—particularly Sam Epstein—Heinz became ever more interested in the processes through which various living organisms use to control their mineral hard parts. Initially these studies were driven by the necessity of having "ground truth" for the study of fossil materials; if the paleotemperature measurements did not work on a modern clam grown in open ocean waters of known temperature, how then could one interpret results of ancient fossil materials?

Similarly he was interested in developing geochemical methods that could be used to obtain other important information about ancient ecosystems, such as salinity and barometric pressure. These problems led him to study the environments of modern reef systems, particularly those in Bermuda and Palau, which had long-term oceanographic records of temperature and salinity, and for which collection of materials of various depths was relatively easy.

As an early recipient of support from the Office of Naval Research Heinz was allowed to travel freely through the Pacific using the military air transportation system in the 1950s. Caltech and the Jet Propulsion Laboratory had played a leading educational and research role in the war effort, and apparently some bureaucrat back then had decided

that a Caltech professor had the rank equivalent to an admiral, so Heinz and his assistants were treated royally. When he realized how the military bureaucracy worked, Heinz exploited the system to gain access to remote areas and did not hesitate to request the military flyers to do reconnaissance aerial photographic surveys over areas of special ecological and geological interest. As always he was a dedicated naturalist and managed to survive and flourish despite extreme conditions in the field. One of the amusing legends of Heinz during this time concerns his attempt to extract a particularly interesting organism from the reef front in Palau while snorkeling. The small motorboat with his Palauan driver and assistant were nearby when they noticed a large shark swimming rapidly toward them. Despite their shouted warning Heinz refused to stop hammering away at the reef. As his crew started to panic, and as the shark closed in for the kill, Heinz turned around precisely on time and smacked the animal firmly on its snout with the flat end of his rock hammer. Dazed, and with most of its sensory organs out of commission, the animal wandered away and let Heinz return to his work.

As most of the biomineral products produced by reef organisms were forms of $CaCO_3$ (the minerals calcite, aragonite, and more rarely, vaterite), Heinz focused most of his research activities during the 1950s on them. Among other things he discovered that the aragonite needles that form most of the sedimentary mass in the back-reef lagoons of Bermuda were actually produced by microscopic algae; this triggered a vigorous debate with carbonate petrologists, all of whom had assumed that they formed through inorganic processes. The carbon and oxygen isotopes, however, convincingly pointed toward the biological origin.

Heinz's discovery of magnetite biomineralization is a premiere example of how a good eye and a keen mind can

lead to important discoveries even today. The story begins in 1961 when he was sitting at low tide on a wave-cut platform in Bermuda and began to wonder how the erosional processes had produced such a level, almost beveled-off substrate. He had seen similar benches in Palau, where the limestone had eroded into hundreds of nip islands, each resembling a large mushroom with waves splashing around the base and dense vegetation on top. At the time the dogma was that these were wave-cut benches, perhaps with some help from salt crystal formation at low tide. For some reason this did not satisfy Heinz, who took out a hand lens and examined the limestone substrate more closely. Surprisingly the surface was covered with long strips of small chevron-shaped groves that wandered over each other and overlapped in complex patterns, something like tangled noodles. While he was examining this, a chiton (a mollusk of the class Polyplacophora) wandered by, leaving a fresh noodle trail like this chiseled into the rock surface. Heinz realized immediately that the chiton was scraping off the outer (somewhat greenish) layer of the rock surface, feeding on endolithic algae growing in small cracks in the limestone. But for this to be the case the animal's teeth needed to be harder than the limestone substrate it was feeding on. The biological belief at the time held that the teeth of mollusks were made of a proteinaceous material like fingernails, which would not have been nearly hard enough to use as a rock chisel. A quick dissection revealed that the teeth along the animal's tongue plate (the radula) were black and very hard, obviously mineralized with something but clearly not calcium carbonate or a calcium phosphate mineral like apatite (such as in human bones and teeth). The black tooth mineral was present in every individual and every chiton species he examined. Tooth shape was even species spe-

cific, some having several prongs and others curved, cup-like structures.

Determining just what the hard black stuff was proved to be more difficult. Back in the early 1960s the best analytical tool for precise mineral determination was X-ray diffraction, and the standard technique was to use a narrow beam of Cu-Kα radiation. However, when the chiton teeth were measured in this fashion the photographic emulsion came out completely fogged. The technician operating the instrument, Art Chodos, suggested that it might be some interference or fluorescence and recommended changing the X-ray source from Cu to a different metal like Ni or Co. That eliminated the interference problem and produced a nice set of diffraction lines. Unfortunately, they did not match any of the standard minerals that are commonly found in the reef environments. Stumped, Heinz and his assistant decided to search methodically through each mineral in the standard diffraction compilation until they found something that matched. After several days of searching, pure magnetite (Fe_3O_4) popped up suddenly as a perfect match. Intrigued, Heinz then took a small hand magnet and discovered to his amazement that the entire radula stuck to it as strongly as if it were a nail: It was obviously ferromagnetic. Subsequent chemical analyses confirmed that iron was the main component in the teeth; it also explained the problem with the X rays, as the Cu-Kα line causes iron to fluoresce, fogging the film.

It is important to put this discovery into the proper historical perspective. In 1961 magnetite was known to be a dense, inverse-spinel mineral that formed exclusively in high-temperature, high-pressure igneous or metamorphic environments. It was thought to be terribly out of equilibrium at room temperature and pressure, and was simply not something that could be produced in the mouth of a mollusk.

Mineralogists and petrologists assured Heinz that the chitons had to be picking up grains of magnetite from the sand the same way that sharks and rays were known to accumulate heavy minerals in their inner ear for their balance organs. But, by simply dissecting out the radula and looking at it carefully, Heinz was able to show that the iron was of biological origin. It accumulated first as the iron protein, ferritin, in epithelial cells that were tightly attached to a proteinaceous but unmineralized embryonic tooth. The iron was then transported rapidly into the young teeth in the form of the mineral ferrihydrite (hydrous Fe_2O_3), forming a few rows of bright red teeth. At a very sharp, sudden transition most of the tooth volume was converted into black magnetite, with gradual addition of more ferrihydrite (converting to magnetite) as the teeth matured. This simple series of observations was able to shut up the most severe critics instantly. Magnetite was being formed at low temperatures and pressures, in an animal, no less. Although it is now well known that magnetite can be precipitated from aqueous solution under strongly reducing conditions, it was not appreciated in 1961.

Of additional importance was the fact that the radular teeth stuck strongly to a magnet. That was the first clear, macroscopic, and easily reproducible effect of a magnetic field on a biological structure, and in one sense earns Heinz the title of father of biomagnetism. (This was actually a much simpler biomagnetic effect than Linus Pauling's 1933 discovery that deoxyhemaglobin is paramagnetic.) In his seminal 1962 paper reporting this discovery Heinz noted that chitons were known to have a local homing instinct, with individuals returning to their own preferred depressions in the rock during low tide. Interestingly enough he did not suggest explicitly in that paper that they might be using a magnetite compass as a navigational aid, but it is

clearly implied from the context. It is a pity that the paper was published in the *Bulletin of the Geological Society of America,* because not many biologists read it.

Numerous claims of apparent magnetic field sensitivity in animals had been made prior to 1960. Biophysicists, however, were vociferous in denouncing those studies for the simple reason that they knew of no plausible mechanism through which the weak magnetic field of the Earth could influence the diamagnetic and paramagnetic materials present in living organisms, and magnetic induction was too weak to be of use with an electrical detection system. Prominent neurobiologists had even stated flatly in print that there were no physiological ferromagnetic materials and hence, magnetoreception was impossible. Heinz's discovery of magnetite in the chiton teeth obviously undermined the basis of this biophysical argument (and paved the road for much of my research). Subsequent discoveries have confirmed the central role of magnetite as the biophysical transducer of the magnetic field in living organisms spanning the evolutionary spectrum from the magnetotactic bacteria to mammals, with a fossil record extending back at least 2 billion years on Earth and perhaps 4 billion years on Mars. (As of this writing the best evidence for ancient life on Mars is the presence of probable biogenic magnetite in the ALH84001 meteorite.) In the vertebrates, chains of uniform-size magnetite crystals, optimized for their magnetic properties, have been found recently in specialized cells connected to the ophthalmic branch of the trigeminal nerve; this nerve is now known as the main conduit of magnetic field information to the brain. This magnetite system is one of the few truly novel sensory modalities discovered in the past 50 years, and Lowenstam's discovery in the chiton teeth was the first hint that anything like this might be possible.

Rather than pursue the neurophysical aspects of the

magnetite discovery, Heinz wondered what other weird minerals living organisms might form. Within a few months he discovered goethite (γ-FeOOH) capping the teeth in another primitive group of mollusks, the Archaeogastropods. During the 1960s and 1970s the mineral list grew steadily beyond apatite, carbonates, and opal to include lepidocrocite, vaterite, ferrihydrite, weddellite, dahllite, and a variety of amorphous iron and phosphate minerals, to name a few. In addition Heinz began a systematic compilation of the phyletic distribution of these materials, as well as efforts to track the time of their evolutionary origin. In this process he made another fundamental observation concerning the biological processes that different organisms used to form biominerals—there was a clear spectrum of biological control. Some organisms actively direct every aspect of the mineral formation process, including chemical purity, crystallinity, crystal orientation, and crystal shape and size. By precipitating the minerals inside the cell they produce mineral products that are unlike anything produced inorganically. Because of the complex assemblage of biomolecules involved in this type of mineralization, Heinz termed this process "matrix mediated," or "biologically controlled," biomineralization. On the other hand some minerals simply form as an indirect result of biological activity, associated with metabolic by-products; these he termed "biologically induced." By standing back and looking both at the temporal distribution of fossil forms and their phyletic distribution, Heinz was able to observe new patterns in the data relating to the underlying biochemistry. Of particular importance was his observation that virtually all the mineral products that appeared nearly simultaneously in the Early Cambrian (the Precambrian-Cambrian boundary interval) in approximately 40 phyletic-level groups involved the use of calcium minerals (phosphates and carbonates).

In a seminal paper coauthored with Lynn Margulis in 1980 he noted that all of the requisite biochemical transport systems for this process had to have been present in the last common ancestor of all animals, as all eukaryotic cells rely on the precise control of calcium ion concentrations to regulate the mitotic processes (through microtubule polymerization) and for second-messenger systems. Hence, most of the difficult evolutionary prerequisites needed for the widespread biomineralization of evolving animal groups were already present long before something associated with the Cambrian Explosion (like a runaway predator/prey interaction) triggered the biomineralization cascade. This concept certainly is the foundation of a "grand unified theory" of biomineralization, which may help to unravel the complex genetics and biochemistry of biomedically important processes like tooth and bone formation.

Despite the pain and the suffering that Heinz experienced as a youth in Germany, California life and professional beachcombing calmed him. For many years after World War II he had severe aversions to all things German, including a sincere inability to speak the language and a strict injunction against traveling there. How could he? German citizens in his age group bore responsibility for the Holocaust that destroyed his family, even though his ancestors had lived in Germany for at least the previous 400 years. Those of us who knew Heinz well were therefore stunned when the Faculty in Munich presented Heinz with an honorary Ph.D. in 1980, *and he accepted it.* This apparently took several years of careful advance preparation by Lynn Margulis, Dolf Seilacher, and Wolfgang Krombine, who gradually managed to persuade Heinz that it would be a good signal to the younger German scientists who bore no responsibility for the errors of their parents. Even so, Heinz remembered the experience as troubling, particularly when

he saw elderly Germans catching the bus in Munich and wondering, "What were they doing during the war? Were they responsible?"

To Heinz's academic children he was a quiet intellectual giant who spoke with a soft Milwaukee-German accent, which for many years was muffled severely by the use of cigarettes. During class lectures we had to sit quietly near the front simply to hear him, but no one ever complained, as he was a stimulating and fascinating lecturer. In one episode in the early 1970s we counted no less than five cigarettes lit at the same time scattered along the chalk tray, as Heinz would become so excited and immersed in his subject that he would forget that he already had some lit. Even on his field trips—particularly those memorable excursions to Baja California shared with Leon T. Silver—Heinz would grab our attention for hours on end and amaze us with his ability to see subtle relationships between form, function, chemistry, and biology of natural and ancient ecosystems. In the evenings around the campfire under the protection of beautiful groves of California oak trees, he would tell us endless stories of the South Pacific, Palau, Japan, South America, and his childhood in a fractured and war-torn Europe. We at first thought most of these were fairy tales, until friends and family confirmed them later. Heinz inspired all of us to pursue our own intellectual interests wherever they would lead, with total disregard for personal fame, fortune, or personal safety. We miss him dearly.

Heinz is survived by three talented and caring women who shared his life, three children, many talented grandchildren, and many more academic offspring, including the present author.

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Clement L. Markert

CLEMENT LAWRENCE MARKERT

April 11, 1917–October 1, 1999

BY GERALD M. KIDDER

C LEMENT L. MARKERT DIED on October 1, 1999, in Colorado Springs, Colorado, at the age of 82. He and his wife, Margaret, had been living there since his retirement from North Carolina State University in 1993. Markert was born in Las Animas, Colorado, and grew up in the area around Pueblo. He and Margaret returned to "their mountain" near Westcliffe, Colorado, each summer. It was in their beloved mountain wilderness that he was laid to rest. Margaret joined him in death the following year. They are survived by three children: Alan, Robert, and Samantha (Betsy) Schreck.

A MAN OF IDEALS AND ACTION

Clement Markert was a man of ideals whose devotion to social causes was evident from early in his career. His father had been a steel worker, and the family had suffered during the Great Depression, when the mines and steel mills were closing. This experience undoubtedly influenced the development of Markert's social conscience. Grateful for scholarships awarded for his academic achievements, he enrolled in the University of Colorado at Boulder to study biology. At the same time, however, he was concerned about events on the world stage, especially what he perceived to

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be the failure of capitalistic economies to meet the needs of working-class people. He embraced socialism and even organized a communist group at the university. He was very soon presented with an opportunity to put his social ideals into more direct practice. Responding to the threat of fascist movements taking hold in Europe in 1938, he interrupted his studies and, along with his college roommate, rode freight trains to the East Coast, where the two men stowed away on a merchant ship bound for France. From there they joined the famous Abraham Lincoln Brigade, which was fighting the forces of Generalissimo Franco in Spain, hoping to prevent his toppling of the democratically elected government. Markert later explained that he had been one of the few members of his combat unit to survive the Spanish Civil War (his roommate was one of the casualties). In an obituary for Markert in *The New York Times* (October 10, 1999) he was quoted as having said in a 1986 interview, "I felt the most concrete thing I could do at the time was to destroy fascism, and Spain was the battleground on which to do that."

After the defeat of the anti-Franco forces Markert returned to the University of Colorado to complete his undergraduate studies. He was awarded a B.A. summa cum laude in 1940. In that same year he married Margaret Rempfer, who was to be his partner for life. The couple moved to California so that Markert could do graduate work at the University of California, Los Angeles, where he conducted research in vertebrate embryology; however, world events again intervened. The United States became involved in World War II, and Markert chose to reactivate his personal fight against fascism. He took a master's degree in 1942 to terminate his graduate education and tried to enlist in the U.S. Army. Not surprisingly, given the political climate of the time, his previous associations with American

and Spanish communists, who had also been fighting against Franco, made him unacceptable for military service. In response to this setback he moved to San Diego to serve as a dockworker until being accepted into the merchant marine. He served out the war as a radio operator on a ship supplying U.S. forces in the Pacific.

When his war years were finally behind him, Markert enrolled in the doctoral program in biology at Johns Hopkins University, where he conducted research under the mentorship of one of the country's foremost developmental biologists at the time, Benjamin H. Willier. After earning the doctorate in 1948 he completed his research training as a Merck-NRC postdoctoral fellow at the California Institute of Technology. There he specialized in biochemical genetics under the influence of George W. Beadle, the foremost proponent of that emerging field.

A MAN OF INTEGRITY AND COURAGE

Markert's first independent academic appointment was at the University of Michigan in Ann Arbor, where he accepted an assistant professorship in the Zoology Department in 1950. He became the intellectual leader of a group of junior faculty who were in tune with the recent advances in biochemistry and genetics that led in 1953 to Watson and Crick's publication of the structure of DNA. The Markert family, which by this time included all three children, settled into the pleasant life of the Ann Arbor academic community, and it seemed that Markert's earlier life as a social activist was a thing of the past.

This notion was shattered in 1954 when Markert and two colleagues were called before a subcommittee of the House Un-American Activities Committee meeting in East Lansing, Michigan. The subcommittee, chaired by Michigan Representative Kit Clardy, was mandated to identify

and root out communists from academia. Those who were targeted by the committee were threatened with being exposed as communists unless they named their former associates who might be considered communists or sympathizers. The three men declined to cooperate, refusing to name anyone. As a consequence all three were suspended from their positions with the university, which set up review committees at various levels to examine their cases. Markert was the only one of the three who was reinstated. According to David Nanney, a departmental colleague of Markert's at the time, Markert survived the ordeal because of support from his academic colleagues, who were convinced of his personal integrity, as well as scientists elsewhere (including George Beadle) who were impressed with Markert's scientific acumen and wrote letters on his behalf. Markert would later relate this experience to his students to emphasize the importance of standing up for one's convictions, whether scientific or political, regardless of the cost. Years later the university invited the three men back to Ann Arbor to receive an apology for the way they had been treated.

The controversy surrounding Markert's youthful socialist activism did not end there. In 1957 he applied for the position in developmental biology at Johns Hopkins that was being vacated by his retiring mentor, Professor Willier. When the search committee recommended Markert's appointment, administrative resistance developed. Markert had made no secret of his past; indeed, he was proud of it! The impasse was resolved when, after interviewing Markert himself, the president of the university, Milton Eisenhower (brother of the President), recommended Markert's appointment as a full professor and threatened to resign if the appointment was not confirmed. Markert accepted the position and remained at Hopkins until moving to Yale University in 1965 to become chair of the Department of Biol-

ogy. Once again Markert took pains to ensure that Yale's president at the time, Kingman Brewster, was fully aware of his past and his intention to remain involved in social causes. During the late 1960s Markert was an outspoken opponent of the government's continuing involvement in the Vietnam conflict and took an active role in public protests. Other causes that received his outspoken support included affirmative action to promote women in academia and the "Zero Population Growth" campaign (his car license plate for a time was ZPG). Through this entire advocacy, as always, Margaret was by his side. Indeed, Markert attributed much of his confidence during those difficult times in Michigan to the knowledge that his wife would be able to cope with whatever hardship his political activism brought upon them.

MOST NOTABLE SCIENTIFIC CONTRIBUTIONS

Throughout his career Markert aimed high: He wanted to tackle the big questions in biological science, questions like how genes control development and how the genome of an organism can be manipulated to bring about genetic improvement. In many cases answering such questions required the development of new research techniques. His scientific contributions covered a wide range from biochemistry through developmental and reproductive genetics.

Markert was best known early in his career for elucidating the importance and structural basis of isozymes, multiple molecular forms of enzymes. The stage was set for that work when in 1957 Markert and his University of Michigan colleague, Robert L. Hunter, combined enzyme histochemistry with the starch gel electrophoresis technique newly developed by Oliver Smithies to show that there are more than 10 separable forms of esterases in mouse liver (Hunter and Markert, 1957). Using different substrates or inhibitors

in the histochemical staining reaction, they obtained evidence that the different esterase bands in the gel were enzymatically distinct. The same technique but using different histochemical reagents also revealed multiple forms of other enzymes, demonstrating that this phenomenon is not limited to esterases. The investigators termed their stained gel, showing multiple bands representing the same enzymatic function, a zymogram. In a subsequent paper communicated to *Proceedings of the National Academy of Sciences* by Benjamin Willier, Markert and Freddy Møller used the zymogram technique to show that the number of molecular forms of lactate dehydrogenase (LDH) in mammalian tissues is greater than had been appreciated and proposed the term isozyme to denote these forms (Markert and Møller, 1959). They also showed that tissues differ in the number of LDH isozymes they contain and their relative proportions. Most importantly, their data made it clear that the isozyme patterns of embryonic tissues change through ontogeny until the tissue-appropriate adult pattern is achieved, a phenomenon that was interpreted as indicating changes in gene expression related to cell differentiation. This insight into the utility of isozyme studies for understanding developmental mechanisms was to influence Markert's research for years to come. Møller, a Dane who had been trained in veterinary medicine before joining Markert's lab (by then at Hopkins), later credited the excitement of those days with his decision to make research his career. Markert's insights into the importance of differential gene activation during development provided a new way of looking at abnormal development as well, and he was one of the first to point out that diseases such as cancer can be viewed as cell differentiation gone awry (Markert, 1968).

As important as it was, Markert and Møller's 1959 paper

left unexplained the molecular basis of isozymes. There was little appreciation at the time of the existence of gene families, evolutionarily related genes encoding proteins of similar or overlapping function. Yet Markert and Møller did offer that as one explanation, citing the multiplicity of genes encoding fetal and adult hemoglobins. They also suggested that a single gene might somehow encode an array of isozymes differing in "structural variations," a concept that seems to presage our current understanding of alternative mRNA splicing and post-translational protein modification. It was several years later, through the efforts of Ettore Appella, an Italian postdoc, that the Markert laboratory finally came to a clear understanding of the molecular basis of LDH isozymes. By treating the enzyme with denaturing agents it was learned that LDH is a tetramer of two types of polypeptide chains (Appella and Markert, 1961). Thus the multiple-gene hypothesis was partially correct: Two different LDH subunits, each encoded by a distinct gene, re-sort themselves in various tetrameric combinations to give rise to five different isozymes (Markert, 1963). During the succeeding years Markert and his students and postdocs continued to study the molecular basis and biological significance of isozymes and showed how the study of isozymes could contribute to our understanding of the biochemical variation that underlies cell differentiation and evolution. The culmination of this work was the new perspective presented in a *Science* paper (Markert et al., 1975) entitled "Evolution of a Gene," coauthored with former graduate students James B. Shaklee and Gregory S. Whitt. Markert took particular pride in his role in elucidating the isozyme concept, not least because this was a case of a developmental biologist teaching something about biochemistry to the biochemists. For several years he served as editor or coeditor of the multivolume

series "Isozymes" that emanated from the annual International Congress on Isozymes.

Markert's predilection for tackling the big questions sometimes caused problems for the person in his laboratory who was taking the lead on a project. For example, one idea that was tested during Markert's Hopkins years was that the program of gene expression within a cell is dictated by the constellation of nuclear proteins interacting with its DNA. If so, then it was hypothesized that introducing nuclear proteins from another source should reprogram a cell's genetic machinery. This was tested by injecting liver nuclear proteins into fertilized frog eggs with the expectation that the embryos would develop characteristics of liver cells. Instead the embryos arrested their development, and little was learned from the experiment despite exhaustive attempts to analyze the embryos using the techniques of the day. Markert was later criticized for investing resources and student time in such a simple-minded approach to a very complex problem, but if the experiment had worked at least partially, it would have been a major step forward.

Shortly after moving to Yale, Markert's laboratory became involved in a new research topic that was to have an impact at least as important as that of the isozyme concept. Yoshio Masui, a young scientist from Konan University in Japan, arrived at Yale in 1966 on sabbatical leave to study biochemical aspects of cell differentiation and development. Masui had become intrigued by Markert's view of development as emanating from differential gene activation and wanted to contribute to the elucidation of that concept. He began working on LDH isozymes in penguin embryos, characterizing their changing expression patterns during development. After less than a year, however, Masui came to the conclusion that the complexity of regulation of even a single enzymatic function during development was too great to be

elucidated by the technology available in the 1960s. He wanted a more tractable problem to work on. Markert encouraged him to choose a project of his own interest, one that he could continue working on after returning to Japan.

Masui decided that to understand cell differentiation it would be advantageous to study an unambiguous cell change induced by a well-defined external signal. Remembering the classical experiment by Heilbrunn et al. (1939) in which oocytes were induced to be released from frog ovaries treated in vitro with a pituitary gland suspension, Masui reasoned that this must be an example of a developmental induction evoked by a hormone. He was impressed that a hormone could act directly on its target tissue in vitro. Furthermore, Masui realized that hormonal induction of meiotic maturation and ovulation of the frog oocyte could provide a highly advantageous system for studying the control of cell cycle events: It would allow the investigator to use distinct stimuli to induce oocyte maturation (response to the hormone) and egg activation (cleavage in response to fertilization), thus separating the signals that drive the cell cycle from G2 to M phase and from M to G1 phase, respectively. He hoped in this way to develop a research program in nucleocytoplasmic interactions that he could continue in Japan, where research resources were not as plentiful at the time, taking advantage of the ability to obtain large numbers of synchronous frog oocytes for biochemical analysis. For his part Markert was enthusiastic about that line of investigation, because he had often mused about the possibility of suppressing meiosis in oocytes as a route to parthenogenesis. Masui's proposed experiments were seen as an early step along that road, since they could reveal how meiosis is controlled (Masui, 2001).

In early 1967 Masui started research on oocyte matura-

tion by repeating Heilbrunn's classical experiment using *Rana pipiens*. His experiments eventually led him to conclude that pituitary gonadotropin acts on the follicle cells of the ovary to stimulate them to release a progesterone-like hormone that directly acts on the oocyte. Further work revealed that progesterone could have an effect only when it acted from the outside of the oocyte or on the cell surface, leading him to propose that the oocyte cytoplasm carries the hormonal signal to the oocyte nucleus to induce the first meiotic division. To test this hypothesis Masui injected the cytoplasm of oocytes induced to mature by progesterone into immature oocytes and found that these oocytes were induced to mature without hormone treatment. That was the now famous experiment that demonstrated the presence of a cytoplasmic factor, which Masui and Markert called *maturation promoting factor* (MPF), that caused oocyte maturation by triggering meiosis (Masui and Markert, 1971). Using the same bioassay it was shown that MPF appears before the oocyte enters M phase, but declines when the oocyte proceeds to G1 phase after fertilization. Masui also demonstrated that maturing oocytes contain another factor, named cytostatic factor (CSF), that is responsible for the arrest of oocyte meiosis until fertilization. The manuscript reporting these exciting results (Masui and Markert, 1971) was published shortly after Masui moved to the University of Toronto, where he is still working. It was the first significant step in understanding how cell division is controlled. That work was followed by research in other laboratories studying cell cycle regulation in yeasts, where the power of genetics was used to identify specific molecules having the properties of MPF and CSF. Today we know that MPF, more generally known as *M-phase promoting factor*, is a complex of cyclin B2, a regulatory protein that is synthesized and then destroyed in each cell cycle, and Cdc2, a

catalytic protein that promotes entry into M phase. CSF is a Mos protein-containing complex that acts to prevent cyclin B2 degradation, thus maintaining the cell in M phase (Duesbery and Vande Woude, 2002). The importance of Masui and Markert's 1971 paper was recognized in 1992 with the awarding of the prestigious Gairdner Award (<http://www.gairdner.org/>) to Masui along with Leland Hartwell and Paul Nurse, two of the scientists whose work in yeasts had identified genes involved in cell cycle regulation. In 1998 the Lasker Foundation (<http://www.lasker foundation.org/>) recognized the same three scientists with the Lasker Award; but in 2001, when the Nobel Prize was awarded for contributions to understanding the cell cycle, the winners were Leland Hartwell, Paul Nurse, and Tim Hunt, the last of whom had discovered the cyclins in his work with rapidly dividing embryos. Many of Masui's students and colleagues, particularly those who had shared in the excitement of his discoveries while working alongside him in Markert's laboratory, were deeply disappointed at his being omitted from receiving the ultimate science prize.

In the final phase of his research career at Yale, Markert turned the attention of his laboratory to early mammalian development, a field that had lagged behind other areas of developmental biology until techniques were developed to allow experimentation with embryos developing outside the womb. He undertook an ambitious project that was ahead of its time for its sheer boldness: the production of a homozygous diploid mouse. His approach was to remove one pronucleus from a fertilized egg, a very delicate procedure, and then suppress the first mitotic division to restore the diploid condition in the remaining pronucleus. Markert saw homozygous diploidy as an indirect route to cloning, since the offspring of successive generations produced in the same way would theoretically be identical. Homozygous diploid

blastocysts were obtained by this procedure, but none survived to term after transfer to foster mothers (Markert and Petters, 1977). Soon afterward another team of researchers claimed to have succeeded with the same procedure (Hoppe and Illmensee, 1977). Those results have not been replicated. The current view, based on a large body of data, is that differential epigenetic modification of sperm and egg genomes precludes normal post-blastocyst development when the embryonic genome is derived from a single parent. Markert lived just long enough to see mammalian cloning, now performed by nuclear transfer into enucleated oocytes, become a reality (Wilmut et al., 1997).

Markert and postdoc Robert Petters did succeed with another technically demanding experiment: the production of hexaparental chimeras, mice made up of cells from three different embryos having different genotypes (Markert and Petters, 1978). They then repeated the experiment with four different embryos, producing octaparental mice (Petters and Markert, 1980). This result proved that at least four embryonic stem cells of the early embryo give rise to the fetus. Pictures of those hexaparental mice are still featured in developmental biology textbooks. At the same time, a graduate student in Markert's laboratory, Vijay Thadani, was showing that rat oocytes can be fertilized by sperm of other mammalian species if the sperm are injected directly into the oocytes (Thadani, 1980). This experiment demonstrated that fertilization can occur without the normal processes of sperm activation, penetration of the zona pellucida, and sperm-oocyte binding, processes that are sometimes defective in infertile men; it presaged the now widely used technique of intracytoplasmic sperm injection (ICSI) as a treatment for male infertility.

Ever the adventurer, Markert was eager until the end of his active research career to tackle the most difficult and,

as he saw it, the most important biological questions. After retiring from Yale he finished his career as Distinguished University Research Professor in Animal Science and Genetics at North Carolina State University.

SERVICE TO SCIENCE

Markert believed that scientists have an obligation to do their share of administrative work and to serve on volunteer boards and committees for the good of the scientific enterprise. In addition to serving as chairman of the Department of Biology at Yale (1965-71) he was director of the Center for Reproductive Biology (1974-85). He was managing editor of *The Journal of Experimental Zoology* (1963-85) and coeditor (with John G. Scandalios) of *Developmental Genetics* (1979-92). He served terms as president of the American Institute of Biological Sciences (1966), American Society of Zoologists (1967), and the Society for Developmental Biology (1973-74). Agencies and institutions that benefited from Markert's advice as a board member included the Bermuda Biological Station (1959-83), President's Biomedical Research Panel (1975), American Cancer Society (1976-78), Bioscience Information Service (1976-81), La Jolla Cancer Research Fund (1977-86), National Research Council (1979-83), Jane Coffin Fund for Medical Research (1979-87), American Academy of Arts and Sciences (1981-84), and the Federation of American Societies for Experimental Biology (1987-93). As a member of the National Academy of Sciences he served on several committees and was elected to the Academy's governing board, the Council.

MARKERT AS TEACHER AND MENTOR

Markert was a superb teacher whose lectures were legendary among undergraduates. Like his research interests, his lectures emphasized the big questions. He taught a course

at Yale entitled "Biology of Reproduction" that covered, in addition to the important biological principles, hot-button issues of the time such as overpopulation and abortion rights. The course also presented cutting-edge reproductive technology, including actual production of chimeric mice. Markert returned to Yale for several years after his mandatory retirement to give lectures in the course that he had pioneered.

For many of us who trained with Clem Markert, our memories are as much about the culture of his laboratory as about the science that was done. Graduate students even more so than postdocs were given free reign to choose their own research topics and to pursue them more or less independently, the only requirement being that any project needed to fit within the broad scope of Markert's research interests, which was certainly not difficult. In the late 1960s, for example, research in the Markert laboratory ranged from LDH isozymes in various species through maturation and fertilization of frog and mouse oocytes to ribosomal gene redundancy and the molecular biology of molluscan development. Given the independence with which graduate students pursued their research, Markert usually declined to add his name to their publications; he did, however, receive explicit acknowledgement for financial support of the work and his mentorship. Despite his heavy administrative responsibilities he was often available to talk with individual trainees without prior appointment and, unless he was traveling, could be expected to sit down to a bag lunch with laboratory members on a daily basis. In addition to science, the conversations often focused on history (the American and Russian revolutions, for example), politics (a topic on which Markert was never hesitant to share his views), and even religion. An avowed atheist, Markert nonetheless was knowledgeable about and respected the beliefs of his trainees and colleagues. Whether his trainees agreed with him

or not they knew they were being mentored by a man of superior intellect and strong social convictions who was willing to put his life and career on the line for what he believed in. That, most of all, was Markert's legacy.

THIS MEMOIR COULD not have been compiled without the assistance of former students and colleagues of Clem Markert. I am especially indebted to Richard Elinson, Yoshio Masui, David Nanney, Robert Petters, George Seidel, Vijay Thadani, and Gregory Whitt for providing documentation and commentaries pertaining to Markert's life and career.

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PETER MEYER

January 6, 1920–March 7, 2002

BY EUGENE N. PARKER

PETER MEYER WAS AN experimental physicist who devoted his career to the mysterious origins and behavior of the cosmic rays, contributing substantially to present knowledge of the diverse components of the cosmic rays. He was a friend and colleague whose presence made the day more interesting and the difficulties less onerous. He was a devoted family man. He and his first wife, Luise Meyer-Schützmeister, a prominent nuclear physicist, were enthusiastic skiers, campers, and mountain hikers. Music was a continuing passion. He was an excellent cellist and Luise a pianist. They participated in regular chamber music evenings at their home, for their own pleasure and for the pleasure of those privileged to join in or merely to listen. Luise died in 1981, and Peter married Patricia Spear, a microbiologist, in 1983. Peter and Pat actively pursued their common interest in music and the outdoors and traveled widely, in addition to working intensely on their respective research interests. These many intense activities seemed only to refresh him for his continuing scientific assault on the elusive cosmic rays. Peter had to give up many of his activities during the last few years of his life due to illness, but he did so with grace and style and continued to engage his friends and family with his wit and humor.

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Peter Meyer was born in 1920 in Berlin. He studied at the *Technische Hochschule* Berlin with the famous physicist Hans Geiger as one of his teachers. His *Diplom Ingenieur* thesis in 1942 dealt with proportional counters. As the son of a Jewish physician and German mother he was denied the "honor" of fighting for the fatherland, with the result that he survived the war as a factory worker. His father also survived, thanks to the efforts of some of his patients.

After the war Meyer continued his studies in physics at the University of Göttingen. He obtained his Ph.D. in 1948 under the direction of Wolfgang Paul (Nobel Prize in physics in 1989) and Hans Kopfermann with a precise measurement of the binding energy of the deuteron (1949). He continued working in experimental nuclear physics at Göttingen, with a year at the Cavendish Laboratory at Cambridge University (1950). Then from 1950 to 1953 he was a staff scientist at the Max Planck Institute for Physics in Göttingen.

In 1953 Meyer came to the United States and accepted an invitation from John Simpson to work in the pursuit of cosmic rays as a research associate in the Institute for Nuclear Studies at the University of Chicago. His scientific prowess as an experimentalist was soon appreciated at Chicago, and he was appointed assistant professor in the Institute for Nuclear Studies (now the Enrico Fermi Institute) and the Department of Physics in 1956. He was promoted to associate professor (tenure) in 1962 and professor in 1966. Meyer remained at the University of Chicago for the rest of his scientific career, becoming emeritus in 1990.

It was my good fortune to make Meyer's acquaintance when I arrived in Chicago in 1955 to work with John Simpson on the theoretical implications of the cosmic-ray variations that Simpson and Meyer were observing. Meyer's two sons, Stephan and Andreas, were born in about the same years as my daughter and son, and the children were soon acquainted

through our socializing. It was Peter's performing with his cello that encouraged my daughter to take up the violin and my son the cello. Peter was supportive of their musical activities, even to the extent of locating an excellent old cello in Germany and traveling by plane back to Chicago accompanied by the cello in a monster carrying case. This was but a small sample of his relationships with the younger generation. He was a sympathetic mentor and supportive friend of his many Ph.D. students over the years.

Meyer worked with John Simpson in pursuit of the mysterious time variations of the cosmic-ray intensity. It must be understood that the term "cosmic rays" is a generic term for the ionizing radiation coming down through the atmosphere of Earth. When Meyer began his professional career in 1948, it had just been established that the top of the atmosphere is continually bombarded from space by energetic protons, accompanied by a smaller number of heavier nuclei with speeds up to that of light. The impact of these energetic protons on the nuclei of the air atoms near the top of the atmosphere produces π mesons (quickly decaying to μ mesons) and gamma rays and leading to electrons, positrons, antiprotons, neutrons, and more secondary protons, which all come showering down through the atmosphere. These particles ionize ambient air atoms along the way. Indeed, it was the discovery of the slight but ubiquitous ionization of the air in the laboratory a century ago that led to the recognition of the cosmic rays. In 1912 the Austrian physicist Victor Hess ascended in a balloon to a height of several thousand feet to find that the ionization increases dramatically with altitude, thereby demonstrating that the ionization is caused by something from outside the atmosphere. The alternative explanation had been the recently discovered natural radioactivity of the rocks and soil, whose effects would diminish rapidly upward from ground level. With

the external origin of the ionization the term *cosmic rays* was coined to refer to whatever was responsible. And after many years of speculation as to the precise nature of cosmic rays, they turned out to be mostly energetic protons. Over the last half century it has been established that the protons are accompanied by small numbers of heavier nuclei and by a few electrons, positrons, and antiprotons. Protons are not rays, of course, but the terminology "cosmic rays" survives nonetheless. We are, after all, creatures of habit.

The studies of cosmic rays moved forward rapidly after World War II with the advance of technology (e.g., high resolution nuclear emulsions and sophisticated electronic detectors). Over the course of his career Meyer designed many innovative instruments to explore the energy distributions of both the major and minor components among the cosmic-ray particles.

Simpson recognized that time variations of the cosmic-ray intensity, often correlating with solar activity, were somehow a consequence of conditions in space. Lacking spacecraft in those days to carry instruments into space for a direct look, he sought to use the cosmic-ray variations as a probe of those conditions. The idea was to obtain quantitative measurements of the dependence of the time variations on the energy of the protons, so that various speculations on electric fields in space or modifications of the geomagnetic field or, whatever, could be tested and confirmed or ruled out. Thus, besides the five neutron monitor stations set up by Simpson at geomagnetic latitudes from 0° to 60°, Simpson and Meyer exploited the magnetic field of Earth as a spectrometer with extensive north-south flights with neutron monitors, etc., in aircraft supplied by the U.S. Air Force. They also launched many balloon-borne instruments to the upper atmosphere (~100,000 ft) to connect the ground measurements of the cosmic-ray intensity to the intensity at the

top of the atmosphere. The gigantic cosmic-ray flare on the Sun on February 23, 1956, was a lucky event in this respect, showing the direct arrival of energetic protons from the Sun, followed by a slow decline, indicating that the inner Solar System is open out to about the orbit of Mars and enclosed by magnetic fields beyond (1956). Together with the energy dependence of the day-by-day time variations inferred from the neutron monitor stations, it became clear that the variations of the cosmic rays could be a consequence only of time-varying magnetic fields in interplanetary space, implying that space was filled with plasma (ionized gas) strongly influenced by solar activity (1959).

They showed that the occasional abrupt Forbush decrease in the cosmic-ray intensity, discovered by Forbush with ionization chambers some years earlier, extended to energies of 20-30 GeV and could be understood only in terms of broad domains of magnetic field in interplanetary space. These revelations set the intellectual stage for the construction of the theoretical solar wind concept in 1958.

The space age was beginning at about this time, and Meyer collaborated with Simpson in studies of the outer Van Allen radiation belt. The outer belt is fed by fast particles from the Sun and by the decay of neutrons produced by the cosmic-ray proton bombardment of the terrestrial atmosphere. The distribution of the trapped particles is continually modified by diffusive losses and by azimuthal drift of the particles in the active geomagnetic field. The structure and behavior of the outer radiation belt was a challenge to experimentalists and theoreticians alike. The studies carried out by Simpson and Meyer (1961) showed that electrons were sometimes accelerated in place, and, during times of large variations in the outer magnetosphere, the particles were carried with the displaced magnetic field.

While this work was going on, Meyer was thinking about the still undetected electron component of the cosmic rays, estimated to make up perhaps one in a hundred of the cosmic-ray particles at any given particle energy. The detection of these rare relativistic electrons among the numerous protons was quite a challenge to the ingenuity of the experimentalist for two reasons. First, an occasional proton produces a signal in the detector that mimics the signature of an electron, and second, it must be ascertained that a detected electron comes from somewhere out in space and is not produced as a secondary particle in the upper atmosphere. Thus, a sophisticated detector system is required and must be flown at high altitude on stratospheric balloons.

The successful electron detection was reported by two teams just a couple of weeks apart. First, James Earl of the University of Minnesota succeeded by visualizing the characteristic showers generated by electrons in a multiplate cloud chamber flown on balloons. Peter Meyer with his graduate student Rochus Vogt developed a purely electronic detector system. The range of the electron shower, and hence the electron energy, was measured in a sandwich of alternating layers of lead and plastic scintillators; backward-moving particles, or interacting protons that could simulate shower signals, were excluded by analyzing the signals in two NaI scintillators above and below the sandwich. The contribution of secondary electrons generated in the atmosphere could be determined as the instrument ascended toward the top of the atmosphere. One would expect that the intensity of downward-moving secondary electrons would decline in proportion to the declining air mass overhead. However, the measured electron intensity reached a constant value before the balloon approached its maximum altitude, with only 3-5 g/cm^2 of air left overhead. This clearly indicated a flux of cosmic-ray electrons arriving from space.

Meyer and Vogt measured 4×10^{-3} incoming electrons/ cm^2sec sr in the energy range 100-1000 MeV (1961), to be compared with about 300×10^{-3} protons/cm^2 sec sr in the same energy range. So there was indeed an electron component of the cosmic rays, of the same general magnitude as estimated from the observed nonthermal synchrotron radio emission from the Galaxy.

Meyer and Vogt were able to show how the electrons varied through a Forbush decrease (1961), receiving the same modulation as the cosmic-ray protons, thereby showing that the electrons originated outside the Solar System. They were soon able to identify the temporary increases of energetic electrons produced by solar flares (1962).

The next step after the measurements of the cosmic-ray electrons was the question of the cosmic-ray positrons (the anti-electrons) among the cosmic rays. Cosmic-ray electrons and positrons must be produced throughout the Galaxy in about equal numbers by the occasional collision of high-energy protons with the nuclei of atoms in interstellar space. In fact, for positrons this secondary process must be the predominant production mechanism, while electrons might also be accelerated from a sample of "ordinary matter," just like the protons and other nuclei. Thus it would be interesting to measure the abundance of positrons relative to electrons. Again the experimental difficulties are that the positron intensity is much smaller than the protons, and positrons are produced in great numbers by the proton collisions with the nuclei of the atmosphere and collisions with the instrument itself. After the electron studies were well in hand Roger Hildebrand related how Meyer asked him one day what he thought it might take to distinguish the positrons. Hildebrand replied that it would require a whole physics laboratory to go up with a balloon to the top

of the atmosphere. Meyer smiled and said, "Why don't we give it a try?"

Positrons differ from electrons in their opposite electric charge, of course, so the electron-positron separation could be accomplished with a suitable magnetic field. Meyer and Hildebrand developed a sophisticated instrument much along the lines of the electron detector but with a strong magnetic field between the poles of a permanent magnet, through which the particles had to pass if they were to be recorded. The electrons were deflected one way by the magnetic field and the positrons the other. They used spark chambers instead of NaI scintillators, and the system was again enclosed in guard counters so as to be sensitive only to particles from above. The Meyer-Hildebrand collaboration led to a clean separation and measurement of the positrons and electrons as a function of energy (1965). Very roughly, they found that there were far fewer positrons ($\sim 10^{-1}$) than electrons over the energy range 40-3000 MeV. As the positrons are produced by collisions of cosmic-ray protons with the nuclei of the ambient interstellar gas, their relative number provides a measure of the amount of matter through which the cosmic-ray protons have passed while being accelerated in their sources and subsequently in their passage through interstellar space before arriving at the Solar System. The surplus of electrons over positrons shows that there must be cosmic accelerators that produce the electrons directly, perhaps together with the protons and nuclei that constitute the majority of the cosmic rays.

The next few years were devoted to improving the systems detecting the electrons and positrons, with an eye to obtaining the combined energy spectrum of electrons and positrons up to several hundred GeV. Gas Cerenkov counters and time-of-flight measurement techniques were introduced to reject background protons and were combined with mas-

sive shower counters to analyze the electron cascade in detail. The instruments were calibrated at laboratory accelerators (e.g., at the Stanford Linear Accelerator Center) (1968, 1972, 1973, 1974, 1976).

Meyer advanced the particle detection technology to do a number of other measurements. One interesting episode was the detection of the electrons from the Jupiter electron beacon. Simpson et al. and Teegarten et al. had found, from particle detectors carried on spacecraft out to the general vicinity of Jupiter, that Jupiter emits a powerful burst of relativistic electrons once each 10-hour rotation period. These electrons can be detected at distances up to 1 AU or more and can be identified by their precise period of recurrence. Jupiter orbits the Sun at a distance of 5 AU, and the electrons dash from Jupiter along the spiral magnetic field in interplanetary space. Working with Jacques L'Heureux and using the electron detector on the OGO-5 spacecraft, they found that when Earth was passing through the spiral magnetic lines of force connecting out to Jupiter, Earth was bathed in the electrons from the Jupiter beacon, no longer clearly pulsing but occurring only when the field connects Earth to Jupiter.

At the same time Meyer and Dietrich Müller became interested in the composition of cosmic-ray nuclei at high energies. With graduate student E. Juliusson they designed a new detector system to measure the abundances of heavy nuclei at energies above 10 GeV/nucleon (1972, 1974, 1975, 1978). The essential point is that cosmic rays presumably consist of ordinary matter in an ionized state when the matter is caught up in the acceleration process and the individual particles are hurled away at nearly the speed of light. Thus, determining the precise relative abundances of the different elements among the cosmic rays tells us something about where the cosmic rays were accelerated. As had

already been observed at lower energy, they found the relative abundances of the nuclei to be more or less along the lines of the standard cosmic abundances determined from meteorites, etc, except for such nuclei as Li, Be, and B. These nuclei are rare in the general cosmos because they are burned up quickly in stellar interiors.

Most of the matter in the Galaxy (including ourselves) has been processed through one or more massive stars, as indicated by the general presence of the heavier nuclei C, N, O et al. synthesized in the late stages of evolution of the individual massive star. Thus when the matter is dispersed by the supernova explosion at the end of the short life of the massive star, the matter is sent on its way with C, N, O, etc., but very little if any ^{2}H, ^{3}He, Li, Be, and B. On the other hand it was found that cosmic rays contain substantial amounts of these otherwise rare nuclei. The explanation is that these nuclei are spallation products (i.e., chunks of heavier nuclei C, N, etc., among the cosmic rays knocked off by a collision with the nucleus of an atom or ion of the interstellar gas). On this basis one could determine that the cosmic rays have passed through about 7 gm/cm^2 of interstellar matter. The discovery by Meyer and colleagues was that the Li, Be, and B became less abundant with increasing energy above about 10 GeV/nucleon. This indicates a shorter path length and consequently shorter life in the Galaxy with increasing energy of the heavy cosmic-ray nuclei. It shows that the cosmic rays are not gradually accelerated by reflections from the magnetic fields of moving interstellar gas clouds. The gradual acceleration was originally suggested by Fermi as a possible origin of the cosmic rays. The gradual acceleration predicts that the particle energy increases with the time spent in the Galaxy. Instead the measurements require that the cosmic rays be accelerated to their final energies in some initial short-lived event

(e.g., a supernova explosion or supernova remnant). The more energetic cosmic-ray particles seem to be able to escape sooner from the magnetic fields of the Galaxy, so they generate fewer spallation nuclei.

Meyer and Juliusson subsequently extended the measurements beyond Fe, covering atomic numbers up to 36, the very heavy nuclei (1975). They found the relative abundances among the very heavy cosmic-ray nuclei to parallel the normal cosmic abundances, further supporting the idea that the cosmic rays originated from ordinary cosmic matter that just happened to be hit by an exploding supernova or other catastrophe.

One of the more exciting results in the next few years was the direct observation of the particles accelerated by shocks in interplanetary space created by an outburst associated with a solar flare. (We would recognize the shock today as the result of a coronal mass ejection at about the same time as the flare.) A flare often produces a burst of fast particles, sometimes called solar cosmic rays, although their numbers diminish more rapidly with increasing energy than the true galactic cosmic-ray particles, and the relative abundances of the nuclei show a strong enhancement of elements with low first ionization potential. Meyer, assisted by Paul Evenson and S. Yanagita, found a population of nuclei accelerated in interplanetary space within the shock wave from an explosive event on the Sun (1982). A little later accelerated electrons were found as well (1985). The measurements demonstrated again the remarkable efficiency of nature to accelerate nuclei to high energy. Nothing more than the common shock front is needed. Indeed it is now believed that the shock front is probably the universal particle acceleration mechanism, because little else shows promise for converting so large a fraction of the bulk kinetic energy into fast particles.

Another result was the detection of the energetic protons produced by the decay of neutrons created by flares on the Sun. The vigorous acceleration of nuclei (mostly protons) to high energy in flares bombards the Sun and provides many nuclear reactions in the solar atmosphere below the flare, emitting gamma rays and neutrons, etc. The gamma rays can be observed directly, of course. The neutrons, equally free to escape from the magnetic fields of the flare, do not get as far as Earth (8 light minutes from the Sun) because their speeds are only about a tenth of the speed of light and they enjoy only a 15-minute half-life. They decay into protons of the same kinetic energy, which then channel along the spiral interplanetary magnetic field and can be detected whenever a suitable particle detector meets that spiral. Detection at Earth requires only that the neutron have a direct spiral line of communication to Earth at the time it decays, perhaps having come from a flare on the back side of the Sun (1983, 1984, 1990).

Inasmuch as cosmic rays are observed to extend up to energies above 10^{20} eV/nucleon (from unknown sources) it was clearly desirable to extend the work on the relative abundances of the cosmic-ray nuclei to above the 100 GeV/nucleon region achieved in the work already cited. However that extension required new technology. The number of cosmic-ray particles in a given energy interval declines with increasing particle energy E approximately as E^{-n} with n lying somewhere in the interval 2.7 to about 3, depending upon E. It is obvious then that to go to higher energies means far fewer particles among the general background of cosmic rays. That is to say, the background "noise" becomes deafening. Meyer with Müller and others came up with the idea of looking for very energetic nuclei using the transition radiation produced as the nuclei pass from air into a transparent solid and from the solid into air. The transition

radiation is very weak but increases rapidly as the speed of the particle approaches the speed of light. Thus an instrument detecting the passage of energetic nuclei by their transition radiation fades out for particles below about 100 GeV/nucleon (traveling at a speed of 0.99995c, where c is the speed of light). That is to say, a transition radiation detector would be deaf to most of the background noise, but it would begin to respond to nuclei of 100 GeV/nucleon or more. Even so, the instrument would have to be large, to intercept enough of the very-high-energy particles and then to pass the particles through enough air-plastic interfaces to get a detectable signal.

The result was the "Chicago Egg," which was flown on Spacelab 2 on the space shuttle. Designed and built by Meyer and Müller, the Egg was 9 feet in diameter and 12 feet high. The instrument was enclosed in a welded aluminum tank: the shell of the egg. Inside the shell the instrument consisted of scintillation counters, to define and delimit the paths of the cosmic rays that it recorded. The heart of the instrument was the large volume of commercial polyolefin fiber forming the transition radiation generator. The essential aspect of the generator was that the individual high-energy cosmic-ray particle should pass through many air-plastic interfaces, producing transition radiation at each interface, and that the transition radiation not be absorbed by the plastic fibers. The transition radiation was soft X rays and was detected in xenon-filled proportional chambers interspersed between layers of fiber material. The whole thing weighed 2.5 tons and cost about $10 million. The size was limited by the cargo bay of the shuttle, and the Chicago Egg flew on the *Challenger* in 1985 for several days' exposure to the cosmic rays. During that time it acquired the most detailed data ever obtained on the composition of cosmic rays at extreme energies (1988, 1991).

Briefly, the Chicago Egg recorded the atomic number and energy of nuclei above 150 GeV/nucleon based on their transition radiation. The measurements faded out at high energies of several thousand GeV because of the declining number of cosmic rays at increasing energies. Nuclei in the lower energy range 40-400 GeV/nucleon were detected and sized with gas Cerenkov counters. The results of this investigation showed that the relative abundances of the secondary nuclei (e.g., the abundance ratio B/C) continually decreases up to very high energies. This can be understood with the assumption of an energy spectrum $E^{-2.1}$ produced in the unknown cosmic-ray source, as is predicted for shock acceleration processes, followed by more rapid escape from the Galaxy with increasing E. As was already known at lower energies, the data indicate the enhanced abundance of nuclei with low first ionization potential, much as one finds for energetic nuclei from solar flares, etc. Detailed comparisons with the relative abundances of cosmic-ray nuclei at lower energies begins to give a picture of the conditions under which cosmic rays are created in their various sources.

There are numerous other investigations that Meyer accomplished along with the major achievements summarized here. In addition to the ambitious scientific program that marked his career he took on many responsibilities at the University of Chicago and in national and international scientific organizations. For instance, he was chair of the Cosmic Ray Physics Division of the American Physical Society, 1972-73. He was a member of the Space Science Board of the National Academy of Sciences, 1975-78 and served as chair of the Committee on Astronomy and Astrophysics of the Space Science Board, 1975-77. He served as director of the Enrico Fermi Institute at the University of Chicago, 1978-82. He was then chair of the Department of Physics,

1986-89. These responsibilities all involve considerable time and energy, but he handled them in some of his scientifically most productive years. His commitment to undergraduate teaching was recognized in 1971 by the Llewellyn John and Harriet Manchester Quantrell Award for Excellence in Undergraduate Teaching.

Meyer's scientific productivity was also recognized in the land of his birth, where he became a foreign member of Germany's Max Planck Society and the Max Planck Institute for Physics and Astrophysics in München in 1973. In 1984 he was a recipient of the Alexander Von Humboldt Award for Senior United States Scientists.

He was elected a member of the National Academy of Sciences in 1989 in recognition of his many fundamental contributions to present understanding of the fast particles (cosmic rays) that come from everywhere, near and far, in the active universe. He leaves behind a scientific legacy and the fond memories of his many colleagues. He is survived by his second wife, the renowned microbiologist Patricia Spear, who is chair of microbiology-microimmunology at the Northwestern University Medical School; by his two sons, Stephan Meyer, professor of astronomy and astrophysics at the University of Chicago, and Andreas Meyer of Portsmouth, New Hampshire; and by two grandchildren, Samantha Meyer and Niels Meyer of Chicago.

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ALFRED NISONOFF

January 26, 1923–March 12, 2001

BY LISA A. STEINER, KATHERINE L. KNIGHT,
AND J. DONALD CAPRA

ALFRED NISONOFF, WHO DIED on March 12, 2001, was a ma-jor contributor to many basic aspects of immunology throughout his career. In addition to fundamental work that helped to define the nature of antibodies and the genes encoding them, he was an astute critic with penetrating analytical skills. His monograph *The Antibody Molecule* stands as the definitive reference work on the subject to 1975, the time of its publication.

Nisonoff's parents immigrated to the New York area from Hungary and Russia as teenagers. Al was born in Corona on January 26, 1923. When he was about two years old, his parents moved into a working-class, largely immigrant community in South River, New Jersey, to join other family members. They operated a kosher butcher shop and grocery store. Al's parents had little formal education and his initial exposure to books and reading was in school, where his exceptional intelligence was soon recognized. At age 6 he found himself in third grade, and by 15 he had graduated from high school. One of the few students in his school to go to college, Al received a state scholarship and enrolled at Rutgers, which was within hitchhiking distance and allowed him to live at home. He became interested in chem-

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istry when a high-school friend gave him access to his home laboratory, and decided to major in this field. It also seemed to offer opportunities for practical future employment.

Upon graduation from Rutgers in 1942 at age 19, Al set off in a Model A Ford to take up a job with the U.S. Rubber Company in Detroit. It was the first time he had been more than 50 miles from home. He later recalled being told by an upper management person that he should be proud because U.S. Rubber did not ordinarily hire Jews. He was probably not surprised to hear this, because it was generally accepted at this time that many chemical companies would not hire Jews (see Dan A. Oren, *Joining the Club: A History of Jews and Yale,* p. 357, footnote 28. New Haven: Yale University Press, 1985).

Although Al was assigned to a fairly routine task, testing various latex compounds for their ability to adhere to the nylon cord required to strengthen airplane tires, he soon made a critical observation that changed the production of these tires so important for the war effort. One day while walking through the plant, he stopped to watch the construction of self-sealing gasoline tanks made from rubber and strengthened with nylon cord dipped in a water-based latex adhesive. Combining the keen power of observation and imagination that was to characterize his future research, Al adapted this process to the problem of adhering nylon cord to rubber tires—so U.S. Rubber was launched into making nylon-belted tires. Describing this practical discovery many years later, Al with typical self-deprecation said it was "primitive stuff . . . a mindless sort of thing." Another significant event of the time in Detroit was that Al met Sarah (Sally) Weiseman at a Jewish community center. They corresponded through the war years and were married immediately after his discharge from the Navy.

By 1943, with the war raging, Al became anxious to join

the armed forces. Even though he had an occupational deferment, he enlisted as a midshipman in the Navy. He served until the end of the war, missing the invasion of Okinawa only because his ship developed an engine problem. He had not given much thought to the future, but a college friend whom he met while passing through San Diego told him about the G.I. Bill, and he decided to pursue graduate work in chemistry. He was discharged from the Navy in July 1946 and entered graduate school at Johns Hopkins University in September, receiving his M.A. in 1948 and Ph.D. in 1951. His research, supervised by Frederick W. Barnes, Jr., was on the enzymatic mechanism of transamination.

Following graduate school and on the strength of his previous success at U. S. Rubber, Al joined a branch of the same company in Naugatuck, Connecticut. After two years, however, he decided to return to work related to biochemistry and took a position with David Pressman's group at the Roswell Park Memorial Institute in Buffalo, beginning work that set the direction for much of his research in the remainder of his career.

In the early 1940s David Pressman, then working in Linus Pauling's group, carried out an extensive series of experiments exploring the specificity of antibodies directed against haptenic determinants. These studies introduced the technique of quantitative hapten inhibition, an important extension of the experimental approach pioneered by Karl Landsteiner. Throughout his career Nisonoff applied quantitative approaches, often with anti-hapten antibodies, to a number of problems in immunology. With Pressman, Nisonoff explored the heterogeneity in the binding of antibodies with haptens and introduced means of estimating this heterogeneity quantitatively. In an important paper from this period he demonstrated that the two combining sites on a single antibody molecule have the same specificity. This

result, which confirmed earlier experiments by Landsteiner, Felix Haurowitz, and Herman Eisen using precipitin methods, was important in that it rendered unlikely that specific antibody sites would simply be generated by folding around an antigen template, as had been specified in the "instruction" theories of antibody formation, in most detail by Pauling.

Toward the end of his stay at Roswell Park, Nisonoff initiated experiments on the enzymatic cleavage of rabbit antibodies, which contributed importantly to the growing understanding of their structure. Rodney Porter had shown that two active univalent fragments, now known as Fab, could be produced from each antibody molecule by digestion with papain. Because papain is always used in the presence of a mercaptan, Nisonoff originally proposed that two steps, proteolysis and disulfide cleavage, were needed to generate the active univalent fragments. Accordingly, he repeated Porter's experiment with a different enzyme, pepsin, which does not require activation by a mercaptan. Although the initial premise was incorrect, as Nisonoff himself later pointed out, the experiment led to an even more interesting conclusion. Disulfide bond cleavage is not required to produce the active univalent antibody fragments after papain cleavage, but it is required to produce univalent fragments after limited digestion with pepsin. The explanation is that papain cleaves on the amino-terminal side of the single disulfide bridge connecting the two heavy chains in rabbit IgG, whereas pepsin cleaves on the carboxyl-terminal side of the same bond, generating a single bivalent fragment, $F(ab')_2$. Reduction of the inter-heavy chain bridge in the bivalent fragment yields univalent Fab' fragments.

Nisonoff's studies provided critical insights into the nature of the fragments produced by digestion with papain and their disposition in the intact antibody molecule. His experiments with pepsin digestion implied that the two frag-

ments containing the active site (Fab or Fab′) are located on the same side of the molecule, away from the Fc fragment. The deliberations by Porter's group that led to the formulation of the polypeptide chain structure of IgG were summarized by Julian Fleischman in a "citation classic" review of the work. As Fleischman recalled, Porter initially favored the then popular cigar-shape model in which the two active fragments are disposed on either side of a central Fc. However, this model was not easily reconciled with Nisonoff's results with pepsin digestion and was therefore abandoned in favor of the now familiar four-chain model in which the two Fab fragments are on one side of the molecule. Nisonoff's work also clarified the nature of chromatographic fractions I and II obtained by Porter after papain digestion of rabbit antibodies. The similar yield initially found for fractions I and II was fortuitous, the result of charge heterogeneity in the antibody population and the choice of column conditions. In fact, the more negatively charged antibody molecules were found to contain two Fab fragments of type I and the more positively charged two Fab fragments of type II.

The $F(ab′)_2$ fragment produced by pepsin retains the bivalence of the original antibody molecule and therefore the ability to precipitate or agglutinate antigen. However, it lacks the Fc fragment and will not bind to cells expressing Fc receptors, eliminating much undesired "non-specific" antibody binding. The next logical step, taken by Nisonoff just as he was moving from Roswell Park to a position as associate professor of microbiology at the University of Illinois, Urbana, was to show that the univalent Fab′ fragments generated by successive pepsin digestion and reduction could be recombined into the bivalent $F(ab′)_2$ fragment by oxidation, allowing the creation of bivalent antibodies of mixed specificity. Such hybrid antibodies have had many practical

uses, for example, bringing a pharmacological agent into contact with a particular cell type.

Throughout his career Nisonoff retained an interest in the three-dimensional structure of antibodies. As early as the late 1950s this led to collaboration with Cecil Hall and Henry Slater at the Massachusetts Institute of Technology in an attempt to visualize the antibody molecule by electron microscopy. Although resolution was insufficient to discern the shape, the data provided a reasonable estimate of the size of the molecule. Methods of X-ray crystallography began to be applied to proteins in the 1960s. Recognizing the importance of applying these techniques to antibodies, Nisonoff soon succeeded in obtaining crystals of Fab fragments derived from human IgG myeloma proteins. Preliminary structural work was carried out in collaboration with Roberto Poljak's group; later more detailed studies carried out by Poljak and others led to a detailed understanding of the structure of the Fab fragment, including localization of the active site, the basic features of the Ig fold, and the orientation of V and C domains.

In 1966 Nisonoff moved from Urbana to the University of Illinois College of Medicine in Chicago, where in 1969 he assumed the chair of the Department of Biological Chemistry. In Chicago he continued a fruitful collaboration with Sheldon Dray, relating structural features of rabbit antibodies to genetic variations known as allotypy. In work using Nisonoff's characteristic quantitative approach, they showed that the population of IgG molecules in a rabbit heterozygous for allotype consists only of molecules displaying one or the other allotypic determinant, but not both. Coming on the heels of the proposal of the four-chain model for IgG, this finding suggested that the IgG molecule is symmetrical (i.e., with two identical heavy chains and two identical light chains).

Thinking that quantitative immunochemical methods would also be useful for investigating idiotypy (the unique antigenic specificity possessed by individual antibody molecules), Nisonoff embarked on a series of studies that laid the groundwork for the widespread use of idiotypes as genetic markers. Indeed, studies of idiotypy were to occupy him for the rest of his career. He drew on his experience with antibodies directed against haptenic determinants to address such questions as the relationship of the idiotypic site of an antibody molecule to the antigen-binding site. In other studies Nisonoff addressed such questions as the size of the repertoire of antibody-binding sites and the relationship of the idiotypic site of an antibody molecule to the antigen-binding site. For example, an important insight provided by Nisonoff, as well as others, was the recognition that some idiotypic specificities can be shared by different individuals, so-called public idiotypes, and that these are probably encoded by germline genes. The relationship between idiotypes and genes encoding antibody V regions provided means for tracking clonal lines of B-lymphocytes.

In the 1960s evidence began to accumulate indicating that a single germline gene could not encode both the variable and constant regions of an Ig heavy or light chain. One of the critical findings was provided by Nisonoff, who in collaboration with Hugh Fudenberg showed that IgG and IgM myeloma proteins obtained from the same patient had identical idiotypes, and therefore identical V regions, as was later confirmed by sequence analysis. Because the C regions of the gamma and mu chains must be encoded by distinct genes, the V and C segments had to be specified by separate genetic units.

He showed that antibodies directed against idiotypic determinants could compete with hapten in binding to antibody-combining regions. Nisonoff and J. Donald Capra in a

collaboration that extended over a number of years showed that idiotypes could be defined structurally and that idiotypic differences between different strains of mice reflect genetic variability. With Paul Gottlieb, Nisonoff provided evidence that both heavy and light chains in an immunoglobulin molecule are required for expression of the idiotype. Nisonoff's work and that of others on idiotypy is summarized in his presidential address for the American Association of Immunologists meeting of 1991.

A major occupation and preoccupation of the later Chicago years was the writing, together with John Hopper and Susan Spring, of the monograph *The Antibody Molecule* (1975), a monumental annotated work providing a scholarly and comprehensive review of what we now call the B-cell receptor. Choosing to review the field at this time was a reflection of Nisonoff's astute insight, for it provided a definitive summary of the protein phase of molecular immunology and set the stage for the genetic era that was soon to follow. A decade later Nisonoff wrote an introductory text of molecular immunology that showed not only his superb command of the subject but also his skill in presenting complex material. His extensive knowledge and clear, rigorous thinking made him an excellent teacher both in the laboratory and in the classroom.

In 1975 Nisonoff moved to the Rosenstiel Research Center at Brandeis University, where he helped to bring younger colleagues to a group whose focus was research in immunology. His own work continued to be centered on idiotypy. Interestingly, he was recruited to Brandeis by Harlyn Halvorson, then director of the Rosenstiel center, whose father, H. Orin Halvorson, had brought Nisonoff to the Microbiology Department at the University of Illinois, Urbana, at the outset of his academic career.

Nisonoff's well-deserved reputation for critical scientific

insight and sound judgment meant that he was much sought after to serve on review panels, advisory committees, and editorial boards. In what may be a record, he served three terms, once as chair, on the allergy and immunology study section of the National Institutes of Health. He was president of the American Association of Immunologists in 1990-91. Even after giving up his research program in 1996, Nisonoff continued as an advisor to NIH and played a major role in preparing a comprehensive report on current knowledge and future directions in immunology (*Report of the NIAID Task Force on Immunology,* National Institutes of Health, 1998). Retirement was not easy for him, as he missed the give and take of the lab, but he remained as sharp as ever and was always available for criticism and discussion with former colleagues.

One of Nisonoff's outstanding qualities was intellectual honesty. Always direct and outspoken, he disliked pretense in any form and was himself without any pretension. He saw right to the heart of any question and brooked no fuzziness of thought. The high standards he set for himself were a model for colleagues, as well as for the many students he mentored. He paid little attention to the external trappings of fame, his or anyone else's. He was interested in science for its own sake and was forever in pursuit of the rigorous experiment that would provide an unambiguous answer to a meaningful question.

Nisonoff's characteristic modesty is epitomized in the format of his curriculum vitae in which his honors are buried in a section captioned "Other Data." He received the Medal of the Pasteur Institute in 1971, was a foreign correspondent of the Belgian Academy of Medicine in 1977, a fellow of the American Academy of Arts and Sciences in 1982, and became a member of the National Academy of Science in 1984.

As a young person Nisonoff had little exposure to the visual arts or to music, but he came to love classical music passionately and was a regular at Boston Symphony concerts. He loved the works of many twentieth-century composers but was generally not enamored of the newly commissioned works that are often included in these concerts. He was moved to express this view in a letter sent to the Boston Symphony just a few months before his death. Why, he asked, were new compositions so rarely played again after their premiere? If they are worth hearing once, he reasoned, surely they are worth hearing twice. As far as is known, the question remained unanswered.

Nisonoff's sense of fun and good humor were legendary. In addition to music, he loved to play tennis and did so regularly. He was invariably good for a lively discussion of the current political scene. He had a strong lifelong sense of social justice and always took the side of the underdog. He quietly set about doing what he could to make his corner of the world a better place. After retirement from Brandeis he coached kids in math and recent immigrants in English, and he was planning to take a course on teaching English as a second language.

Nisonoff was as honest in his human relationships as he was in his science. To colleagues and students, as well as family and friends, he was loyal and committed. Although he was divorced from Sally in 1978, he continued to care for her on a daily basis. He had a close relationship with his children, Don and Linda, and was a devoted grandfather. He was the best friend of his younger sister, Lorraine. The last decade of his life was immensely enriched by his friendship with Patricia Carella, who shared his love of music and travel.

Al Nisonoff was one of a small number of investigators whose accomplishments span the classical and modern eras

in immunology. His work provided critical insights into the molecular nature of the antibody molecule and the genetic basis for antibody diversity. He approached important biological questions with the rigor of the chemist. His understanding of this complex field was as broad as it was deep. His publications stand as a model of clear thinking and vision.

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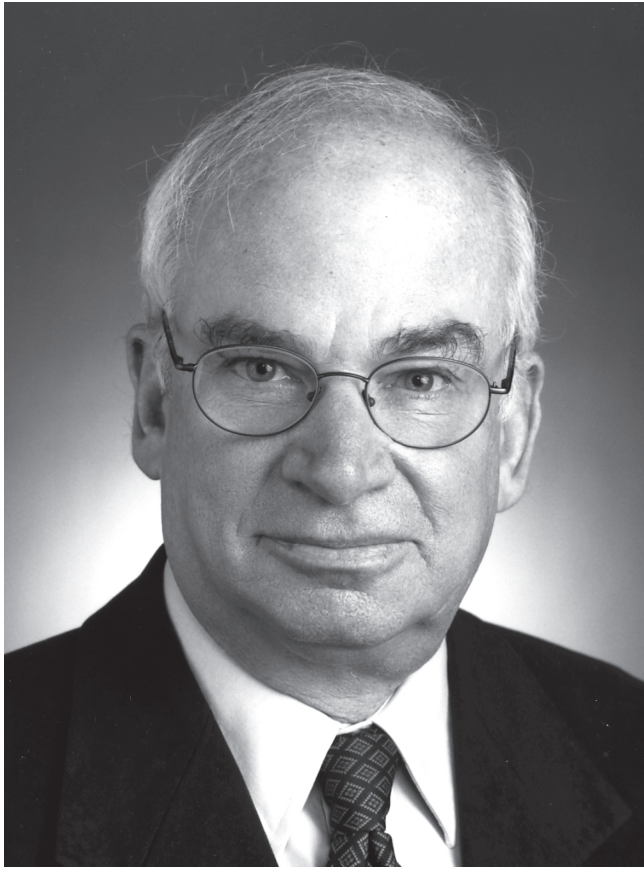
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SHERWIN ROSEN

September 29, 1938–March 17, 2001

BY EDWARD P. LAZEAR

S HERWIN ROSEN WAS ONE of the great applied microeconomic theorists of recent decades. His life was devoted to understanding how diverse people, products, and technologies could be brought together and allocated appropriately. As an example of the kind of analyses that Rosen pioneered, consider the many varieties of automobiles that are produced. Some are higher quality than others, some are small, some are large, some fast, some slow, some are beautiful, and others are comfortable. People have different preferences with respect to these attributes. A larger person might prefer a larger car. A daredevil might like a faster one. How does the right car get to the right person? The obvious answer is that the market ensures that cars are available and consumers, through free choice, purchase the car they want. But at what price? How are the prices of the various attributes set so as to equate supply with demand, not just for some homogeneous commodity like wheat but also for some complex good like an automobile?

Most economists would probably classify Rosen as among the twentieth century's finest labor economists because much of his work focused on labor markets. In labor markets, too, diversity is key. Workers have different skills and tastes

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for job attributes (like hours flexibility, danger, location) and jobs have different requirements and abilities to accommodate worker preferences. How do wages get set to ensure that workers and jobs are paired appropriately? Much of Rosen's work centered on labor allocation and wage determination in the context of heterogeneous workers and jobs.

Sherwin was born to Nell and Joe Rosen in Chicago in 1938. His mother was Canadian and his father was from Illinois. His parents met on a kosher dairy farm in Quebec, Canada. Sherwin's father, Joe, and his Uncle Harry jointly owned a hardware store and Sherwin spent a good bit of his childhood playing in that store. Despite this on-the-job training Sherwin was hopeless at performing any kind of repair work. Sherwin was very close to his brother, Eddie, who died when he and Sherwin were both only in their 30s.

Sherwin spoke often of his father, describing him as a bit of a character who had an eye for women and a slight wild streak. Sherwin inherited part of that from his dad. Sherwin loved fast cars and enjoyed an occasional journey to the track to bet on a horse or two. He described these field trips as educational, of course, as he attempted to understand at the purely intellectual level the system of pari-mutuel betting.

Sherwin attended Purdue University and studied engineering. This served him well as an economist. In our joint work he would put me to shame when it came to integrating-by-parts and teased the rest of us mercilessly for our ineptitude at differentiating complex integrals. But Sherwin was not cut out to be an engineer and decided to attend graduate school in economics at the University of Chicago. At first there was concern that he did not have the touch for economics either. He failed the general exam known as "the core" and was advised by Milton Friedman to drop out

of economics to pursue another discipline. Perhaps, suggested Milton, he might make a better accountant. Even Milton Friedman errs occasionally, and fortunately Sherwin did not follow his advice. He persevered and eventually received his Ph.D., studying under one of the great teachers in labor economics, H. Gregg Lewis.

The most important event of Sherwin's undergraduate career consisted of a trip back to Roseland, Illinois, where he met a girl named Sharon Girsburg from the north side of Chicago. Sharon would become Sherwin's wife of 40 years. Sharon is herself a remarkable person, having both charm and strength. Sherwin's tendency to experience occasional mood changes was regulated by Sharon's love and consistency. Sharon and Sherwin had two daughters, Jennifer and Adria. Jennifer still lives in Chicago and Adria, now a teacher in Berkeley, California, has just provided a grandchild appropriately named Leonardo Sherwin.

Sherwin was a truly sophisticated person. He had a deep understanding of music, art, and literature. He was an intellectual in the best sense of the word, curious about everything and able to enjoy the finer things that the world had to offer. He had many hobbies. He was an avid golfer from childhood; he played jazz piano and enjoyed a good meal and fine wine.

SHERWIN THE TEACHER

Sherwin was my most important teacher. In many respects he was a superb teacher, but his classes were often tough sledding. Sherwin was a clear speaker, but hardly an impassioned orator. The truth is, he was sometimes hard to follow. What set Sherwin apart as a teacher (and also as a scholar) was the depth of his understanding. Because he understood things at a level deeper than most economists, what he taught was sometimes less than transparent. But

eventually the student fell in love with both the substance and style of what he said. He made it clear that the superficial understanding of a topic that we had was simply insufficient. He understood issues at so many different levels and would think about the same problem literally for years, each paper tackling another layer of it. For this reason his classes could be daunting to the unwashed graduate student.

My early impressions of Sherwin as a teacher were not only from the class that he taught when I was a graduate student at Harvard. Sherwin was then a 34-year-old visiting professor teaching labor economics. Perhaps equally important was our interaction in the Chicago-style seminar at Harvard that was attended by Chicago expatriates like Zvi Griliches and by Chicago wannabes like myself. Sherwin attended that seminar. I was constantly amazed by his insight. Sherwin would appear to be thinking about something else much of the time, drawing elaborate doodles on the day's paper, and staring out the window. He literally seemed out of it, almost ignoring the talk that was taking place. Then, in a somewhat clumsy manner, he would blurt out a one-sentence comment that would completely change the nature of the talk. Sherwin would see right through the problem and cut to the key point, or more often, key flaw in the speaker's logic. The point was never delivered in an aggressive or belligerent way. Sherwin never tried to look good at the speaker's expense. He just understood the issue at a level far deeper than that contemplated by the speaker and made it clear to all. As a teacher, that was his style throughout his career, and many in this audience have benefited from his insights.

Sherwin began his teaching and research career at the University of Rochester in 1964, where he remained until 1977. He was a dominant figure in the economics department because of his ability to look deeply into so many

issues. He made many friends there, the closest of which was Stanley Engerman, and they remained friends until Sherwin's death. Much of Sherwin's early important research was done at Rochester, including the classic paper on hedonic prices. Additionally, Sherwin influenced a number of Rochester students who are now themselves fine economists.

But Sherwin was not really home until he returned to the University of Chicago in 1977. The University of Chicago is unique. It epitomizes intellectual activity. Those of us who have spent significant parts of our careers at Chicago view it as the center of the universe. Despite Sherwin's happiness with the University of Rochester and despite his many good, productive years there, he could not resist the sirens that beckoned him to return to Chicago. It was for him the pinnacle, and he came home. Chicago defines the term "tough love," and like the rest of us, Sherwin enjoyed a number of "romantic" experiences in the Chicago workshops, where his work, although admired, was taken apart piece by piece. And this made him better.

Sherwin and I worked closely together and we were each other's most frequent coauthor. But Sherwin also enjoyed the personal and intellectual company of a number of Chicago greats, most notably Gary Becker and Bob Lucas. Both influenced Sherwin. It is impossible to overstate the significance of the workshop that he ran jointly with Gary for many years, not only on his own work but also on that of the rest of us who participated.

Sherwin had a number of offers to move elsewhere during his career, but Chicago was his soul. He spent summers and occasional winter months at the Hoover Institution at Stanford, but was unwilling to leave the Chicago department even for the beauty and climate of the San Francisco Bay area. His Chicago students and colleagues

and Chicago's intellectual atmosphere were simply too much a part of him.

Since his death, so many of his students have talked about Sherwin in much the same way. He was as kind as any man I have ever known. Although sometimes gruff, Sherwin spent much of his life ensuring the well-being of his students and junior colleagues. He was generous with his insights. He shared them with others, especially his junior colleagues, and so many of us profited as a result.

SHERWIN THE SCHOLAR

Although Rosen's impact on his students was profound, one can only affect a few through direct classroom contact. By far his greatest impact was through his written work, of which there was much. Rosen published about 80 papers in scholarly journals, and many have become classics. Probably his best-known paper is "Hedonic Prices and Implicit Markets" (1974). This paper forms the basis for understanding diversity—how the market solves the problem of matching buyers and sellers along many different dimensions of quality.

Two examples help clarify the issues: one from the labor market and one from product markets. A product market example has already been mentioned and it involves the pricing of attributes of quality.

To make things simple, think about automobiles as having one dimension of quality, namely horsepower. (This is consistent with Sherwin's love of speed.) Individuals have preferences over horsepower, and it may be that other things equal, most prefer more horsepower to less. Now, individuals might be willing to pay more for higher levels of horsepower, but the relationship need not be linear. In fact, one might expect it to be concave; it is worth more to increase the horsepower from 50 to 100 than it is increase it from 350 to 400. But the problem is that it is costly to produce

cars that deliver more power, especially in a package that is small enough and light enough to be practical. There is an analogous relation on the producer side that matches that of the consumer. Producers can supply more output to consumers but only at increased cost. Furthermore, the increased cost relationship is probably not linear and is likely to be convex. It costs more to increase horsepower from 350 to 400 than it does to increase it from 50 to 100.

Which level of horsepower is provided and at what price? The Rosen analysis showed that if all consumers had the same preferences and all producers had the same cost technology, there would be one and only one type of car produced and its price would be determined uniquely. Of course, this is the extreme case. In the real world both sides of the market would be characterized by heterogeneity, and again the Rosen analysis explained under which circumstances an investigator could infer either preferences or cost technology. If consumers were identical, but firms differed in their ability to provide increasing horsepower at increased costs, then there would be many varieties of cars produced and the price would rise with horsepower in a concave fashion. The concave function that related price to horsepower would be an exact representation of consumer preferences. That is, it would tell us how much consumers were willing to pay for additional horsepower at every level of horsepower. For example, if the price of a car with 100 horsepower were priced at $15,000 and an identical car with 150 horsepower were priced at $18,000, this would imply that every consumer (since they are identical) viewed 50 additional horses as being worth $3,000.

The converse is also true. If consumers differed in their preferences, but producers were identical in their ability to produce horsepower at increasing cost, then the market relation of price to horsepower would trace out the producers'

cost relation. For example, if the price of a car with 150 horse power were $18,000 and the price of one with 200 horsepower were $25,000, then this would imply that the extra 50 horses cost $7,000 to produce.

If, as is typical, both sides of the market are heterogeneous, then the market prices provide neither the preferences nor costs of any given producer. This is because sorting occurs and the market facilitates this sorting. Those producers who produce cars with 150 horsepower at $18,000 could not increase horsepower to 200 at a cost of $25,000. Although there is some firm that could provide that higher level of power at that price, the firm that chooses to produce the lower horsepower car is the one that has a comparative advantage at low horsepower and a comparative disadvantage at high horsepower. Analogously, the person who buys the 150-horsepower car at a cost of $18,000 would not be willing to pay an extra $7,000 for 50 more horsepower. Indeed, that is why he chose the low-cost, low-horsepower car in the first place. Conversely, the individual who buys the $25,000 car with 200 horsepower would not settle for a 150-horsepower car at $18,000. She preferred the high-horsepower car at a cost of $25,000 to the low-horsepower car at a cost of $18,000. This revealed preference is generated by the market mechanism that Rosen identified.

The point is even more profound in the labor market context. To put it simply, when choosing a job, money isn't everything. People care about other aspects of the job and Rosen showed us how to analyze and understand the tradeoffs. Again, to make it simple, suppose that jobs differed in only one dimension—flexibility of hours. Some people (e.g., mothers of small children) prefer jobs that offer a great deal of flexibility and might be willing to accept significantly lower wages to have such jobs. Others (e.g., 54-year-old men) might be less interested in flexible hours. Although

they would accept somewhat lower wages to obtain flexibility, the amount they would be willing to give up to obtain flexible hours is not as large as the amount mothers of small children would give up.

On the employer side, it is costly to provide flexible hours, but more costly to some types of firms than to others. For example, firms that can accommodate telecommuters, like bill-tracking operations, can offer flexible hours with less harm to production than those running assembly lines. Factories will prefer to pay relatively high wages and require rigid work schedules, whereas bill-tracking firms prefer to pay lower wages and allow flexible hours. The market will sort accordingly so that we should see few mothers of small children on assembly lines and few 54-year-old men who prefer high wages working for bill trackers. The wage mechanism established by the market induces people to self-sort.

Furthermore, the Rosen approach allows a conceptually appropriate way to value nonmonetary amenities of a job. If firms that offer flexible hours pay $100 per day less than those that require rigid schedules, we can say that the market value of flexibility is $100, that the marginal worker values flexibility at $100 and the cost to the marginal firm of offering flexibility is $100. Thus, we have found a monetary equivalent for nonmonetary attributes. All of this is possible in a world of heterogeneity.

An extension of valuing attributes allowed Rosen to conceptualize and estimate the value of a life. This approach is still used today both in academics and in litigation that involves damages for wrongful death. The idea is to examine different earnings in risky and less risky occupations. If an occupation that has a slightly higher probability of death also carries with it a 10-percent higher salary, then that 10-percent additional salary must compensate for the higher

probability of death. By using estimates from real wage and hazard data it is possible to estimate how much one's heirs would have to inherit to compensate for one's own life. Many researchers have used this approach, with some modifications, in the health economics context to determine the cost effectiveness of various medical treatments.

The Rosen work on hedonics is probably his most important contribution, but there are many others as well. Sherwin and my collaboration in the late 1970s resulted in a literature called "tournament theory." Our paper "Rank-Order Tournaments as Optimum Labor Contracts" (1981) was followed by Sherwin's paper "Prizes and Incentives in Elimination Tournaments" (1986). Tournament theory explains wage dynamics in hierarchies. How large a raise should individuals receive when they are promoted from director to vice-president? There are a number of puzzles and basic questions that can be answered by using tournament theory. For example, why do salaries jump so dramatically when an individual is promoted from vice-president to chief executive officer? If he would work for $500,000 per year as a vice-president, would he really turn down the CEO job at $800,000? Is it necessary to pay him $2 million, and if so, what function does it serve the firm? Why are earnings skewed so that the promotion from assistant vice-president to vice-president carries a lower raise than the promotion from vice-president to president?

The basic idea behind tournament theory is that a firm's internal labor market can be thought of in the metaphor of, say, a tennis tournament. There are three main points.

First, in the tournament all prizes are fixed in advance and based on relative performance. The player who wins the championship does so not because he is good—all players in the tournament are excellent—but because he is *better* on that given day than his rival. The statement is relative.

In firms the person who receives the promotion is generally the one who is regarded as the best of all the choices. Furthermore, to a first approximation, when he is promoted, he receives the salary that goes with the job, not the one that matches his ability.

Second, the larger is the spread between the winner's and loser's prizes, the more effort that goes into the contest. Players work harder in a winner-take-all contest than in one where the prize money is split evenly between winner and loser. In the firm the larger the difference in salary between the president and vice-president, the more effort the vice-presidents will put into their jobs so that they can win the presidency. The president's salary serves as a motivator for the vice-presidents as much or more than it does for the president.

Third, the spread can be too large. If the difference in prize money is too great, effort is too high and individuals will not voluntarily join the firm. Recruitment and retention difficulties place limits on the size of the spread and create equilibrium where a unique, optimal salary structure is determined.

The theory helps explain why there is a larger spread in earnings between the top and bottom in new industries than in old ones. Think about playing tennis in a hurricane. Players would tend to give up because their effort would have little impact on the probability of winning. Similarly, when luck is an important component of the industrial environment, the managers tend to give up as well because their effort has little impact on the probability of being promoted. To counter this tendency, the spread between the prize of the winner and prize of the loser must be increased, which results in a larger difference in earnings. New industries are riskier; they have more luck associated with the production process. To counter this, new

industries reward winners in a bigger way than do old industries, which results in a large difference between the top and bottom wages in the firm.

The mathematics of the tournament theory is perhaps the earliest application of game theory to the labor market. Rosen was a pioneer in bringing new formal techniques to a field that was previously institutional.

Always interested in why wages take the form that they do in the real world, Rosen often revisited the topic of earnings skew. The most important paper on this topic was probably "The Economics of Superstars" (1981). This was a truly remarkable paper because it provided a simple and convincing explanation for the existence of a highly skewed income distribution. Rosen's analysis explained why there were a few very high earners in each occupation and which occupations were most likely to have a skewed earnings distribution. His argument relied on economies of scale, best illustrated by the example of performers. Suppose that there are two or three great tenors in the world. Among them are clearly Luciano Pavarotti and Placido Domingo. Suppose further that most opera fans rank Pavarotti above Domingo (although many aficionados might reverse the ranking). Even if the difference between the two were minuscule, Pavarotti could end up with earnings many times that of Domingo. The reason is that there are tremendous economies of scale in the recording business. Pavarotti can, with the same effort, produce one CD of *Tosca* or 100 million CDs of *Tosca.* As a result, if most view Pavarotti as better, then he will sell many more CDs than Domingo and his earnings will be many times higher, despite his talent being only trivially greater.

The theory implies that occupations that are subject to the greatest economies of scale will be the most skewed. Furthermore, over time, as technology allows greater econo-

mies of scale (e.g., the invention of the phonograph and radio), earnings of workers in those occupations will become more skewed.

Chief executive officers leverage their talent by combining it with capital and other labor. A variant on the superstars theory helps us understand why CEOs of large firms earn more than CEOs of small firms. They are essentially combining their talents with other factors of production to make greater use of the given amount of talent, which can be spread over a larger unit. Just as Pavarotti can entertain many simultaneously, the CEO of a firm that has $1 billion in assets can make the same amount of talent more productive than the one who presides over a firm with only $1 million in assets.

Sherwin was a major contributor to the theory of hierarchies and related this to the relation of earnings to firm size just described. In a couple of papers, including "Authority, Control, and the Distribution of Earnings" (1982), Rosen determined how individuals with various talents would sort among firms of different sizes and levels. This is the question of whether it is better to be a big fish in a small pond or a small fish in a larger one. Again relying on his deep understanding of diversity and equilibrium, Rosen affirmed that the marginal individual must be indifferent between being a level-two individual in a large firm or a level-one individual in a small firm. This idea, coupled with some assumptions about underlying technology and talents, not only provides a rich theory of wages within a hierarchy but also has implications for the size distribution of firms and the number of hierarchical levels that each has.

Rosen examined so many different areas in labor economics that it is impossible to discuss all of them. But it is important to feature the work that he did with Robert Willis on sorting in labor markets. A problem that plagued labor

economists for many years (and still does to some extent) is whether the positive relation of earnings to education is causal or simply indicates that more able people go to school. While few doubt that some is causal, the question of bias in statistical estimates remains. In "Education and Self-Selection" (1979) Willis and Rosen were able to shed light on this question. Through a very clever technique that relied on revealed preference in a sorting context, they found that not only were those who went on to college better at doing college jobs, but those who did not were better in an absolute sense at high school jobs. Thus, those who got college degrees did so for two reasons. First, they were good at jobs that required a college degree. Second, they were bad at jobs that required only a high school diploma. This meant that the biases in estimates of the return to investing in education were unlikely to be biased very much, which is the prevailing view after 30 years of statistical estimation.

Rosen worked in a large number of other areas, including labor market segmentation, discrimination, agricultural economics, housing, occupational choice, risk, and product market pricing. His contributions were profound and will have lasting impact on the profession.

SHERWIN THE MAN

Despite Sherwin's many accomplishments he was an overwhelmingly modest person. His own view of his accomplishments was far less favorable than that held by his colleagues, students, and the economics profession at large. Sherwin loved to laugh and had a wonderful sense of humor. I remember Sherwin once talking admiringly about one of his colleagues. He described him as a "real man" and said that the expression, although not politically correct in these times, captured the essence of the individual. More than anyone I have known, *Sherwin* was a real man.

He didn't gloat over his many successes. More important, he never revealed his displeasure when things didn't go his way. Sherwin took his lumps in silence and bore the pain without comment.

Sherwin's recognition came late in life. His election to the National Academy of Sciences came when he was 59. I remember how thrilled he was at the news. The following year he was elected president of the American Economics Association, which is the 25,000-member, preeminent society in economics. This, too, brought him great pleasure and he enjoyed enormously organizing and attending the January 2001 meeting.

It was at this meeting that he began to feel some of the symptoms that were associated with the disease that took his life. He found out that he had very advanced cancer in February 2001. Knowing that there was not much time left, I suggested to Sherwin that we have a conference that would bring together all his friends to talk about his work. "Nah, I don't want people to have to do that," he replied. "If my work is any good, people will talk about it after I am gone." But his wife Sharon and I persuaded him that he would enjoy the conference and seeing everyone at least one last time. He agreed. Unfortunately Sherwin's first instinct prevailed because he died just one month after hearing his diagnosis.

The memorial service held in Chicago in May 2001 attracted a huge crowd from around the world. Sherwin truly underestimated the feelings that others had for him. He was a scholar who had a deep understanding of the world. He was teacher who inspired and nurtured his students. He was a man who was a beacon to his family and friends. His career was cut short while he was still writing insightful papers, but the economics profession is fortunate

that he was so productive during his career. The vast and important literature that stems from his work is his legacy.

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Arthur L. Schawlow

ARTHUR SCHAWLOW

May 5, 1921–April 28, 1999

BY STEVEN CHU AND CHARLES H. TOWNES

ARTHUR SCHAWLOW, the J. G. Jackson and C. J. Wood Professor of Physics at Stanford University and coinventor of the laser, contributed to many aspects of nuclear, atomic, and molecular physics. He was awarded the 1981 Nobel Prize in physics for "contributions to the development of laser spectroscopy." His early work included examination of the shapes, radial charge distributions, and moments of nuclei, the first microwave spectroscopy of a free radical, and coauthoring a widely used text on microwave spectroscopy. After the laser invention he introduced many innovative techniques for very-high-precision spectroscopic measurements, including new types of two-step spectroscopy of molecules. With Theodor Hänsch, Schawlow proposed the idea of laser cooling atoms in a vapor to extremely low temperatures. This new field has progressed to the point where atoms can be cooled to temperatures of less than 10^{-6} degrees above absolute zero, and where new states of matter have been created. (David Wineland and Hans Dehmelt proposed a closely related idea in the same year.) His work has had far-reaching effects—in physics, chemistry, biology, medicine, communications, and many other aspects of modern technology.

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In addition to receiving the Nobel Prize Arthur Schawlow was elected a member of the National Academy of Sciences and was accorded many additional awards and honors, including the National Medal of Science in 1991. He was one of two people who had the distinction of serving as both president of the American Physical Society and president of the Optical Society of America. He was also chairman of the Physics Division of the American Association for the Advancement of Science.

Arthur L. Schawlow was born in Mount Vernon, New York, on May 5, 1921. His mother, Helen Mason, was from Canada and his father, Arthur Schawlow, was an emigrant from Latvia. They moved to Toronto, Canada, when Arthur the son was only three years old, and he was brought up there, though remaining a U.S. citizen. As a youngster Arthur enjoyed the famous *Book of Knowledge*, read about engineering and science, liked to tinker, was intrigued by radio, and built radio receivers. His intellectual skills were notable, resulting in completion of high school at the age of 16, and receipt of a scholarship in science at the University of Toronto. The latter was important because his family had no excess funds, and it steered him toward physics rather than engineering, which he had been seriously considering.

Arthur very much enjoyed jazz music, and while at Toronto he played the clarinet in the Delta Jazz Band, which he helped to organize. This and his engineering interests led him to record and collect jazz records, an avocation he continued during his entire career. This resulted in an extensive jazz record collection that is now in the Stanford University archives.

After earning his undergraduate degree Arthur continued in graduate school at the University of Toronto. His graduate work was interrupted during World War II. After receiving a master's degree in physics he took a job at Research Enter-

prises building radar equipment for several years. Toward the end of the war he began work on his Ph.D. at Toronto with Professor Malcolm Crawford, a spectroscopist of high standards who was particularly interested in examining nuclear properties. Working with him, Arthur developed a good understanding of electron interactions with nuclei in atoms, and published what he felt was one of his most important papers, on the determination of nuclear size from hyperfine structure. This interest was to show up again when he took a postdoctoral position with me (C.H.T.) at Columbia University.

In the 1950s I (C.H.T.) was in the physics department at Columbia University and fortunately had been given money for a postdoctoral fellowship by the Carbide and Carbon Corporation because Helmut ("Hap") Schulz, a creative, blind theoretical chemist there, thought my work on microwave spectroscopy of molecules might lead to work with infrared radiation and its effect on chemical reactions. The University of Toronto was outstanding in spectroscopy, and I knew professors there, such as Harry Welsh, who told me that Arthur Schawlow would be a good person for this postdoctoral position and would probably be interested. Several faculty members recommended him very highly, and I was glad that he accepted the position and joined me at Columbia University in the fall of 1949. His work at Columbia made it clear to me that he was unusually capable and had remarkable intuition and insight. I would have liked to have seen him in a permanent academic position at Columbia, but another event, though a happy one, unfortunately made this impractical.

My younger sister, Aurelia Townes, had come to New York to study voice and for a time lived in our apartment near Columbia. Arthur has often said that the very best thing that happened to him in New York was that he met

Aurelia; the first meeting being when my wife, Frances, made a point of inviting him to dinner and introducing the two of them. They were married in 1951, and I was delighted. We continued to work together at Columbia, both on research and on writing the book *Microwave Spectroscopy*. I would have wanted our collaboration to continue, with him on the Columbia faculty, however I was moving into the chairmanship of the physics department at Columbia, and potential claims of nepotism made it impractical for me to be instrumental in putting my new brother-in-law on the faculty. He accepted a position at Bell Telephone Laboratories in late 1951 and left Columbia.

The Schawlows had three children, Arthur Jr., Helen, and Edith. The family was religious, and Aurelia sang and conducted the choir at their church. Their two daughters, now Helen Johnson and Edith Dwan, have families and are in Wisconsin and California, respectively. Arthur Jr. introduced a difficult and challenging problem into the family, one on which Arthur Sr. and his wife, Aurelia, worked tirelessly and hopefully. Arthur Jr. was autistic, with very little speech ability. Part of the reason the Schawlows accepted a position at Stanford was that Professor Robert Hofstadter there also had an autistic child and they, the Shawlows and Hofstadters, hoped to help each other find solutions to the problem.

After his early years Arthur Jr. was put in a special center for autistic individuals, and later Arthur Sr. put together an institution to care for autistic individuals in Paradise, California. This was named the Arthur Schawlow Center in 1999 shortly before Arthur Sr.'s death. Both parents worked intensively toward finding ways for communicating with autistic individuals. One somewhat controversial method on which Arthur Sr. did research and became well known was for the autistic individual to spell words with a small handheld

machine. Arthur and Aurelia wrote a chapter in a book *Integrating Moderate and Severely Handicapped Learners* under the title "Our Son: The Endless Search for Help." The two parents spent many weekends at the center in Paradise, and in 1991 Aurelia Schawlow died as a result of an automobile accident during the long drive from Stanford to see her son at the center. The Arthur Schawlow Center continues to give important service to individuals with autism or related problems and their families.

In 1961 Arthur left Bell Laboratories to join the faculty at Stanford University, where he remained until he retired to emeritus status in 1996. During this time he embarked on his remarkable career developing laser spectroscopy.

In addition to being an eminent scientist, Arthur was an entertaining lecturer and beloved mentor. He was a jovial and friendly person who enjoyed his own jokes so much that he would burst out laughing as he came to the punch lines. He attracted a large group of students and postdocs who affectionately called him "the boss." While his brilliant insight produced many striking and incisive experiments, and yielded new phenomena and high-precision instruments, his guiding maxim for experimental physics was "keep it simple."

Arthur showered fatherly advice and maxims to the point where "the sayings of Art Schawlow" became known beyond Stanford's physics department. To a young scientist intimidated by information overload he would say, "To do successful research, you don't need to know everything, you just need to know one thing that isn't known." Art felt that one of the hallmarks of a successful scientist was a driving need "to find the answer" and toward this goal "anything worth doing is worth doing twice, the first time quick and dirty and the second time the best way you can." Having been infected with his charm and vision, many of his flock have

gone on to make their own significant contributions in science.

Arthur's wit and humor became renown. Recognizing that a scientist does his best work on the back of an envelope, he had envelopes with two backs made. They could be bought from Double Think, Inc., a division of Nocturnal Aviation, Art Schawlow Proprietor. The company's motto: "We fly by night." Art was chairing a session of an optical pumping conference in 1959 when Gordon Gould presented a paper entitled "The LASER, Light Amplification by Stimulated Emission of Radiation," thus introducing the acronym that was to soon replace the "optical maser." At the end of the paper Chairman Schawlow could not resist a comment. As Don Nelson of Bell Laboratories recalls, "Beginning with mock solemnity and ending in belly-shaking laughter, Art opined that the laser was likely to be most used as an oscillator and so should be named 'light oscillation by stimulated emission of radiation,' or the LOSER."[1] Once he gave a physics colloquium at Stanford entitled "Is Spectroscopy Dead?" He began the talk by defining at great length what he meant by "spectroscopy." After this long introduction his colleague at Stanford, Felix Bloch, asked him to define "dead." After a thoughtful pause Art answered, "Dead is when the chemists take over the subject." Art could say this and make the chemists laugh.

For Art, physics was fun and he made it more fun for the rest of us. While president of the Optical Society of America, Art initiated a "turvy-topsy" contest seeking the inverse of a topsy-turvy picture. A turvy-topsy slide was one that can never be presented correct side up. Four prizes were offered: first prize, $10; second prize, a copy of Schawlow's latest paper; third prize, copies of Schawlow's two latest papers; honorable mention, a choice of bumper stickers reading "Optics is Light Work," "Spectroscopists Have

Seen the Light," "Light Headed? Stop Eating Photons," or "Photons are Phorever."

Even Schawlow's amusing jokes and demonstrations have turned into profound contributions. Guided by his postulate that "anything will lase if you hit it hard enough," he and Ted Hänsch strove to create the first "edible laser" made out of Jell-O dessert. Working with two flavors per day, they marched through all 12 flavors of Knox-brand Jell-O. Unfortunately, none of the gelatin desserts showed lasing action, and Art retreated back to his office, where he ate each of the failures! Eventually he and Ted spiked the Jell-O with sodium fluorescein, a known laser dye, and immediately saw lasing action.[2] The news of the almost-edible laser spread rapidly and was eventually published in the *IEEE Journal of Quantum Electronics* in 1971. This experiment stimulated an experiment done by Herwig Kogelnik and Charles Shank at Bell Laboratories, where they irradiated a gelatin film with the interference pattern of two laser beams, making the first distributed feedback laser. This type of laser is now widely used in long-distance optical fiber communications.

His well-known demonstration during which he broke a blue Mickey Mouse balloon inside a clear outer balloon with a portable laser (in the shape of a ray gun, of course!) showed us that a beam of light could reach inside an object without puncturing the outer layers resurfaced when lasers were used to repair detached retinas. In a more recent embodiment the concept was used as an application of "optical tweezers," an optical trap fashioned out of a single focused laser beam. This trap, which was invented to hold onto atoms and micron-size particles, has also been used to reach inside a living cell and manipulate an organelle or chromosomes without damaging the cell or nucleus membrane. Similar optical tweezers have been used to manipulate a single molecule of DNA and pull against the force of

a myosin molecule found in muscle tissue tugging on an actin filament.

Schawlow had many productive students and associates. I (C.H.T.) was delighted with our association at Columbia University. The last paper we ever published together was "Infrared and Optical Masers,"[3] which initiated the laser development. At Stanford University he attracted many excellent students and postdoctoral fellows. Perhaps his closest long-term associate was Theodore Hänsch, who with him did much innovative work on high-precision spectroscopy.

Professor Schawlow died of leukemia on April 28, 1999, very close to what would have been his seventy-eighth birthday. He spent his last few months in a wheel chair, gracefully accepting the expected outcome and welcoming the visits of friends and family. Appropriately, the memorial service, which celebrated his remarkable life, included happy music by the Magnolia Jazz Band.

Arthur Schawlow was not just admired, he was cherished by those who knew him. He was a great scientist of remarkable modesty, a supportive teacher, a gentle leader, and a caring human being.

Arthur Schawlow's thesis research, in close collaboration with Professor Malcolm Crawford, led him into high-resolution spectroscopy and study of nuclear characteristics by atomic spectroscopy. His student work produced seven publications, mostly on nuclear spins and magnetic movements. They included an important paper on electric field distribution within nuclei. After he came to Columbia University to work with me (C.H.T.) on a postdoctoral fellowship his interest and ideas about nuclei continued. This resulted in measurements and interpretation of nuclear quadrupole moments and a publication concerning the effect of nuclear charge distribution on X-ray fine structure. At Columbia he also was deeply involved with microwave spectroscopy of

molecules, and with some of my students found the first microwave spectrum of a free radical, OH. This initial measurement was critically important in the later search for and discovery of OH in interstellar gas clouds by Allen Barrett, who was one of my students at that time. This was the first molecular microwave radiation found in interstellar clouds. It helped open up an important series of discoveries of interstellar molecules and molecular masers, OH itself producing many powerful masers. I was also pleased that Arthur agreed to coauthor with me the book on *Microwave Spectroscopy*, published in 1955 by McGraw-Hill. His work on it began at Columbia University but continued nights and weekends after he moved to the Bell Laboratories in 1951.

At Bell Laboratories Arthur initially worked on superconductivity, collaborating with others there, including Berndt Matthias, Harold W. Lewis, and George Devlin. As a consultant at Bell Laboratories I visited him there on occasion, and one day in the fall of 1957 I mentioned my ideas about making optical and infrared masers (later to be called lasers), and found he had also become interested in this possibility. We put our ideas and efforts together and Art came up with the idea of using two parallel mirrors as a way of obtaining a single mode of oscillation. I thought this idea might have somehow come from his early work at Toronto University on Fabry-Perot interferometers, but he always dismissed that as unlikely. After all, I had myself worked with Fabry-Perot systems but somehow missed the idea. Because we felt optical and infrared masers clearly should be patented, and I decided to interpret my own ideas as belonging to Bell Laboratories, from then on we kept the laser idea as a proprietary secret until a patent was prepared in mid-1958. After this our manuscript on the subject could be circulated and it was published in late 1958.

Publication of the paper on "Infrared and Optical Masers"[3] stimulated a number of efforts to build them. The first International Quantum Electronics Conference, held in the fall of 1959, was humming with ideas of possible optical transitions that might lead to the realization of the first laser. Art, along with colleagues Frank Varsani, Dar Wood, Al Clogston, Stanley Geshwind, and Robert Collins at Bell Laboratories, were exploring the optical properties of ruby $(Al_2O_3:Cr^{3+})$ and were thinking that this material could be a potential candidate for a laser. Art's studies of the properties of the narrow R_1 and R_2 resonance lines in ruby[4] generated significant interest, but he eventually rejected the R lines as a potential lasing candidate at the Quantum Electronics Conference.[5] Art was skeptical that a good lasing transition could terminate in the ground state, and suggested instead the near-neighbor pair lines in ruby he had also been studying as a means of obtaining a 4-level system.[6]

In this case Art's intuition proved wrong. The following year Theodore Maiman used a flash lamp to excite a lightly doped "pink" ruby crystal and achieved laser action on the R_1 resonance line. Shortly afterward Art and his colleagues were able to demonstrate lasing on his candidate pair lines with more highly doped ruby using the same type of a flash lamp used by Maiman in his landmark experiment. Art later remarked, "I thought I was being clever, but I outsmarted myself."[7]

Art and his Bell Laboratories colleagues continued to explore narrow resonance impurity lines in solids and how these lines were affected by strain, magnetic fields, temperature, and other perturbations. In 1961 he accepted a professorship at Stanford, where he continued these pioneering studies with his graduate students and postdoctoral fellows. His young colleagues included Roger Macfarland, William Yen, Linn Mollenauer, and Frank Imbush, who went

on to become leaders in solid-state spectroscopy in their own right. Other Art Schawlow students, including John Emmett, John Holzrichter, and Jeff Paisner, became experts in high-energy pulsed lasers, eventually rising to positions of high responsibility at Lawrence Livermore National Laboratory. Warren Moos, a postdoc during these years, went on to Johns Hopkins University to become a leader in astrophysics spectroscopy.

In the spring of 1970 Theodor Hänsch arrived at Stanford, having just finished his graduate studies with Peter Toschek. He recalls, "Walking down the hallway of the second floor of the Varian physics building, a futuristic poster on one of the doors caught my eye. It showed an enormous laser gun blasting at some attacking rockets in the sky. The caption in bold letters read "The incredible laser." In smaller letters below someone had written, "For credible lasers, see inside."[8]

Ted Hänsch and, independently, Christian Bordé invented Doppler-free saturation spectroscopy, based in part on the spectral hole-burning effect (the "Lamb dip") discovered by Roger Macfarlane, William Bennett, and Willis Lamb. With Art's support, encouragement, and council Ted initiated a remarkable series of experiments in which narrow atomic and molecular lines could be observed without the inhomogeneous broadening due to the Doppler effect. Using a prism-tuned, single-mode argon ion laser, Ted, Marc Levenson, and Art resolved the hyperfine lines of molecular iodine. With a pulsed dye laser that Ted built they were liberated from working with absorption lines that accidentally overlapped the narrow tuning range of existing lasers. Ted, Issa Shahin, and Art were able to measure the Doppler-free spectra of the sodium D lines.[9] Upon seeing the sodium spectra taken the night before, Art immediately urged, "You have to do the same with the red Balmer-α line of atomic hydrogen."

Within a few weeks the same team recorded the saturation spectra of the red Balmer line of atomic hydrogen.[10] This quick and dirty experiment with atomic hydrogen was to initiate an experimental program that is continuing today after three decades and seven orders of magnitude of spectacular improvement. In addition to Shahin, other students and postdoctoral fellows that further refined this measurement in these early days included Munir Nayfeh, Siu Au Lee, Stephen Curry, Carl Wieman, John Goldsmith, and Erhard Weber.

During this enormously productive period Art introduced molecular-state labeling, in which a laser is used to preferentially pump molecules out of a specific occupied molecular level. Absorption lines from the labeled level as measured using a second broadband laser were then weakened, as observed by Mark Kaminsky, R. Thomas Hawkins, and Frank Kowalski.[11] Following the invention of polarization spectroscopy by Carl Wieman and Ted Hänsch, Art and his students used polarized light to label specific angular momentum states.[12-15] These methods enabled Art and his associates to greatly simplify and then give assignment to the forest of absorption lines in molecular spectra.

Other advances during this time included the two-photon Doppler-free spectroscopy of sodium using a CW dye laser with Ted Hänsch et al.,[16] near-resonant enhancement of two-photon spectra with Sune Svanberg et al.,[17] observation of quantum beats with Serge Haroche and Jeff Paisner,[18] and Doppler-free opto-galvanic spectroscopy with James Lawler, Allister Ferguson et al.,[19-20] and polarization intermodulation spectroscopy with Ted Hänsch et al.[21] Also during this time William Fairbank, Jr., and Gary Klauminzer studied the excited-state absorption spectra of ruby, emerald, and $MgO:Cr^{3+}$,[22] and Fairbank demonstrated that it was possible

to use resonance fluorescence to detect a single atom in a laser beam.[23]

In 1981 Arthur Schawlow was named co-winner of the Nobel Prize for his many contributions to the development of laser spectroscopy. In his Nobel lecture "Spectroscopy in a New Light" he listed 21 of his most significant papers out of the 168 papers he had coauthored. Conspicuously absent from this list is a two-page paper published in *Optics Communications* in 1975 entitled "Cooling of Gases by Laser Radiation."[24]

In their paper Ted and Art outlined a proposal to cool atoms by surrounding the atoms with light from all sides, realizing that the atoms would lose kinetic energy by preferentially scattering laser light opposing the motion of the atoms due to the Doppler effect. They made a rough estimate of the final temperature by assuming that the initial Doppler width of the absorption line could be reduced to the natural line width of the scattering transition. In the case of magnesium they estimated that atoms in the vapor phase could be cooled to temperatures of ~0.24 K.

Their idea was demonstrated by Leo Hollberg, John Bjorkholm, Alex Cable, Art Ashkin, and myself (S.C.) 10 years after their publication. In our initial experiments sodium atoms were cooled to temperatures of ~0.24 thousandths of a degree above absolute zero. Progress in this field developed rapidly and by the year 2000 billions of atoms could be laser cooled to temperatures as low as 300 nanokelvin at densities greater than 10^{13} atoms/cm^3. Further cooling by evaporation in magnetic or optical traps has led to the formation of new states of matter: Bose condensates in a dilute gas and degenerate Fermi gases.

The field of laser cooling and trapping of atoms was recognized with a Nobel Prize in 1997 in recognition of the

revolutionary impact of this work on atomic physics, laser spectroscopy, and metrology. And in 2001 on the one-hundredth anniversary of the first Nobel Prize, a Nobel Prize was given to researchers who used laser cooling and atom trapping methods to achieve Bose condensation of a dilute alkali gas.

In 1987 Arthur Schawlow succeeded in convincing me (S.C.) to leave Bell Laboratories and join the faculty at Stanford University. Soon after arriving I settled into the enjoyable routine of retreating often into his office to unwind and discuss what was happening in my laboratory, with physics at large, and life in general. During one of these conversations I asked Art why he did not even *mention* his seminal laser cooling paper in his 1981 Nobel lecture. He shrugged in his characteristically modest and self-effacing way, "In 1981 how was I to know it was going to become important?"

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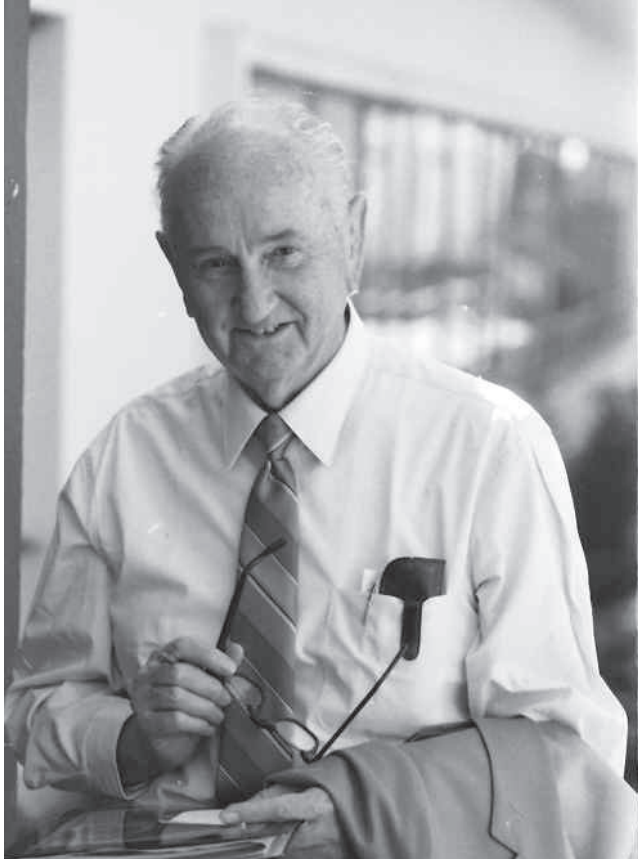
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CHARLES GALD SIBLEY

August 7, 1917–April 12, 1998

BY ALAN H. BRUSH

CHARLES GALD SIBLEY WAS born in Fresno, California, on August 7, 1917, and died at age 80 in Santa Rosa, California. He was not a small-town boy who simply moved upstate. Between his early years in Fresno and his ultimate move to Santa Rosa, Charles traveled worldwide to conduct and report on his research. He was one of the leading ornithologists during the latter half of the twentieth century, one of the founders and a major player in the emerging field of molecular systematics, and contributed significantly to our knowledge of the evolutionary relationships among the higher avian taxa.

Charles's intellectual intensity and excitement touched the lives of many of his contemporaries in ways both good and bad, and he influenced several generations of students. Few ornithologists have so polarized their students and colleagues. Ultimately his greatest impact may be the transmission of his ideas and intellectual fervor to students, which he did with an evangelical intensity, sometimes threatening his wrath but usually with the grace of a master communicator.

Charles was an exceptionally well-organized person, blessed with a fine intellect and an unyielding belief in himself. Those at the receiving end of one of his famous

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verbal debates or attacks may not have looked beyond their own bruised egos to appreciate his finer qualities. He was a generous person, giving freely and frequently of his time to students and colleagues, particularly if it involved discussions of science. He took pride in his broad understanding of biology and its processes, but he stuck to his own beliefs and understanding of biological "facts" until presented with unequivocal information that he was wrong. Then, immediately, he would champion the new information, never looking back to dwell on the fact that he may have been wrong. This contrary nature of being dogmatic on the one hand, while always welcoming new information on the other, made it difficult for some people to deal with Charles and his science, but for his students he was an endlessly variable, fascinating, and challenging role model.

Charles was associated with six universities over the course of his academic career. His first appointment was a one-year assistant professorship in 1948 at the University of Kansas. A year later he returned to his native state to join the faculty of San Jose State College (now California State University at San Jose) as an assistant professor of zoology. In 1953 he went to Cornell University as curator of birds and associate professor of zoology in the Department of Conservation. During his 12 years there Charles advanced to professor, taught ornithology to overflowing classes of both graduate and undergraduate students, developed Cornell's scientific collection of bird specimens, and mentored nine graduate students and one postdoctoral fellow. In 1959-60 he took a sabbatical year at Oxford University as a Guggenheim fellow. Back on the Cornell campus during the summer of 1962, he oversaw the activities of the 13th International Ornithological Congress. Broadly speaking, his research during the Cornell years dealt with hybridization between species-pairs and the molecular systematics of avian orders and families.

Charles, who prided himself as an ornithologist, joined the American Ornithologists' Union (AOU) in 1939, became an elected member in 1949, and a fellow in 1955. He served as treasurer for 11 years, from 1953 to 1963, and as president during the 1986-88 term. Before becoming president Charles served twice as vice-president and was elected to several terms on the Council. In 1971 he was awarded the Brewster Memorial Medal by the AOU, and in 1986 both he and his wife, Frances, became patrons of the organization he had served so often and well.

In addition to his AOU activities Charles was a secretary of the Cooper Ornithological Society, a fellow or corresponding fellow of six foreign societies, and an officer or council member of five societies. From 1958 to 1962 he served as the secretary-general of the 13th International Ornithological Congress, and from 1986 to 1990 he was president of the 20th International Ornithological Congress. Altogether he was a member of about 15 scientific societies, including all major ornithological societies of the United States, as well as Deutsche Ornithologen-Gesellschaft, Société Ornithologique de France, Asociación Ornitologíca del Plata, and Suomen Lintutieteellinen Yhdistys. He served on the editorial boards of *Evolution*, *Journal of Molecular Evolution*, and *Molecular Biology and Evolution*.

In 1965 Charles moved to Yale University as a professor of biology, the William Robertson Coe Professor of Ornithology, and curator of birds of the Peabody Museum of Natural History. In 1970 he was appointed director of the Peabody Museum of Natural History. During his years at Yale Charles advised another seven graduate students and three postdoctoral fellows. In 1986 he was elected to the National Academy of Sciences. That same year Charles retired and was named a professor emeritus of Yale University. Later that year he and Fran again moved back to California. There

he became affiliated with San Francisco State University as a Dean's Professor of Science and Professor of Biology. In 1988 Charles and colleague Jon E. Ahlquist received the Daniel Giraud Elliot Medal from the National Academy of Sciences in recognition of their contributions to our knowledge of avian systematics, and in 1991 Charles was awarded the Alessandro Ghigi Medal by the National Institute of Wildlife Biology (Italy). His final appointment occurred in March 1993 after moving to Santa Rosa. There he was named adjunct professor of biology at Sonoma State University, in part so that he could have continued access to his extensive personal library that he had given to the university.

In his conversations with students and colleagues Charles could generate great excitement about the potential of his research. He delighted in invitations as plenary or keynote speaker and he occasionally organized mini-symposia at scientific meetings, where he and his students would give papers updating their current research. Throughout his career he attracted individuals upon whose lives he made an indelible mark. Among those who studied with him are four AOU elective members, eight AOU fellows, an AOU secretary, an editor of *The Auk*, and an AOU treasurer.

Every project that Charles undertook demonstrated his talent for enlisting the help of an extraordinary diversity of people and expertise. For example, in 1961 when he first conceived of a DNA hybridization facility at Cornell, he sent K. W. Corbin to Bethesda to learn the techniques from the three investigators who had only months earlier developed the methodology. In 1966 when Sibley wanted avian blood samples from European species, he contacted a number of friends who would be at that year's International Ornithological Congress in Oxford, asking for their aid in that early work on hemoglobin; Charles was never hesitant

to enlist knowledgeable individuals well outside academia in order to achieve his goals in fieldwork.

No fieldwork of his illustrates this better than the immense effort he put into planning for the 1969 National Science Foundation expedition to Papua-New Guinea aboard the research vessel *Alpha Helix*. A year prior to that expedition Sibley and Prof. George A. Bartholomew (of the University of California, Los Angeles) made a comprehensive assessment of the potential field facilities, logistics, and personal contacts in that vast region. There they enlisted the cooperation and help of an amazing group of individuals, some of whom were local officials, administrators, ministers of either the Lutheran or Catholic churches, an archbishop, ranchers, pilots, local scientists and educators associated with the Australian National University facilities, members of the Australian Bush Patrol, telegraph operators, directors of sanctuaries, and native Papua-New Guineans.

As a youngster Charles was an avid birder and kept precise records of his observations very early on. He was introduced to natural history by reading John Burroughs and Ernest Thompson Seton. Close friend Robert Failing encouraged his interest in birds, and high-school teacher Jean M. Nelson was particularly supportive of his interests in natural history. Together they founded the natural sciences club at Oakland High School. In the mid 1930s as an undergraduate at the University of California, Berkeley, he gravitated to the Museum of Vertebrate Zoology (MVZ). MVZ had become a major center for the study of natural history under the direction of Joseph Grinnell, whose field notebook methods Charles would later use to fill 15 volumes that detailed years of fieldwork in his precise, unedited script. The MVZ maintained an emphasis on the fauna of the region, as well as an association with the museum of paleontology. Accordingly,

his first publications were on fossil birds obtained from the tar pits at Rancho La Brea in Los Angeles.

After graduation from Berkeley in 1940 (A.B. in zoology), Charles worked one year for the U.S. Public Health Service on plague suppressive measures. Military service intervened, and he was commissioned as an ensign in the U.S. Navy reserves. During the later stages of World War II he was called for active duty and rose to lieutenant as a communications officer in the Pacific theater during the last 19 months of the war. His primary station was on Emiru Island in the St. Matthias group, 75 miles off the northern tip of the Bismarck Archipelago. During his off-duty time he collected locally and sent scientific specimens back to the MVZ. That effort on Emiru was supplemented while on rest-and-relaxation expeditions to the Solomon Islands and the Philippines.

This combination of travel and the collection of scientific specimens was pure pleasure for Charles and would typify family travel experiences over his lifetime. As the years passed, his collection of museum specimens was replaced by the collection of egg-white and blood samples for serum, hemoglobin, and ultimately the extraction of DNA. For example, following the 14th International Ornithological Congress in Oxford, England, Charles organized a month-long European vacation around visits to zoological gardens, aviaries, and the homes of European colleagues in an ongoing effort to obtain critical species for his research.

After the war and now married, Charles returned to Berkeley in 1946 to pursue a doctoral degree under the direction of Alden H. Miller, who was himself a protégé of Joseph Grinnell. By the mid-1940s Miller had followed Grinnell into the directorship of the MVZ and was particularly interested in species-level taxonomic problems. At that time Charles met John Davis, another incoming Miller doc-

toral student, whom he joined on a series of collecting trips to Mexico. As a result Charles became fluent in Spanish, learned the ropes of carrying out fieldwork in Mexico, and was introduced to some peculiar Mexican bird specimens collected by Helmuth Wagner.

Those specimens turned out to be hybrids between two species of towhee in the genus *Pipilo.* Subsequently, for his doctoral research Charles decided to examine the complex patterns of plumage variation caused by hybridization and the breakdown of species-specific reproductive isolating mechanisms between the red-eyed towhee, *P. erythrophthalmus,* and the collared towhee, *P. ocai,* along the transvolcanic plateau of Mexico. This was a zone of hybridization that stretched nearly 500 miles from southeastern Jalisco to the states of Veracruz and Puebla. His thesis "Species Formation in the Red-eyed Towhees of Mexico" was published as volume 50 of the University of California Publications in Zoology and was the first of 17 of his publications that dealt with avian hybridization.

A major contribution of his doctoral work was the application of a method for summarizing the plumage variation among hybridizing individuals as a single number, a hybrid index value. The establishment of a species-specific hybrid index scale was an extraordinarily powerful and ingenious method for analyzing complex, multigenic traits whose morphological patterns shifted geographically due to hybridization between incipient species. The method was later used by his first group of graduate students to study the complex patterns of hybridization between species-pairs in the Great Plains of North America. In retrospect, Charles's doctoral research can best be described as an early descriptive stage in the development of his understanding of the role played by hybridization, both during the process of speciation and as a result of the breakdown of reproductive isolating mecha-

nisms. These were significant conceptual and methodological contributions to our understanding of hybridization as a mechanism of evolution.

After Sibley moved to Cornell University the hybridization studies were extended to include other species-pairs that hybridized throughout the Great Plains of North America. They included Bullock's and Baltimore orioles, yellow-shafted and red-shafted flickers, indigo and lazuli buntings, and rose-breasted and black-headed grosbeaks. Those years were heady, exciting times for him, involving his first graduate students, David A. West, Lester L. Short, Fred C. Sibley (unrelated), and Paul A. Johnsgard in many field trips to collect hybrids along the Platte River and elsewhere in Colorado, Kansas, Nebraska, and the Dakotas. In addition he revisited the Mexican highlands to extend his earlier work there.

Although the hybrid index method had proven to be a powerful tool for studying the complexities of hybridization for the breakdown of reproductive isolation, by 1958 Charles was looking for better ways to quantify the degree of introgression between species-pairs. Simultaneously Paul Johnsgard was in need of financial support to complete his own doctoral thesis. In an attempt to resolve both issues Charles wrote a small proposal to the National Science Foundation to examine the possibility of using the new technique of paper electrophoresis to study species-specific variation in the serum proteins of game birds. If successful, it might be applied to the analysis of genetic variation in hybrid populations.

As the research assistant in this small study Johnsgard followed Charles's instructions to the nth degree—almost. It was the "almost" that would prove to be serendipitous. Like most of Charles's students both then and subsequently, Paul stood in mortal fear of invoking his wrath. Departure

from the laboratory protocols was a cardinal sin. Paul, however, had read McCabe and Deutsch's earlier paper on the electrophoresis of egg-white proteins. Out of curiosity and a broader interest, but without Charles's consent, Paul included a few egg-white samples along with the serum samples during his electrophoretic analyses.

At it turned out, even with the crude technique of paper electrophoresis, the serum protein electrophoretic patterns seemed much too variable among individuals to be applied to the hybridization studies. (Recall that at that time nothing was known about protein variation, either within or between species.) Lamenting this and greatly discouraged, Charles began to write up the results as a report to the National Science Foundation. It was then that Paul mustered the courage to reveal his covert analyses. The egg-white electrophoretic patterns were consistent among individuals of a species and differed among the few species that had been examined. Charles instantly recognized the implications of those observations. A powerful new tool and a new set of characters were awaiting application by systematists. Almost overnight he put aside his plans for using serum proteins to study the variation among hybrids and began to lay plans for an electrophoretic study of egg-white protein variation in birds. Over the subsequent decade and a half that research would become a massive comparative taxonomic study of the higher avian taxa. Indeed, the relationships among avian orders and families would be at the forefront of his research interests for the remainder of his life. Thus began the next phase of Charles's research, which would overshadow the earlier work throughout the 1960s and into the early 1970s.

The move to electrophoretic analyses of egg-white proteins involved a major shift in Charles's career. Along with Herb Dessauer of Louisiana State University, who studied reptiles and amphibians, and Morris Goodman of Wayne

State University, who studied primates, Charles became one of the founders of molecular systematics. For each of these men this shift required a great deal of retooling both mentally and in the laboratory. The transition involved a move from activities that primarily used classic fieldwork coupled with comparative morphology to one of daily laboratory analyses using the methods of comparative biochemistry. As one might expect, the new approach was also encumbered with some of the old thinking.

A peculiar bias that Charles carried concerned the genetic variation of structural proteins versus enzymes and the ways that natural selection would constrain the latter. He, along with one of his colleagues at Cornell, believed that enzymes would be invariant in their amino acid sequences due to evolutionary constraints on their activity. Enzymes, in their view, functioned only at specific temperatures and pH values, and natural selection would weed out all but the most effective structure for each enzyme and species. Indeed, during the early 1960s Charles and his colleague believed that an enzyme's primary structure might prove to be identical both within and among species. Any variation in an enzyme's structure would render it inactive according to their logic, and they knew little about the newly discovered phenomenon of allozymes being studied by Allan C. Wilson at the University of California, Berkeley, and Clement C. Markert at Johns Hopkins University. Thus, in their view enzymes would be unlikely to carry phylogenetic information and would be useless for both systematic and population genetic studies. Throughout much of the 1960s, informal debates on this issue occurred between Charles and Wilson.

Wilson's careful studies of allozyme variation, coupled with Markert's research on picine lactate dehydrogenases, eventually convinced Charles that enzymes did in fact vary within species. This conversion provided the basis for another

attempt to study the hybrids of the Great Plains. Though the shift in research was tangential to his main interests, it began in 1969 during the *Alpha Helix* expedition to Papua-New Guinea, where the laboratory work took place aboard the ship. Though the primary thrust of that expedition was to be a general sampling of the fauna of the world's second largest island, Charles's team also carried out some population genetic studies. Among other research problems, these included both hybridizing species-pairs (birds of paradise of the genus *Paradisaea*) and non-hybridizing species complexes (starlings of the genus *Aplonis*). In fact, of the 22 members of that expedition, 9 subsequently focused their activities on different studies of allozyme variation within and among populations. In addition to Charles, who was the prime mover and organizer of the expedition, the molecular systematists were H. C. Dessauer, A. C. Wilson, K. W. Corbin, A. H. Brush, A. Ferguson, J. E. Ahlquist, R. Storez, and V. M. Sarich.

From the outset of that work Charles was impressed by the analytical results involving two classes of enzymes, the esterases and the dehydrogenases. Both were variable within and among populations, and the frequencies of their variants (i.e., alleles) could be used to characterize individual populations. Within a few weeks of seeing the first electrophoretic results aboard the *Alpha Helix*, Charles began to think about applying the new methods to the hybrids of the Great Plains. The approach would be to sample populations of hybridizing species-pairs at intervals across the hybrid zone, just as in the earlier studies of plumage variation. This time, however, in addition to the construction of hybrid indexes, polymorphic enzymes, esterases perhaps, would be analyzed for their variation by means of electrophoresis. In contrast to the introgression of complex multigenic traits as quantified by hybrid indexes, the electrophoretic studies

of gene flow would involve single gene traits with simple patterns of inheritance.

The following year those plans began to unfold. The research vessel would be a modern prairie schooner, an Airstream trailer, outfitted with all essential electrophoretic equipment. A full crew was put in the field. After the first week the collecting focused on orioles and a study of the introgression of genetic variation caused by hybridization between the Bullock's and Baltimore orioles. The results flowed in. Specimens were collected in the mornings and late afternoons; during the midday periods enzymes were extracted and analyzed by means of starch gel electrophoresis. The database mounted and soon became impressive, encouraging the collecting party westward in 50-mile leaps across the zone of hybridization, and then back eastward, filling in the gaps between the initial collecting localities.

The collecting continued in 1971 and 1974. The results of the population genetic analyses confirmed the earlier morphological studies. Gene flow across the Great Plains was extensive, at least among populations of orioles. Alleles at esterase loci were being exchanged between the eastern and western populations, just as the plumage characters flowed eastward and westward through the filter of the zone of hybrids along the Platte River in Nebraska and Colorado. Presumably gene flow was comparable in the other riparian habitats stretching across the plains, although Charles's studies of the patterns of hybridization in the Mexican towhees showed that such assumptions might be unwarranted. Nevertheless, these studies and those by others revealed that the species of these hybridizing species-pairs might in fact be subspecies. This recognition was reflected in later versions of the *AOU Checklist of North American Birds.*

By 1974 Charles was already a decade and a half into

the taxonomic comparison of the egg-white proteins. The early electrophoretic methods for the separations of proteins on paper strips soon became obsolete. Paper electrophoresis gave way to starch gel electrophoresis, whose relatively crude resolution potential was supplanted by polyacrylamide gel electrophoresis and eventually by isoelectric focusing in either polyacrylamide gels or agarose plates. In an ongoing attempt to refine and improve his comparative data, Charles adopted each new improvement almost as soon as it became commercially available.

Early on he was convinced that the comparative study of protein variation could aid significantly in determining avian phylogenetic relationships at the higher levels of classification. He was equally certain that the methods would not be much help at the levels of species and genera. Although protein differences were basically phenotypic characters, they differed in one significant way from the traditional morphological characters used by most systematists at that time. Namely, protein structure, determined by amino acid sequences, was only one step removed from the genetic code itself. Consequently, differences among proteins were a more direct reflection of the underlying genetic similarities and differences among species than was gross morphology. It was this relationship between genes and the traits they encoded, in this case the primary structure of proteins, that convinced Charles he was on the right track.

The first results of the early electrophoretic studies suggested that the relationships among the higher taxa might be determined with relative ease. The protocols were simple: obtain egg white from the species of interest, separate the proteins of each sample on either starch or polyacrylamide gels under appropriate controls and standard electrophoretic conditions of wattage and time, stain the gels with amido blue black, photograph the gels, and then compare the

resulting patterns. Voila! Evolutionary relationships were revealed like never before. It was a heady time, and the world was watching and waiting for the results. Some were envious that Charles was making such headway in solving age-old taxonomic problems, others were bitter that their own expertise was being eclipsed, but most ornithologists were enthusiastic about the progress being made.

By as early as 1959 the Cornell laboratory was deeply involved in a comparative study of the egg-white proteins by means of acrylamide gel electrophoresis in small glass tubes. Soon thereafter, and with his usual skill, energy, and enthusiasm, Charles was extolling the virtues of those data in resolving longstanding systematic problems. At annual scientific meetings and through invited lectures in North America and Europe he spread the message about the wonders of the new comparative methods. In 1960 he eagerly presented data that demonstrated the affinities of the Old World sylviids and muscicapids in contrast to their more distant New World cousins, the parulids. By the time of the 13th International Ornithological Congress, which was held in 1962 in Ithaca with Sibley as secretary-general, there were electrophoretic data bearing upon the relationships of many more avian families.

The methods of electrophoretic analysis may have been relatively uncomplicated, but the effort to examine the evolutionary relationships of all the higher avian taxa by means of electrophoresis was daunting. There were the nests of thousands of species to find. Each egg-white specimen had to be compared electrophoretically over and over again. Thousands of analyses were carried out over almost two decades. Nothing but unequivocal data would satisfy Charles's objectives. How else could one compare all of the higher avian taxa by means of this new technology? The museums of the world housed the scientific specimens needed for

comparative morphological studies, but there were no depositories of egg-white specimens. Every species used in Charles's research program had to be collected by him and his collaborators.

Charles set out to do that, encouraging volunteers from throughout the world to collect samples and ship them to Cornell University. The effort was massive and profoundly successful. For over a decade the samples came in from every continent. Willing students acquired collecting permits, risked their necks climbing trees and cliff faces, combed forests, prairies, and tundra, all in search of samples from both common and rare species. Hosts of both professional ornithologists and amateur birders collaborated in the effort. Along the way more than a dozen technicians carried out the lab work that was completed at Cornell and Yale. The effort was monumental and culminated in two monographs published by the Peabody Museum of Natural History at Yale University: the first authored by Charles alone (1970) and the second coauthored with J. E. Ahlquist (1972). Charles was proud of these publications, as well he should have been. Many taxonomic problems were resolved, although others remained.

In addition to the egg-white protein studies there were side excursions to utilize other protein systems either by way of confirmation or for specific taxonomic problems. One of these, coauthored with A. H. Brush, involved an extensive study based on the electrophoretic variation of eye lens proteins. Another, coauthored with H. T. Hendrickson, involved the plasma proteins. Two particularly intractable taxonomic problems, one involving the relationships of the flamingoes and the other the relationships of the seed snipe, were tackled by using ion-exchange column chromatographic techniques to examine variation in the tryptic peptides of hemoglobins. Other studies were never published. The most

important of these was a massive database developed at Yale dealing with the electrophoretic variation of avian hemo-globins Sanples were obtained from over half of the then recognized bird species. Another study involved the use of serology to examine the blood serum proteins of muscicapids and sylviids. Ultimately it was the study of the egg-white proteins that paid the highest dividends.

The egg-white studies of the birds of the world, following those of avian hybridization on the Great Plains, would have been a life's work for most individuals in academia, but not for Charles. As the successes of the electrophoretic analyses of the egg-white proteins began to accumulate, a new technique was being tested in his laboratories at Cornell and later at Yale. The method's early development by others was an attempt to examine differences in DNA molecules by means of annealing, or hybridizing, short fragments of DNA to one another. The technique soon became known as DNA-DNA hybridization. Although Charles's laboratory at Cornell began to explore the potential of the method as early as 1963, another decade would pass before Charles had perfected the "DNA machine" in his laboratories at Yale.

The DNA-DNA hybridization studies involved the development of another tissue collection. Initially, while at Cornell, an attempt was made to use tissue culture methods to grow avian fibroblasts obtained from embryos. This method was soon abandoned due to technical problems and the availability of a more direct method. Because birds have nucleated red blood cells, blood samples were the obvious and expedient source of DNA. By the mid-1970s studies of the proteins of egg white, blood, and eye lenses were all but complete; it was time for the DNA studies to begin in earnest.

The years at Yale were some of the best for Charles and some of his worst. The best saw the publication of his egg-white monographs by the Peabody Museum of Natural His-

tory and the development of the DNA-DNA hybridization database. By 1986 the latter was being used to piece together a comprehensive phylogeny of the orders and families of the birds of the world. In printed form the dendrogram spanned more than 20 feet along the walls of poster sessions held in conjunction with annual scientific meetings during the 1980s. It thus became known as the tapestry and was a phenomenon in itself, as groups of people simultaneously examined its details.

The worst moments at Yale involved allegations against Charles for two kinds of scientific impropriety. The first was a federal indictment alleging that he had illegally imported the egg white of six European species, including one that was wholly fictitious and contrived by unknown individuals, either within or outside the U.S. Fish and Wildlife Service. After a good deal of media attention and the paying of a substantial fine, this episode eventually led to Charles's resignation of the directorship of the Peabody Museum of Natural History. It was a sad moment, indeed, for a man who had prided himself for following the federal guidelines regarding the necessary scientific collecting permits here and abroad. It was simultaneously a black mark against the scientific community that did so little to protest this injustice. Sibley never explained why he chose to pay the fine uncontested.

From a scientific point of view the second allegation was much more serious. It involved the informal charge that the analyses of DNA-DNA hybridization data had been manipulated to yield results that conformed with preconceived notions of phylogenetic relationships. One could argue that the methods of data analysis were not as rigorous as they might have been. There were certainly differences of opinion among the members of Sibley's own research group on how best to quantify and summarize the data; however,

this was an aspect of natural growth and did not constitute fraud. In fact, the issue probably would never have arisen if Charles and his group had not ventured into the treacherous waters involving human evolution. The debates in that arena are legendary, beginning with Raymond Dart and leading up to today's antagonists. In Sibley's case the issue revolved around rates of genetic change along different phylogenetic lineages: specifically, the one that led to the genus *Homo*, the other leading to the remaining higher primates. It was this debate that focused the attention of the scientific community on Charles's preferred methods of analysis of the DNA hybridization data. At its heart the issue was whether the entire genome of an organism evolved at a constant average rate, as Charles maintained. Although there is solid evidence to suggest that rates of change do differ among different lineages, the issue is still unresolved.

As in all other matters of his life Charles believed in himself. He believed unequivocally that his analyses of the relationships of the birds of the world were correct. In 1990 Yale University Press published two massive scientific contributions. One, in collaboration with his close friend and colleague Burt Monroe, Jr., was *Distribution and Taxonomy of the Birds of the World,* a comprehensive treatment of all avian species recognized as of 1990. The other, with his longtime associate Jon E. Ahlquist, was *Phylogeny and Classification of the Birds of the World: A Study in Molecular Evolution.* This was the tapestry, along with all of the supporting data.

Charles knew the history of systematics well. He knew better than most that classifications were always under review and modification, and he did not delude himself into believing that his classification would be the final word on avian taxonomy. One of his dreams, however, during the early phase of the DNA research was to be able to read off

nucleotide sequences from a DNA molecule. That was the
kind of precision he sought, knowing full well that the tech-
nology of the 1970s and 1980s was not up to that task.
Today automatic DNA-sequencing methods produce long
sequences of nucleotides, and several genome projects are
at or nearing completion. Already his students and their
students have built upon the contributions made by Sibley
and his group. The possibility of eventually reaching a con-
sensus with regard to the phylogenetic relationships of birds
is certainly obtainable, something that would give Sibley
immense satisfaction.

Charles passed away at his home in Santa Rosa on Easter
Sunday, April 12, 1998, from myelogenous leukemia. He is
survived by Frances, his wife of 56 years, whom he met as
Frances Louise Kelly, and their daughters, Barbara Susanne,
Dorothy Ellen, and Carol Nadine.

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JOSEPH SLEPIAN

February 11, 1891–December 19, 1969

BY T. KENNETH FOWLER

JOSEPH SLEPIAN, INVENTOR of the ignitron and other main stays of the electric power industry, after a lifetime career at the Research Laboratories of the Westinghouse Electric Corporation, died on December 19, 1969. Elected to the National Academy of Sciences in 1941, Slepian was a member of Section 31, now called Engineering Sciences. Indeed, his career exemplified the union of these disciplines.

Holder of 204 patents at Westinghouse, Slepian began his career as a pure mathematician. He was born in Boston on February 11, 1891, son of Russian immigrants. Advanced student status in high school allowed him to enroll at Harvard University at age 16; he made Phi Beta Kappa and received his bachelor's degree in 1911, his master's degree in 1912, and a Ph.D. in mathematics in 1913. All during this time he maintained odd jobs to help support himself, including a stint as a licensed motorman on the Boston Electric Railway.

After Harvard Slepian was able to continue a year of postdoctoral studies as a Sheldon fellow, first at the University of Gottingen in Germany and then at the Sorbonne in Paris. He returned to the United States in 1915 and accepted a position as instructor of mathematics at Cornell

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University. After only a year at Cornell he resigned his position to join the Westinghouse company at its East Pittsburgh Works as a student apprentice in the railway motor department. By 1917 the company had moved Slepian to the research department, shortly before the establishment of its pioneering independent research facility at Forest Hills in 1918. He advanced quickly, as head of the General Research Section in l922, research consulting engineer in 1926, and associate director for research from 1938 until his retirement in 1956.

Slepian's move to Westinghouse proved a happy transition for all concerned, his prolific output of patentable inventions for the company being exceeded only by those of George Westinghouse himself. According to colleagues Slepian made maximum use of his mathematical talents in his new career, his inventions invariably being the consequence of careful science and theoretical analysis. In fact his talent for invention had already emerged at Cornell, where in 1915 he filed a patent for a device to measure the speed of a boat by means of magnetohydrodynamics. By 1919 he had produced his first patent at Westinghouse, for circuit interrupters. He was still pursuing inventions when I first met him, late in his career, when he was developing a new plasma method of isotopic separation, his ionic centrifuge that he pursued before and after retirement, with 20 publications on this topic alone, most of them in the *Proceedings of the National Academy of Sciences*.

Slepian's first major success at Westinghouse led to the autovalve lightning arrester, at a time when the cost and maintenance of conventional electrolytic arresters no longer served the needs of a growing industry. His pioneering research on lightning arresters began in 1920, three years after his transition to a career of engineering research. Characteristically, when presented with the problem, Slepian first

conducted a thorough analysis of the operation of electro-
lytic lightning arresters during a discharge—research that
disclosed the need for surge protection that he would solve
with a countervoltage produced by a glow discharge in air.
This in turn led to his many experimental and theoretical
contributions to the field of electrical conduction through
gases and a familiarity with plasma physics that inspired
even his later work on the ionic centrifuge. Slepian's care-
ful study of ionized gases also prepared the way for other
notable inventions, including the deion circuit breaker and
the workhorse ignitron mercury rectifier familiar to me from
my earliest contact with laboratory experiments on plas-
mas.

Slepian's contributions to the ignitron followed a pat-
tern established in his work on arresters. Though already
commercial, mercury rectifiers had reached an impasse:
unacceptable "arc-backs" that required deep analysis to un-
ravel. Slepian provided this analysis, leading him to pro-
pose separating the multiple rectifier anodes into individual
chambers, which was the first step toward the ignitron de-
sign. There followed an intensive period of research to pro-
vide a means of extinguishing and then initiating anew the
mercury arc on each operation cycle, dependably, when
required, without appreciable time lag. More than 4 mil-
lion kVA in ignitrons had been installed by the late 1940s.

The deion circuit breaker was also the result of detailed
scientific research, in this instance on the nature and ori-
gin of arcs. As in his other research his work always in-
volved observation and experiment as well as theory. Though
first a mathematician Slepian had also become a productive
and careful experimentalist in the laboratory. It was he who
discovered plasma arc regimes not requiring thermionic
emission of electrons from the cathode, at gas densities
well below those thought possible before his work on cold-

cathode heavy-current arcs. The practical result was the deion circuit breaker, employing the cold-cathode technique together with ingenious annular electrodes and voltage distribution that avoided thermionic hotspot emission that would otherwise spoil the almost instantaneous buildup characteristic of the cold-cathode operating regime.

A highlight in Slepian's career was his receipt of the Edison Medal in 1947, in part for his inventions of the autovalve lightning arrester, deion circuit breaker, and ignitron cited above. Marveling that a one-time pure mathematician would receive an award honoring a man like Edison, Slepian in his acceptance speech reflected wisely on the productive interplay of mathematics, science, and engineering. It is appropriate to quote here excerpts from his remarks, published in full in *Electrical Engineering* (67[1949]:258-61).

That a man with my particular kind of talents, abilities and personality should win a high engineering honor may seem very remarkable. . . . The dominant interest of my youth, and the kind of formal education it led me to acquire, certainly did not presage distinction in such fields.

I have pondered on what rightly may be called the really distinctive features of the mathematician, scientist and engineer. There seem to be two ways of logically distinguishing among them. One . . . is by the kinds of skills they display . . . their crafts. The other, and which I think strikes deeper, is by their motivations or compelling interests.

Let me proceed then to ask these questions. When the mathematician is doing that which is uniquely mathematics, and cannot possibly be said to be physics, or chemistry or other science; when the physicist, as a typical scientist, is doing that which is uniquely physics and cannot be said to be mathematics or engineering; when the engineer is doing that which is certainly engineering; what are their respective distinctive motivations and compelling interests?

My answers lead to the following definitions.

The "mathematician" is one whose interests and activities lie in determining and studying how things *may* fit together, that is, what are *possible* systems of order, and what are the details of such possible systems of order.

The "scientist" is one whose interests and activities lie in determining what is the *actual* order of things in the physical world and studying the details of that order.

The "engineer" . . . is one whose interests and activities lie in devising, designing, constructing or controlling the operation of physical devices, machines, technical processes, or services which have practical utility . . . [making] use of the accumulated knowledge, skills and techniques of the "mathematician" and the "scientist."

We know now that while "mathematicians" and "scientists" carry on their activities for "their own sake," that is for aesthetic reasons or other intellectual satisfactions, nevertheless, their work will lead to radical and revolutionary advances in technology in the future. The invention of the number system in which all algebraic equations, including $x^2 + 1 = 0$, have solutions, had to be done by the "mathematician." The "engineer" could not anticipate its utility for solving practical A-C problems. Only a "physicist" would be engrossed with the faint glows given off by certain rare minerals. How would the "engineer" know that these faint glows were the indications of tremendous technically utilizable forces within the atom?

With these examples before us, we see that while there are also other important reasons, we must support "mathematics" and "science" in the United States because of the inevitable future advances in technology which they will induce. To make "mathematics" and "science" flourish, we must create for "mathematicians" and "scientists" a favorable atmosphere.

High above all other requirements in the favorable atmosphere is that of freedom; freedom to choose their work or object of interest, freedom to write and publish, freedom to communicate with their fellows.

Slepian found his own favorable atmosphere at the Westinghouse Research Laboratories, a model for other corporations at the time the Forest Hills laboratory was cre-

ated. "Sometimes," he wrote for his twenty-fifth class reunion at Harvard, "I look with envy at the apparently more leisurely and less harassed lives of acquaintances in university circles, and at one time I nearly changed over to this field, but on the whole I think I am in the work and place best suited to me . . ."

Besides his own research and inventions Slepian was a valued consultant, much sought for his advice by others in the company. During World War II he both participated in the Manhattan Project and served as consultant to the Office of Scientific Research and Development, and as a dollar-a-year man with the War Production Board.

Despite leaving academia as a profession Slepian never lost interest in teaching, fulfilled at Westinghouse by his own initiative in organizing informal courses on a variety of topics, including vector analysis, the theory of electricity and magnetism, the kinetic theory of gases, and the conduction of electricity through gases. In addition, besides practical inventions, in 1922 he filed for a patent, issued in 1927, for the idea of accelerating electrons by magnetic induction, later employed in the betatron accelerator developed by Donald Kerst at the University of Illinois and used widely in nuclear physics research.

Slepian published 121 technical papers, articles, and essays, some of which are listed below. In 1933 Westinghouse Electric Company published his book, *Conduction of Electricity in Gases*, a compilation of his lectures for Westinghouse colleagues. This book became a classic, used by physicists and educators throughout the world.

In addition to receiving the Edison Medal in 1947, Slepian was the recipient of the John Scott Medal at the Franklin Institute in 1932 and the American Institute of Electrical Engineers' Benjamin Garver Lamme Medal in 1942. He was elected a fellow of AIEE in 1927 and the Institute of Radio

Engineers in 1945 (predecessors of the Institute of Electrical and Electronic Engineers). He received the Westinghouse Order of Merit in 1935. In 1939 his scientific contributions were recognized by the French with the title Officer de Academie. In 1949 he was awarded an honorary doctor of engineering degree by Case Institute of Technology (now Case Western Reserve) and in 1955 an honorary doctor of science by the University of Leeds.

At the Lamme medal ceremony L. W. Chubb, then Westinghouse director of research, painted a charming picture of the young mathematician turned engineer.

When he first arrived at the engineering laboratories, I happened to be in charge and in a position to recognize his unusual qualities.

On one occasion the rest of us were so busy on some development that I could not assign Doctor Slepian to a new job at the moment. Instead of marking time until we finished, Slepian asked my permission to study a complicated setup of large motors, electrolytic condensers, reactors, instruments, transformers and disorderly wiring and cables in a nearby room. Permission granted, he traced the circuits and made a complete schematic diagram of the system on a large piece of paper. He did not recognize the electrolytic condensers, and I explained them to him.

Without further assistance, he deduced that the setup was designed to explore operation of polyphase induction motors from a single-phase power line. He not only learned about this specific problem but went on from there, in a short period analyzing the general problem of phase conversion, and making several inventions for both static and rotating phase splitters. His initiative and independence have not lessened during the years since then.

Slepian suffered a stroke in 1951, but though handicapped by health problems, he continued at the Westinghouse laboratory until his retirement on February 28, 1956. In private life he loved music, art, and literature. He was a season ticket holder for the Pittsburgh Symphony Orches-

tra for over 40 years. He liked to joke, and his friends enjoyed his incisive sense of humor.

He married Rose Myerson in 1918. They had two sons, Robert and David, both of whom followed with distinction in their father's footsteps, Robert at Westinghouse and David at Bell Laboratories. David was elected to the National Academy of Sciences in 1977.

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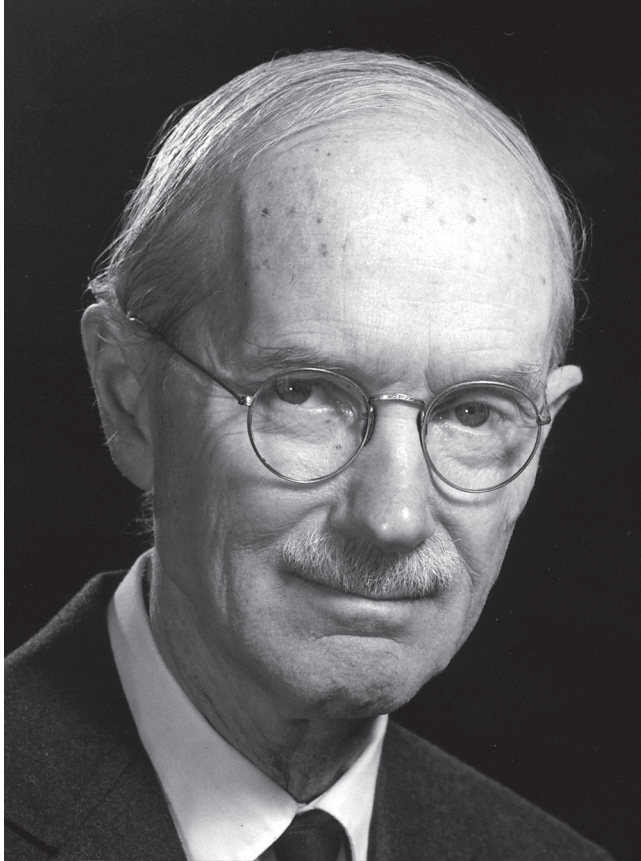Failure of the ionic centrifuge. *J. Appl. Phys.* 26:1283.
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George D. Snell

GEORGE DAVIS SNELL

December 19, 1903–June 6, 1996

BY N. AVRION MITCHISON

G ENETICIST GEORGE SNELL is known principally for his part in the discovery of H2, the major histocompatibility complex (MHC) of the mouse and the first known MHC. For this he shared the 1980 Nobel Prize in physiology or medicine. He was elected to the National Academy of Sciences in 1970. Most of his life was spent at Bar Harbor, Maine, where he worked in the Jackson Laboratory.

George was proud of his New England roots, moral and intellectual. His life was passed in the northeast, apart from brief spells in Texas and the Midwest. He was born in Bradford, Massachusetts, and at the age of 19 went to Dartmouth College, where he obtained his B.S, degree in biology in 1926. He went on to Harvard University, where he obtained his D.Sc. four years later at the Bussey Institution. During his last year he served as an instructor back at Dartmouth, and in the following year served again as an instructor at Brown University. He then obtained a National Research Council Fellowship to work at the University of Texas in the laboratory of H. J. Muller (1931-33) and returned there 20 years later to spend a sabbatical year reading up on ethics, as mentioned below. He moved to Washington University in St Louis as an assistant professor

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(1933-34). In 1935 at the age of 32 he joined the Jackson Laboratory, then directed by its founder Clarence Cook Little, where he remained until retirement in 1973. His death followed a year after the loss of his beloved wife, Rhoda. They had three sons, who became respectively a manager of a data processing center, a manufacturer of hi-fi loudspeakers, and an architect, all in New England. Sadly, one son suffered an untimely death in 1984.

In an autobiographical note written in 1989 George writes,

My paternal grandfather, my father, and a brother all held patents; now a son has one. None were big money makers, but in each case at least one had commercial value. I would thus assume that insofar as I have an inclination to invent, this came from my father's side of the family.

My mother was . . . a natural planner, a faculty which showed in her carefully designed and tended garden. Gathering and arranging facts are, I think, important antecedents to scientific creativity, and insofar as I have been effective in coping with these antecedents, I think my debt is mostly to my mother.

As a boy, aside from enjoying science and mathematics in school and reading an occasional book on science at home, I don't think I showed any unusual scientific bent. My family spent the summer months in South Woodstock, Vermont, which was then primarily a farming community. Every farmer had a rifle for hunting. . . . I remember trying to devise a mechanism for a repeating rifle that would be different from the two I was familiar with. This never got beyond the thinking stage and I doubt if it had a design that would work, but it was an activity that I enjoyed. In our year-round house in Brookline, Massachusetts, one of my friends and I had a rainy day activity—telling what we called change-around stories—that certainly required some imagination. The idea was to get the hero of the story into the worst possible predicament and then leave it to the other storyteller to extricate him. It was not until I studied genetics with Professor John Gerould at Dartmouth College that I became sufficiently involved in any branch of science to think of making it a career. Even then, it was not until I graduated that I finally decided, with the encouragement of Professor Gerould, to enter a graduate school.

George also mentions his love of ball games, from child-hood on. Later his colleagues remember him playing volley ball with enthusiasm—and he was very good.

My own memory of George is of the warm welcome he gave me for a very happy year spent in his laboratory, in the excellent company of Nathan Kaliss, Sheila Counce, and Gustavo Hoecker. George himself was away in Texas writing his ethics book for much of the time, but a rich moment in my life was at the end of the year when he whisked me off into the awesome presence of Little. I vastly appreciated the liberal encouragement that they both gave (but still with a touch of caution on their part about referring to "antigens"), and was duly impressed when George later encouraged me to publish the work on my own.

Personally George was gentle and considerate, but at the same time intellectually stalwart, determined, and creative. Neither flamboyant nor self-assertive, he never built a school or in his formative years published many multi-author papers, and he found little need for technical innovation. He worked within a tradition of classical Mendelian genetics that flourished through most of his lifetime and still connects today with molecular genetics. The Jackson Laboratory with its magnificent mouse facility suited George perfectly, and he provided exactly the foresight and drive that it needed. He was not a good speaker, so the relative isolation there must have been a benefit. In fact, George defined the Jackson phenotype: Stick to your knitting for as long as it takes and let the breeding of mice set your pace. This is well illustrated by his relationship with cellular immunology. George was already working in transplantation at the end of World War II. He realized that immunology would burgeon and that his work on the MHC would help it to do so. He initiated work on immunological enhancement and reviewed developments in immunology on sev-

eral occasions. Yet he never allowed himself to be diverted from his commitment to genetics.

Stories grew around this friendly and unassuming man. Following the 1947 blaze in the Acadia National Forest that destroyed much of the Jackson facility he restarted his research from the remnants that he helped rescue. In the furor after the Nobel Prize the Jackson receptionist denied knowledge of him, and the reporters were told by his neighbors that yes, they had been expecting him to get a prize— for his vegetables. The stock from his prize chives is still handed down among the Jackson geneticists, and his vegetable patch can still be seen on Atlantic Avenue. Jan Klein cites the mice that bear the label "/Sn" as his living monument.

On the advice of Gerould, George went to graduate school at Harvard under the guidance of William Castle, a pioneer of mammalian genetics. George used to say that Castle assigned him to work with mice because he himself didn't like their smell. The mice of the time were domesticated, but did not belong to defined laboratory strains of the modern kind. To start with, George worked on linkage in mice of the "fancy," using mutations collected by amateur breeders, such as short-ear, dwarf, ringed hair, hairless, and naked. By 1996 (his last and posthumous paper) he had studied a total of 26 such visible mutations. This represented a major contribution to formal genetics, whose task it was to establish the linkage groups of selected species such as the mouse. He delighted in the molecular characterization of these genes that began in the last years of his life. Certainly the visible mutations proved very useful later when he came to map his immunological genes.

In the 1930s George developed an interest in the new field of physiological genetics. The control of growth intrigued him, as it did others at the time, including Little. In

retrospect one is amazed at the temerity of the biologists of that era. In Oxford the young Peter Medawar, whose ideas about immunology were later to converge with those of George, had begun his research career by studying the growth of embryos. George collaborated briefly with Douglas Falconer of Edinburgh University, later a great authority on the genetics of mouse growth. Today the quantitative genetics of growth is still regarded as a formidably difficult subject.

While at Harvard, and as was the custom of Harvard biologists, George spent summers working at Woods Hole. There he joined Phineas Whiting, an earlier student of Castle's, in studying the genetics of the parasitic wasp *Habrobracon.* This species is the prototype example of haplo-diploidy (i.e., haploid males, diploid females), and his 1932 and 1935 papers are devoted to this subject, in particular to the role of male parthenogenesis in the evolution of the social hymenoptera. The topic was to emerge again later, when Hamilton identified the relative genetic proximity of sisters in haplo-diploid species as a key to the evolution of altruism. George discusses the point in his 1988 book on ethics, and one wonders what part this wasp played in forming his abiding interest in the evolution of social behavior. Might he have become a sociobiologist had the right idea struck him in time?

For his postdoctoral work he joined the laboratory of H. J. Muller at the University of Texas. Muller had discovered that radiation induces mutations in *Drosophila.* In a series of papers between 1933 and 1946 George proved that same effect could be obtained in the mouse, as a representative species of mammal. The most striking effect of radiation, he found, was to produce translocations and other chromosomal abnormalities, which often reduced fertility. His careful analysis helped establish that these effects resulted from

chromosome entanglements formed at meiotic pairing that interfere to a variable extent with chromosome segregation. The 1946 paper shows George scrupulously citing the work of a student of his who had been drafted for military service, as well as that of his competitor Peter Hertwig, who had continued to publish papers on mouse genetics in Berlin until 1942! George's pioneering work on translocation in mammals pointed in three future directions. Mis-segregation of rearranged chromosomes was found to underlie the weird phenomena displayed by the t-alleles at H2. Radiation-induced chromosomal rearrangements provided fundamental insight into the life span of human T cells. And postwar studies of the genetic consequences of the atomic explosions hinged largely on chromosomal rearrangements. The advent of nuclear weapons make his 1937 paper on the genetic effects of neutrons seem remarkably prescient. Indeed it was fortunate for immunology that George came to feel that radiation genetics had reached the point of diminishing returns, as otherwise he might have been sucked into the post-1945 resurgence of the subject.

In 1941 the first edition of *Biology of the Laboratory Mouse* appeared, edited by George and largely written by staff of the Jackson Laboratory. It became the standard work on the subject, along with the second edition published in 1966 that contained no less that nine chapters coauthored by George.

George's entry into immunogenetics, in 1943, came in the form of a study of sperm iso-agglutinins (i.e., strain-specific antibodies made in one mouse strain are able to agglutinate sperm of another strain). This approach was natural to him, as he had long been interested in breeding mice, and similar antibodies had long been known against red blood A cells. In his previous work he had encountered male sterility induced by radiation and had studied several

of the aspects of reproduction relevant to running a large mouse colony. In retrospect it is worth noting that these anti-sperm antibodies have since become one of the few human immune responses that show clear-cut regulation by the major histocompatibility complex.

In the same year George published a joint paper with A. M. Cloudman that marked his debut in tumor transplantation, a field of research that he came to dominate and in which he made his great discovery of the major histocompatibility complex. Cloudman had long been working with Little at the Jackson Laboratory. In 1914 Little (*Science* 40:904-906) proposed a genetic theory of tumor transplantation postulating that the susceptibility to a tumor transplant was determined by several dominant genes. And he and Tyzzer (*J. Med. Res.* 33(1916):393-453) went on to estimate the number of these factors by challenging an F2 population with grandparental tumor. Thanks to Little's foresight Jackson Laboratory proceeded to collect and inbreed numerous strains of mice and has ever since served as the world center for the distribution of mouse strains. Using the collection, George formulated the "fundamental rules of transplantation": that tumors could be transplanted freely within an inbred strain, into its F1 hybrids with other strains, and into a Mendelian proportion of an F2. They were however rejected by other strains, as were tumors that originated in F1 hybrids and were transplanted into one of the parental strains. Inbred mouse strains, they concluded, differed by only a few rejection-inducing genes.

Opinion grew that these rules must reflect an immune response to antigens expressed by the tumors, as well as by normal transplanted tissue. From the early years of the twentieth century it was known that transplanted tumors were often rejected, and that this might represent a response to something specific to cancer—a possibility that was to prove

an enduring hope of cancer research. W. Woglom in his influential 1929 review rejected that view and argued instead that tumors and normal tissue share a similar ability to elicit immunity. Later J. B. S. Haldane visited Little and brought back to London on the pet deck of the liner *Mauritania* some of the new inbred strains. In his 1933 lecture to the Royal Institution he suggested that each of Little and Cloudman's rejection genes might be "responsible for the manufacture of a particular antigen, as in the case of the red corpuscles." He encouraged his young colleague Peter Gorer to search for such antigens.

Gorer worked in parallel with Irwin and Coles, who had coined the term "immunogenetics" to describe their work on antigens of avian red cells. Gorer raised rabbit antisera to red blood cells of mice, which upon absorption distinguished two antigens present in different strains. He then joined George in demonstrating that his antigen II segregated in F2 mice together with the gene fused (Fu), which George had found to be linked to transplant rejection. On this basis the gene encoding the antigen was named H2 (H for histocompatibility and 2 for antigen II) and represents the first sighting of what later came to be called the major histocompatibility complex. It is worth noting that their 1947 paper wisely refrains from claiming that the antigen expressed on red blood cell antigen caused the rejection, or that antibodies of the iso-agglutinin type were responsible. For another five years at least, George continued to refer to histocompatibility factors rather than antigens. After all, 20 years earlier Woglom had cited evidence that antibodies did not mediate transplant rejection.

George at this point made the wise decision to split the effort of his laboratory. To Nathan Kaliss he left the problem of characterizing the histocompatibility factors, while his own group concentrated on the genetics. The isolation

work had originally begun in collaboration with Cloudman. They sought simply to preserve tumors by freezing. Next they discovered that the new trick of freeze drying could be used to preserve the immunizing material in tumors, although to their surprise this material often prolonged (enhanced) rather than shortened the survival of subsequent transplants. Kaliss took up the problem with only limited success. Although the conditions under which enhancement takes place were defined, little progress was made with characterizing its mechanism. In 1960 Henry Winn showed that lymphocytes could transfer the effect. In retrospect the effect joins other assorted down-regulatory phenomena such as the transfusion effect (suppressing rejection of transplanted tissue by prior transfusion of donor blood) and the activity of various regulatory T cells.

A development of this work sees that rare occurrence, George abroad. During the "Prague spring" of 1968 he visited Prague to collect the Mendel medal, the first international recognition of his contributions to immunogenetics. He received a warm welcome from Milan Hasek, whose group he recognized for its scientific excellence, its stalwart devotion to science through difficult times, and the extent to which it shared his interest in immunogenetics. After the sad ending of the "spring" Hilgert and Dement joined George's laboratory for a while. Hilgert attempted to carry on the work of Kaliss but with little success: The field was waiting for better biochemical methods.

Meanwhile, the genetics of the MHC, the work for which George received the Nobel Prize, steamed ahead on an expanding scale. The work depended on two simple but ingenious procedures. One was to type existing inbred lines at H2 by means of the linkage with the Fused gene (as described in 1951). The second was to make new congenic lines (originally termed "isogenic resistant," abbreviated to

IR), in which various histocompatibility alleles were back-crossed onto the same background. The H2 alleles were later termed "haplotypes" after the composite nature of this genetic region was discovered. Each step of the backcross-ing required 2 generations, and George decided that up to 20 generations were needed to establish a new line. Over a decade this prodigious task proceeded steadily. By 1953 a total of 102 typings had yielded 9 H2 alleles, by 1958 the number rose to 12 alleles, and by 1969 to 18, encompassing all the main laboratory strains. With his colleague Graff, George later showed that a congenic line would also reject skin grafts from its pair.

In the meantime Donald Shreffler and Jan Klein began to employ antibodies to explore H2 and divide it into its components within George's congenic lines. In this quest they sought and found recombination between end mark-ers of H2 and began to construct the map of the H2 region that figures in modern textbooks. The term "major histo-compatibility complex (MHC)" was coined to describe this series of closely linked genes. In parallel Hugh McDevitt discovered that genes of the MHC had the unexpected func-tion of controlling the level of the immune response. In collaboration with George these two approaches converged in 1972 to map Ir-1 (immune response gene one, now iden-tified as H2A and H2E) within H2. With the advent of mono-clonal antibodies and later of DNA sequencing the map-ping proceeded rapidly, curtailed only by Shreffler's untimely death in the midst of his work on the C4 complement (Ss, Slp) locus. Ian McKenzie from Australia contributed to this effort during his sojourn in George's lab, in collaboration with the main serological work conducted there by Peter Demant and Marianna Cherry.

The prodigious polymorphism of H2 required explana-tion, since obviously it did not exist merely to bother trans-

plant surgeons. George in his 1981 "Future" paper rightly identified regulation of the immune response as the function of the MHC. He saw resistance to viral infection as the main driving force in its evolution, and its polymorphism as sustained by the wider range of reactivity enjoyed by heterozygotes. Both these views are now generally accepted.

Not all congenic pairs differed from one another at H2, as judged by the linkage test with the Fused gene. Differences at the remaining "minor" H loci resulted in a weaker and more variable rejection that often required pre-immunization to prevent tumor growth. Good quantitation of the difference was obtained by Winn's transfer test. Consecutive numbers were assigned to these minor loci (e.g., H1, H3, H4). By this and similar methods some 60 minor H loci have now been mapped. The frequency of single nucleotide polymorphisms in the genome suggests that there may be many more.

The H3 complex is of particular interest, as shown in George's 1964 and 1967 papers. As Roopenian and Simpson write, "Snell and his collaborators' masterful exploitation of the fortuitous linkage of H3 to agouti and other visually detectable linked loci . . . proved that there were a minimum of two H genes within the H3 segment."

Since then minor transplantation antigens have proved valuable tools for probing the working of the immune system, notably in delineating the role of T-cell subsets and in studies of anergy and other forms of peripheral tolerance. They are considered likely to have a therapeutic future, as contributing to the so-called graft-versus-leukemia effect after bone marrow transplantation.

As George's retirement approached, Cherry and McKenzie contributed to the discovery of non-H2 antigens on the surface of mouse lymphocytes, defined by antibodies. The unfortunate name "cluster of differentiation" (CD) is now

given to these molecules, which turn out to have important functions, as George predicted in his 1981 "Future" paper.

Snell had an abiding worry about the contradiction between evolution and ethics. He relates that this first struck him while teaching genetics and evolution at Washington University in 1933-34. He found the genetics easy, but the survival of the fittest did not seem compatible with his New England upbringing. In 1953-54 he took a sabbatical to read further at the University of Texas in Austin and at Dartmouth College, leading eventually to his book *Search for a Rational Ethic* in 1987. This is an extensive survey of human evolution from a genetic and anthropological standpoint, which argues that the origins of ethical behavior can be traced to particular periods and structures of human society.

The book is hard going. The *mea culpa*, surely due to human genetics as practiced in the twentieth century, is missing (could George have been unaware of the ridiculous views about the genetics of human merit expressed by his one-time collaborator R. A. Fisher, a grand old man of genetics?). Mussolini gets favorable mention, for what we would now call anti-terrorist activity (against the Mafia in Sicily) but not Hitler or Stalin. The Old Testament and the Koran receive attention but not the Israeli-Arab conflict. A sensible discussion of kinship in ethology gets mixed up with some far-fetched sociobiology. From this book the author emerges as a true scholar, expert in biology but confused by ethics and the social sciences and quite unconcerned with urgent problems of the day.

George's discovery and characterization of the MHC is of fundamental importance to immunology and medicine. It enabled the MHC to be subdivided into sets of genes of different type. It allowed the normal function of these genes to be determined, and led eventually to the structural and

molecular characterization of the proteins that they encode. It prepared the ground for HLA (the MHC of man), which rapidly gained importance in organ and bone marrow transplantation and has saved many lives. Today it is also important in predicting disease susceptibility and in the design of peptide vaccines. Well did it merit its Nobel Prize.

Science moves on. Immunogenetics, in man and mouse, is now a sub-specialty of molecular genetics and genomics. The laborious methods of immunogenetics in the past are being replaced by DNA sequencing. Worldwide the bone marrow transplantation groups are engaged in deciding whether sequencing HLA-class genes is worthwhile in practice. The old transplantation tests and serology now seem old hat. Nevertheless it was those older methods that laid the foundations on which we now build, and *in vivo* transplantation tests will remain the endpoint for clinical transplantation.

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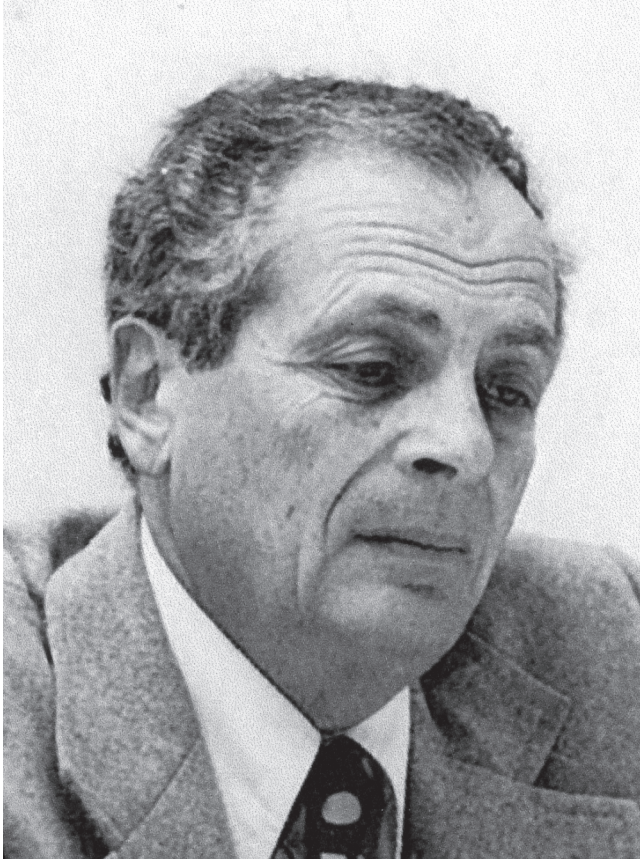
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SIDNEY UDENFRIEND

April 5, 1918–December 29, 1999

BY HERBERT WEISSBACH AND BERNHARD WITKOP

SIDNEY UDENFRIEND'S PARENTS emigrated to the United States from an Austro-Polish region in central Europe in 1913. They had three children; the oldest was Sidney, who was born in Brooklyn, New York, on April 5, 1918. After attending public schools in Brooklyn Udenfriend entered the City College of New York (CCNY) in 1935. At that time CCNY was the dream for so many of the immigrant parents who wanted their children to obtain a college education. Supported by public funds, with no tuition, CCNY provided that opportunity for those students who could pass the rigid requirements for entrance. The Chemistry Department was well recognized in the field of physiological chemistry (or biochemistry) thanks in large part to Benjamin Harrow, who wrote a widely used textbook.

Harrow had a great influence on Udenfriend, and after graduation in 1939 Udenfriend was set on a career in biochemistry and determined to go to graduate school. In 1940 he was accepted at New York University Graduate School in the Department of Biology working with Kenneth Blanchard. At nights he had a position with the New York City Department of Health directing other graduate students in carrying out Wasserman tests on draftees for the Army. In 1942

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he received his M.S. degree and with the country at war, he took a position as a biochemist in the New York University malaria program at Goldwater Memorial Hospital in New York City. James Shannon directed this program, and Udenfriend was placed in a group headed by Bernard B. ("Steve") Brodie. His research involved developing new analytical methods for drugs and studying drug metabolism (1943). The malaria program was considered vital defense research and Udenfriend was deferred from the draft, and obtained valuable research experience in this exciting environment until the end of the war. During this period at Goldwater he married Shirley Reidel. They remained together for 56 years, until his death in 1999, and they had two children, daughter Aliza and son Elliot.

In the fall of 1945 he returned to New York University to complete his graduate studies, initially working with Severo Ochoa in the Department of Biochemistry of the Medical School. Ochoa left the department after one year, and Udenfriend changed mentors and continued his thesis work with Albert Keston. Together they developed the isotope-derivative method for the assay of amino acids and for determining amino terminal residues in proteins (1949). He received his Ph.D. in biochemistry from New York University in 1948 and accepted a position as instructor in Carl Cori's Biochemistry Department at Washington University in St. Louis. Udenfriend could not imagine, as he and his wife Shirley left for St. Louis, that several of the scientists with whom he had interacted at Goldwater Memorial and New York University, including Shannon, Brodie, Julius Axelrod, John Burns, and Ochoa, would cross his path again in the years to come.

The Department of Biochemistry at Washington University, headed by Nobel laureate Carl Cori, was one of the most prestigious biochemistry departments in the country.

Udenfriend applied his isotope-derivative methodology to enzymes that were under investigation in the Cori laboratory. One of his close colleagues during that period was Sid Velick, and their studies resulted in several papers on amino acid analysis and protein N-terminal analysis (1951,1-2).

On April 7, 1949, the *New York Times* informed the public on the appointment of James Augustin Shannon as associate director in charge of research at the National Heart Institute created in June 1948 by an Act of Congress signed by President Truman. This was the beginning of the meteoric rise of the National Institutes of Health (NIH), of which Shannon became director in 1955, from a routine government laboratory to the world's center of biomedical science

Udenfriend received the letter of invitation to join Shannon's expanding research team in 1950 while in St. Louis. His answer when he asked Cori for advice was: "If you join a little known government laboratory, this will be the end of your scientific career!" At that time Udenfriend also had an application pending for an assistant professorship at Columbia University, with little chance of success. So he did not hesitate to ignore Cori's advice and accepted the position of biochemist (at the GS-13 level) in the Laboratory of Chemical Pharmacology under his old boss Brodie in the National Heart Institute, which started in Building 3 on the NIH campus in Bethesda, Maryland. By the early 1950s NIH had attracted a large group of scientists from Goldwater Memorial Hospital, in addition to Shannon and Brodie. At that time NIH was still a fledgling research center, but the scientific talent present in Building 3 in the early 1950s was extraordinary.[1] In Axelrod's words: "Never had such a small group of promising scientists reached such Olympic heights."

In a letter dated June 5, 1950, Shannon informed one of us (B.W.) of the complementarity of current projects at

Harvard University with those of Udenfriend, and so it happened that Udenfriend became a colleague and friend until his passing. In 1953 one of us (H.W.) was recruited by Udenfriend from his alma mater, CCNY, and became his first Ph.D. student, thanks to a graduate program that Udenfriend helped establish between the Brodie laboratory at NIH and the Departments of Biochemistry and Pharmacology at George Washington University. To a young graduate student the quality of science and the excitement and talent that surrounded him in Udenfriend's laboratory and all of Building 3 left a lasting impression never to be equaled.

In this convivial atmosphere at NIH Shannon initiated a weekly interdisciplinary seminar supplemented by more relaxed gatherings of the "Applied Statistics Club," a euphemism for the poker games with high stakes, where Irish Mist was served under the motto "The Irish never missed!"

Just as Shannon never forgot his famous mentor Homer Smith, so Udenfriend acknowledged throughout his scientific lifetime that he stood on the broad shoulders of Shannon. On the occasion of a festive banquet of the Committee for the Weizmann Institute in New York, "godfathers" Udenfriend, Axelrod, and Witkop decided to move the authorities to name the pillared central administrative building, referred to as Building 1, the James Augustine Shannon building. After high-level and congressional deliberative delays a solemn celebration—in the presence of a smiling Shannon—preceded the official christening on January 18, 1983. This was the first and unfortunately the last time that an NIH building was named after a scientist and not a member of Congress.

Of the more whimsical talks on this occasion Hans Stetten compared the Shannon building at NIH to the CNS with numerous afferent and efferent channels, which Shannon successfully controlled in spotting action potentials amidst

much background noise. Like Ben Franklin he looked for helpful temperature-dependent currents to move the large NIH vessel through stormy seas and to avoid unfavorable counter currents the same way as Franklin had advised transatlantic shipping in 1786 (*Transactions of the American Philosophical Society* 2(1786):294-329). Measuring the "temperature" on the "climate of expectancy" in institutes and laboratories and at the same time respecting their integrity and independence was Shannon's style, and therefore, "The style is the man." Hans Stetten later became the first chair of the Scientific Advisory Board to Udenfriend at the Roche Institute of Molecular Biology.

The transition of pharmacology, based on physiological evaluation, to a science based on quantitative analysis using exact colorimetric, fluorescence, or radioactive-isotope methods gave Brodie's laboratory the title " chemical pharmacology" and goes back in part to investigations by Udenfriend with Keston and Velick. Udenfriend always believed, regardless of the project, that the time best spent was working out a rapid and sensitive assay. Here we also have the beginning of research that used isotopically labeled substrates to quantitatively determine enzyme activity, which led to the discovery of the famous "NIH shift," as discussed below.

During the 1950s hydroxylation was a common theme in Udenfriend's research, and it was during that period that he became especially interested in aromatic hydroxylation. His first studies on the enzymatic conversion of phenylalanine to tyrosine were done with Jack Cooper (1952), and this research soon broadened to include studies on tryptophan hydroxylation and the biosynthesis of both norepinephrine and serotonin, and later proline hydroxylation and collagen synthesis. He was intrigued by the discovery of serotonin, which was isolated, identified, and crystallized in 1948 by Maurice Rapport in the laboratory of Irvine Page,

who was then the director of the Research Division of the Cleveland Clinic. These collaborative studies developed into both personal and productive relations between the two groups. The first step in the serotonin biosynthetic pathway studied in detail was the conversion of 5-hydroxytryptophan (5HTP) to serotonin (1953,1; 1954,1) At first it was thought that this enzyme was distinct from the decarboxylase that used dihydroxy-phenylalanine (DOPA) as substrate, but upon purification the enzyme, called aromatic amino acid decarboxylase, was shown to be able to decarboxylate not only 5HTP and DOPA but also tryptophan, tyrosine, and phenylalanine, although to a lesser extent.

By 1953 it became clear that serotonin biosynthesis involved two steps, hydroxylation to 5HTP and decarboxylation to serotonin. By then it was also apparent that serotonin was not only a neurotransmitter but had a role as a vasoconstrictor and potentially other roles because of its high concentration in both platelets and intestinal mucosa. This surge in the central and peripheral importance of serotonin led to extensive basic and clinical investigations in which Udenfriend and his colleagues or disciples, such as Herb Weissbach, Walter Lovenberg, Elwood Titus, and the clinical group headed by Albert Sjoerdsma, were involved. Carcinoid syndrome is just one example of the productive collaboration between the Udenfriend and Sjoerdsma group. These tumors produce large amounts of serotonin that cause the gastrointestinal symptoms and blushing seen in these patients. Weissbach had already developed an assay for 5-hydroxyindole acetic acid (5HIAA), the primary urinary metabolite of serotonin. Thus a simple diagnostic test for the malignant carcinoid syndrome was developed based on the determination of 5HIAA in urine (1955,1). An interesting sidelight to these studies was the observation that Weissbach was routinely running high levels of 5HIAA in

his urine while others in the lab had normal levels. There, of course, was concern that he might have a carcinoid tumor until the high 5HIAA levels were traced to his daily ingestion of bananas that contain high levels of serotonin and other amines. This work was extended to other fruits and vegetables, which brought Udenfriend into contact with nonscientists like the president of the United Fruit Company, which led to an award to Udenfriend and Sjoerdsma sponsored by United Fruit.

The need to localize and assay serotonin was one of the reasons that Robert Bowman, the chief of the Laboratory of Technical Development, helped Sid to design a spectrofluorometer (SPF) with quartz optics that not only extended fluorescence assay into the ultraviolet region but also permitted one to change both the activation and fluorescent wavelengths to achieve increased sensitivity and much higher specificity (1955,2). The initial instrument, put together by Bowman using some parts from an Army and Navy store in Bethesda, took up half a laboratory and because there was no shield to prevent room light from activating the SPF photomultiplier, the room had to be kept dark during the measurements. Using this instrument the sensitivity of the serotonin assay increased by orders of magnitude and it was now possible to assay endogenous serotonin in virtually any tissue (1955,3). This dramatically changed the research efforts and opened up a new dimension in biogenic amine research. The development by the Aminco Company of a small well-designed SPF (called the Amino-Bowman SPF) also made it possible for the scientific community to have access to this new instrument. Numerous assays were developed for all sorts of compounds using the SPF as described in the book Udenfriend first published on fluorescence assay in biology and medicine in 1962, with a second edition in 1969. How this story evolved in 1955 is also described by

Udenfriend in a nostalgic retrospection 40 years later pub-
lished in *Protein Science* (4[1995]:542-51). In a surprising
about-face the mentor-disciple role with Sidney Velick was
reversed when the two Sids collaborated on the use of the
SPF on novel and previously inaccessible problems such as
enzyme-coenzyme complexes or antigen-antibody interac-
tions.

Several Nobel Prize winners have relied on the SPF as
an indispensable tool. In collaborative studies Axelrod iden-
tified labile metabolites of lysergic acid diethylamide (LSD),
mescaline, and norepinephrine. In Axelrod's words,

The SPF made it possible to measure noradrenaline and serotonin . . .
practically. This changed the direction of the whole field of neurobiology.
Quantitive studies established the relationship of the level of these trans-
mitters to certain mental illnesses and aided in the development of mental
tranquilizer and energizer drugs. Continued studies in this area will yield
additional information on the basis for mental illness.

The adage "Transmission is as important as discovery"
could be applied to the time that Udenfriend spent as a
graduate student with Ochoa in the Department of Bio-
chemistry at NYU Medical School in 1946. Udenfriend be-
came aware that hydroxyproline was uniquely present in
collagen from his earlier days at NYU, since Joseph Bunim,
a professor at the NYU Medical School, had impressed on
him how collagen was intimately involved in the health and
disease of connective tissue, in arthritis and other disor-
ders. Bunim and Stetten soon joined NIH at the Institute
of Experimental Biology, which was not accepted by Con-
gress as a serious "disease" and so became the National
Institute of Arthritis and Metabolic Diseases (NIAMD).

That the hydroxylation of proline does not occur in the
free form, but at some step in the formation of collagen
was the discovery of Marjorie ("Marnie") Stetten and in-

spired Udenfriend, already involved in hydroxylation reactions, to pinpoint the exact step at which proline was hydroxylated. Udenfriend had the good fortune of having Beverly Peterkofsky join the laboratory at that time. Peterkofsky, a graduate student with Ochoa at NYU, moved to NIH when her husband Alan Peterkofsky accepted a position in the NIAMD. As Udenfriend said of Beverly Peterkofsky, "It was one of the best things that ever happened to me." She finished her graduate studies in Udenfriend's lab, where she obtained a cell-free system from chick embryos (1961) that incorporated *cis*-and *trans*-4-H^3-L-proline into peptide-bound hydroxyproline in a front-side displacement with complete retention of configuration at C-4 (1964). This reaction was comparable to other enzymes, which directly use molecular oxygen in the formation of hydroxylated products. Years later, in 1975, at a Collagen Symposium at the Roche Institute of Molecular Biology, Udenfriend fondly remembered these early events in the collagen saga that was completed by Darwin Prockop, another of Udenfriend's students. A major discovery was the finding that alpha-ketoglutarate was the cofactor of proline hydroxylase and of a totally new class of enzymes. This enabled Prockop to study in detail the nature of the hydroxylase and of the transformation of "protocollagen" into collagen. Carl Piez at NIH then carried out a kinetic study of collagen biosynthesis, and Prockop showed a role for hydroxyproline in stabilizing the triple helix of collagen that Lubert Stryer in his famous textbook *Bio-Chemistry* likened to a Bach fugue. Prockop continued his studies on collagen after leaving the Udenfriend lab and moving to Philadelphia, where he showed that mutations in the genes for collagen, caused osteogenesis imperfecta, or brittle bone disease in children, or dwarfism (chondrodisplasias), not to mention the role of collagen in more common syndromes,

such as osteoporosis and osteoarthritis. These insights round out the clinical observation by Udenfriend and Sjoerdsma of the increased excretion of hydroxyproline in Marfan's syndrome, which goes back to 1958 and even further when we consider Egypt's eighteenth dynasty with Amenopsis and Tutankhamen being possible victims of this disorder.

As early as 1953 Udenfriend and Samuel Bessman published on the hydroxylation of phenylalanine in patients with the genetic disease phenylpyruvic oligophrenia, called phenylketonuria or PKU (1953,2). This work preceded the exhaustive research on phenylalanine hydroxylase by NIH colleague and friend Seymour Kaufman that extended over 20 years. A model system for aromatic hydroxylation published in 1954 with Brodie and Axelrod was intended to throw some light on the mechanism of this oxidation (1954,2). Witkop informed Udenfriend that his system consisting of oxygen, ferrous ion, and ascorbic acid in the presence of ethylenediaminetetracetic acid (EDTA) is a modification of a system that Heinrich Wieland described for the oxidation of formic acid by ferrous ion, dihydroxymaleic acid, an agent forming metal complexes and oxygen, as mentioned in his Silliman memorial lectures (Yale University Press, 1932, p. 86). "Progress is tradition preserved." Curiously enough this rediscovery went into the literature as "Udenfriend's reagent" (Michael B. Smith, *Organic Synthesis*, McGraw-Hill, 2002, p. 296). Here we deal with the name game (Alex Nickon, *Modern Coined Terms and Their Origins*, Pergamon Press, 1987) to which we will return subsequently. There is a similarity of this Wieland-Udenfriend system with the requirements of proline hydroxylase for alpha-ketoglutarate, ferrous ion, ascorbate and oxygen as found in 1966 (1966,1). The years 1966 and 1967 were the time when insight into the mechanism of hydroxylation was obtained because of the availability of a tritiated substrate,

p-H^3-phenylalanine, for phenylalanine hydroxylase, the important enzyme missing in PKU. When the results of the experiment on the fate of the tritium came in, Udenfriend was perplexed, for there was much tyrosine formed but no loss of tritium. Questioning the location of the tritium in the commercial sample, Sid angrily scolded, "Can't chemists put the label in the right place?" In discussing this dilemma with Gordon Guroff of Udenfriend's laboratory, John Daly, a chemist in Witkop's laboratory, made the suggestion of extending the study to deuterophenylalanine, where NMR could rigorously establish the position of the deuterium. Using this as substrate for the enzymatic hydroxylation some deuterium was lost but most was found in the *meta*-position, as was then shown for tritium (1967,1). This was the birth of the happy child christened the "NIH shift," with several proud parents involved in paternity (1967,1). There even was a twin: Not only did tritium and deuterium slide over to the neighboring *meta*-position but so did halogen (1966,2). Of course, tryptophan-5-hydroxylase, the first step in serotonin synthesis, was the next enzyme to be tested.[2] The reaction had only been demonstrated in whole cells of *Chromobacterium violaceum.* Using as substrate 5-tritio-tryptophan, 4-tritio-5-hydroxytryptophan was formed with little release of tritium into the medium (1966,3).

To strengthen the case for a postulated arene-oxide intermediate[3] Donald Jerina, a chemist in Witkop's laboratory, synthesized benzene oxide, and naphthalene 1,2-oxide, using the synthetic methods of Emanuel Vogel, the pioneer in the arene oxide field. The latter oxide was identified as an intermediate during conversion of naphthalene to 2-naphthol and transnaphthalene-1,2-dihydrodiol by the action of liver enzymes (1970).

The hydroxylation of the antipyretic and anti-rheumatic acetanilide to the more active p-hydroxy-metabolite acetami-

nophen, later sold as Tylenol, was a discovery of Axelrod in Brodie's laboratory. Axelrod often mentioned that he missed becoming a millionaire many times over by not patenting this process. When this same process was reinvestigated with p-tritioacetanilide, radioactive "Tylenol" was formed both in vitro with microsomes and in vivo (1972). The migration and retention of tritium ranged between 38 percent and 56 percent. Nonenzymatic hydroxylations of aromatic substrates lead to the NIH shifts only with peroxytrifluoroacetic acid, a much stronger oxidant than the Udenfriend reagent.

Udenfriend always had close contact with Seymour Kety, because they both tried to find the biochemical basis for mental disorders, a fact that led to the first International Symposium on Catecholamines at NIH in October 1958. Udenfriend and Witkop presented there the observation on the conversion of dopamine to 6-hydroxydopamine, which selectively destroys catecholamine-containing nerve terminals and was at one time thought to be a possible endogenous agent involved in mental diseases.

Sid had an unfailing eye for budding talent, and it is not possible to document the large number of successful scientists who passed through his lab or the impact he had on so many others. One such example is the case of Paul Greengard, who came to Udenfriend's laboratory in the mid-1950s to learn assays and some of the procedures being routinely done in the amine field before beginning a position at Ciba-Geigy. Greengard studied the uptake of tyrosine in the rat brain, a beginning that he gratefully remembered when he received the Nobel Prize in 2000 for extending this initial interest in the brain to highly refined receptor studies.

The fact that Marshall Nirenberg, who received the Nobel Prize in 1968, remained at NIH after his initial experiments in the early 1960s that cracked the genetic code was in

large part due to Udenfriend's efforts, and the coincidence that Nirenberg's wife, Perola, was Udenfriend's assistant. Weissbach remembers clearly when Udenfriend called a lab meeting to tell us that there was a chance that Nirenberg would leave NIH unless he had more space to continue his experiments: "We all agreed to cooperate, and soon thereafter Nirenberg's group moved into the space we made available. I benefited greatly from the proximity of the Nirenberg group and within a short period of time was actively engaged in experiments to elucidate how the genetic information was used in the translation process."

Marshall Nirenberg sums up his memories as follows.

My wife, Perola, worked as a technician for Sid Udenfriend for about ten years, from 1958 to 1968. Perola had enormous admiration for Sid and he valued her work greatly. Theirs was probably the best working relationship I have ever seen.

One of the reasons why it was so successful is that Sid would outline a problem to Perola and suggest a possible mode of attack and Perola then would set up the assays and see if it would work. After a month or so when she had some data she would go back to Sid and show him the data or discuss problems she had encountered. So Perola had all of the fun of solving most of the problems she encountered on her own, and Sid could do exploratory research while investing very little of his own time. It was an ideal arrangement for both of them.

One day Perola asked Sid for a few days leave so that she could go with me to visit an academic institution that had offered me a position, and she told him that I probably would accept the position. By the time we returned to Bethesda Sid had worked out a plan to keep me at NIH by offering me some space and support within his laboratory, which would enable me and my colleagues to continue our work. And so I moved to Sid's lab. Years later Sid often enjoyed telling me that the reason that he had offered me the position in his lab was to keep Perola from leaving NIH, and I would counter by saying that he was just plain lucky to have gotten me to go to his lab. In fact, this arrangement proved mutually beneficial because Sid and

Perola continued to work with one another, and my colleagues and I were able to finish deciphering the genetic code. Our presence in Sid's lab made it easy for Herb Weissbach to begin working on protein synthesis, since we were experts in the field.

Sid Udenfriend always was bubbling over with enthusiasm and ideas for the projects that he was involved in. He had a superb mind and would have been successful in almost any field of endeavor. He always tried to help me in a fatherly way by giving me the benefit of his own experience.

Sid called me a few weeks before his death to find out how Perola and I were, and tell me about his plans for the future. He especially wanted me to convey his best wishes to Perola. I think that Sid was an outstanding human being as well as an outstanding scientist.

Udenfriend's career was flourishing at NIH and by the early 1960s he was continually being approached about positions in both academia and industry. With only a few exceptions he expressed little interest in leaving the wonderful, stimulating environment in Bethesda. It would take a unique challenge to pull him away from this research Mecca, and in 1967 such an opportunity appeared, due in large part to old friendships. John Burns, a former colleague of Udenfriend's from the Goldwater Memorial period, had moved his laboratory to NIH in 1957. Burns remained there for only a short period and then became vice-president of research at Burroughs Wellcome in 1960. In January 1967 he moved to Hoffmann La Roche as vice-president of research and met Udenfriend at a cocktail party in Bethesda shortly after assuming his post at Roche. Burns was anxious to make innovative changes in Roche research, and Udenfriend suggested that Roche establish a basic science institute as part of the company's research effort. Unlike existing programs at most pharmaceutical companies this institute would not be product driven but function much like the intramural NIH, with the scientists having direct

funding, a reasonable time commitment, and freedom to pursue a research project of their own choosing. The benefits to the company would come from the cutting-edge research that would place the company in a unique position to move rapidly into new areas of biology and develop novel therapeutics. It was becoming clear even by 1967 that the discoveries in molecular biology and molecular genetics that Udenfriend was so aware of because of his association with the Nirenberg laboratory, would be the driving force for the development of new drugs in the decades to come.

From this brief casual discussion at a social gathering arose the concept of the Roche Institute of Molecular Biology (RIMB). Within the short span of four months, thanks to the efforts of Udenfriend, Herb Weissbach (whom Udenfriend had asked to join him), and Burns, the RIMB came into being. By April Burns presented a summary proposal and detailed budget to the Roche Executive Committee. Approval from Nutley and Basel came quickly, thanks in part to Alfred Pletscher, who was head of research in Roche Basel. Pletscher had spent time in the mid-1950s in Udenfriend's laboratory working directly with Weissbach and was supportive of the concept. Indeed, due to the efforts of Pletscher, within two years the Basel Institute of Immunology, the sister institute to the RIMB, was established in Basel near the Roche facilities.

The period between May and July 1967 was a critical time in the history of the Roche Institute. Udenfriend, Weissbach, and others were unsure whether a move to industry, despite the attractiveness of what was being planned, was too big a career risk to take. At that time basic scientists were extremely wary of industry. It was clear that Udenfriend would not make the move without a solid contingent of committed scientists. With Shannon the man and his talent

came first and then the mission. In this way he assembled the stellar cast that led NIH to such scientific success in the same way as Udenfriend, after he moved to Roche, had the satisfaction of assembling a similar group. Whether Roche would keep its promise to establish and maintain a basic research institute for a reasonable period (e.g., a 10-year commitment) was the major question. Finally a meeting was scheduled in June of 1967 with V. D. Mattia, then president of Roche in Nutley. A group of scientists from NIH that Udenfriend wanted to recruit, all with great concern, met with Mattia. By the end of the meeting it was clear that the tide had turned. Although a time period was never put in writing, the scientists came away convinced that the Roche commitment was long-term and most of the scientists at that meeting eventually joined the RIMB. Shortly thereafter the freedom the scientists desired would be clearly stated in a charter signed by Mattia on July 14, 1967. That was the day the Roche Institute of Molecular Biology came into being. The RIMB lasted 28 years and during its existence the commitment that Mattia made to the NIH scientists in 1967 was never broken. Although Mattia passed away before construction of the institute was finished in 1971, succeeding presidents, such as Robert Clark and Irwin Lerner, respected the provisions in the RIMB charter.

Once the charter was in place events moved quickly. Within months Udenfriend obtained commitments from a number of young NIH scientists, including Herb and Arthur Weissbach, Nathan Brot, Sydney Spector, Sidney Pestka, Ronald Kaback, and Aaron Shatkin. Richard Snyder was hired to handle the administrative affairs, and temporary office space was rented in Bethesda. A distinguished Board of Scientific Advisors was established and by the summer of 1968 temporary space was available in Nutley and Udenfriend and scientists in his department set up the first laborato-

ries. In 1971 Udenfriend was elected to the National Academy of Sciences, which gave prestige to both the RIMB and the company. By 1971 construction of the Roche Institute was completed, and the RIMB scientists who had been housed in temporary laboratories throughout Roche and in laboratories across the nation and abroad were able to move into the new building. For the first time the institute staff was together under one roof.

Udenfriend was ideally suited to be director of a basic research center serving the pharmaceutical industry. Although the scientists in the institute had free rein, Udenfriend had the unique ability of seeing a practical application to many of the programs. In this way the company always had a direct line to what was happening in the institute and the opportunity to have the technology transferred without interfering with the research philosophy the institute was built on.

Two of the initial members of the RIMB who Udenfriend had brought from NIH made important discoveries early on that were of interest to the parent company. Sydney Spector developed an assay for drugs of abuse, which became a major product of Roche Diagnostics, and Sidney Pestka, whose work on interferon brought Roche into the field of biotechnology, were clear examples of how the concept of a basic research institute within a pharmaceutical company could be successful. Under Udenfriend's leadership the environment at the Roche Institute was conducive to doing good science and the careers of many of the scientists flourished there. Based on the work done at the RIMB, three of the members, Aaron Shatkin, Herb Weissbach, and Ronald Kaback, were elected to the National Academy of Sciences and at one point the RIMB had seven members of the Academy, including Severo Ochoa, Bernard Horecker, and Allan Conney, among a staff of less than 30 scientists.

In addition, the RIMB had a training mission. From the initial discussions in 1967 it was clear that the long-term success of the RIMB as a basic research center would depend on being able to attract postdoctoral fellows and graduate students. Udenfriend was determined that this would be the case. The charter clearly stated training as a mission of the RIMB. At that time, in the late 1960s, universities were reluctant to accept industry scientists (as the institute scientists were viewed) as adjunct faculty and there was a period of great concern for Udenfriend that institute scientists would not have university affiliations and thus not be able to have graduate students. Udenfriend, thanks to old friendships with faculty members at City College, such as Abe Mazur and Mike Fishman, obtained the first appointment from his alma mater, City College. Within a short period a strong relationship was built between the RIMB and Columbia University, thanks to the efforts of Udenfriend and Sol Spiegelman who was the new chair of the Department of Human Genetics at Columbia. Eventually RIMB scientists had appointments at most of the large universities in the New York-New Jersey region. Postdoctoral fellows were anxious to come, and there was no aspect of the RIMB that Udenfriend was more proud of than the fact that through the 28 years the RIMB was in existence more than 1,000 postdoctoral fellows and close to 50 graduate students received their training at the RIMB.

Udenfriend's own research never faltered during the period he was director from 1968 to 1983. He continued his studies on the hydroxylation of proline, tyrosine, and dopamine (1971,1-2; 1972). In addition to a basic interest in the mechanism of these reactions, Udenfriend always considered the in vivo ramifications and attempted to understand how proline hydroxylase was involved in collagen synthesis and how tyrosine hydroxylase and dopamine beta-

hydroxylase were involved in the regulation of norepineph-
rine synthesis. During this period his love and knack of
developing assays led to the use of fluorescamine as a sensi-
tive reagent for the assay of amino acids, peptides, and
proteins (1973). The development of the fluorescamine as-
say made it possible to detect small amounts of peptides
and proteins during purification and was especially valu-
able in Udenfriend's studies on the enkephalins, opioid
peptides, as well as the separation and isolation of various
species of natural α-interferon by HPLC.

The studies on interferon deserve special attention, for
this was the first example of how research in molecular
biology proved valuable to the company. The interferon
project was initiated at RIMB by Pestka, who felt that this
naturally occurring protein might have both antiviral and
antitumor activity. In order to clone the gene for this
chemokine it was necessary to purify it first from white blood
cells and obtain a partial amino acid sequence. The lack of
large amounts of cells and the realization that there may be
a family of interferons made the task much more difficult.
Without the analytical procedures that were available in
Udenfriend's laboratory it is doubtful that the isolation of
the first natural interferon species would have been achieved
so quickly. Once the purification was achieved the sequenc-
ing and cloning of an interferon gene was accomplished in
Pestka's laboratory. By the early 1980s, in collaboration with
scientists at Genentech, α-interferon became the first Roche
drug produced by recombinant DNA technology. It served
as a prototype for other biotechnology products (e.g.,
interleukin-2), and it is well accepted that the RIMB was
the prime factor in making Roche one of the first, if not
the first, large pharmaceutical companies to move into bio-
technology. The influence that the RIMB had on the course
of Roche research was living proof of Udenfriend's vision

of the role of the institute when it was first conceived in 1967.

In 1983 at the age of 65, Udenfriend stepped down as director of the RIMB, and the reins were passed to Herb Weissbach. Udenfriend, of course, was not ready to retire and continued to direct a productive laboratory. His primary research during the late 1980s and early 1990s centered on alkaline phosphatase and its attachment to the cell membrane by a phosphatidylinositol containing a glycolipid anchor. Udenfriend's studies helped to elucidate the biogenesis of this unique linkage, cleavage, and processing of the anchored proteins.

Like the other scientists at the RIMB, many of them younger additions to the staff, he was looking forward to productive years at the Roche Institute. However, Hoffmann-La Roche, although one of the major large pharmaceutical companies in the world, was facing financial constraints that were initially apparent after the expiration of the Valium patent in the early 1980s. By 1994 major long-term decisions were being made about the future direction of the company research, and to the surprise of the RIMB staff Weissbach, who was director at the time, was informed that the RIMB would be phased out. Weissbach had the unpleasant task of terminating the institute in a manner that was least destructive to the institute staff. For both Weissbach and Udenfriend this was the most difficult period in their long careers. What they had started together almost 30 years ago was coming to an end. Weissbach worked with Roche management to insure that all of the members of the institute would leave with their equipment, as well as some support if they were moving to a university position. It took almost two years for everyone in the institute to be placed.

At times Udenfriend found it difficult to deal with the dismantling of the institute, which had meant so much to

him, although he and Weissbach kept in touch during the long negotiations. By December 1995, about a year after the initial announcement of the closing of the RIMB, most of the institute staff had left. Weissbach had decided he would not leave until everyone was placed, and still maintained a functioning laboratory. He would soon leave the institute building, which was being closed, and move to another location within Roche. Dreadful as the closing of RIMB was for Udenfriend, in December of 1995 he would face a major unexpected challenge that would obscure all other concerns.

Early in that month Udenfriend and his wife, Shirley, had stopped at a pharmacy in Cedar Grove, New Jersey, to pick up a prescription. He had parked facing a brick wall and put the car in reverse as he was preparing to return home. What happened next is still not clear. It appears that when the car was put into drive, it accelerated rapidly and crashed into the brick wall some 30 feet in front of the car. Both Udenfriend and Shirley suffered multiple fractures, and Udenfriend was in a coma for several days after the accident. Although both would survive the accident, in that one split second their lives were irreversibly changed. After months of rehabilitation they both were finally able to return to their home. Weissbach had set aside an office for Udenfriend in his new space at Roche, and Udenfriend would come in about once a week, more to chat with Weissbach than to do science. By the fall of 1996 everyone in the institute had been placed, and Weissbach was planning on closing down his laboratory in December and relocate to a position at Florida Atlantic University. The equipment was being moved on a dreary, damp Saturday in December of 1996, and Weissbach, there alone, was unaware that Udenfriend had made it a point to come in that day, since this was the last day of the RIMB. Weissbach did

not have to ask Udenfriend why he had bothered to come. Udenfriend's first words were, " We started this institute together and I wanted to be here when it ended." By noon the two left the building in the freight elevator, through the loading dock. They realized that for the first time in more than 40 years their career paths would diverge.

The reasons for the demise of the Roche Institute of Molecular Biology are still not entirely clear. The end of this world-renowned research center that housed so many outstanding investigators touches at the root of the reasons for research support that perhaps was expressed nowhere better than by Arthur Kornberg (Nobel Prize, 1959).

The difficulty with research support in our society, I have come to realize, is the failure to understand the nature and importance of basic research. This failure can be seen among members of the lay public, political leaders, physicians, and even scientists themselves. Most people are not prepared for the time-scale of basic research and the need for a critical mass of collective effort. Fragments of knowledge [unwelcome] and unexploited are lost, as were Gregor Mendel's basic genetic discoveries. The vast majority of legislators and some scientific directors cannot accept the seeming irrelevance of basic research. Were there a record of research grants in the Stone Age, it would likely show that major grants were awarded for proposals to build better stone axes and that critics of the time ridiculed a tiny grant to someone fooling around with bronze and iron. People do not realize that when it comes to arguing their case for more funding, scientists who do the basic research are the least articulate, least organized, and least temperamentally equipped to justify what they are doing. In society where selling is so important, where the medium is the message, these handicaps can spell extinction.

Udenfriend was an outstanding researcher and teacher but perhaps his greatest contribution to science was in establishing the Roche Institute of Molecular Biology, and during his tenure as director, in creating one of the outstanding industry-supported biological research institutes in the world. The success of the Roche Institute is not mea-

sured only by the papers published or the accomplishments of the individual scientists or the impact on the company. What will be its greatest legacy is the large number of individuals trained at the institute, scattered throughout the world, who remain to this day a living reminder of the Roche Institute. Udenfriend's dream had come true.

When Udenfriend left Roche in December 1996, he already had accepted a position at Drew University as director of the Charles A. Dana Research Institute for Scientists Emeriti (RISE). This institute was specifically established to encourage interaction between some of the top retired scientists from industry in New Jersey and undergraduate students at the university. Udenfriend remained in that post through 1999, and under his leadership the institute expanded its membership and broadened its sphere of activities. Udenfriend obtained great satisfaction from working closely with undergraduate students and his caring for both science and people were apparent to all who knew him at Drew University.

In 1999 Udenfriend made the difficult decision to step down as director of the RISE. He and Shirley had decided to move to Atlanta, where their daughter lived, since it was becoming clear that because of age and the aftereffects of the accident, they both needed help to carry on many of their daily activities. The move south was made in 1999, but soon after they were settled Udenfriend was showing symptoms of coronary artery blockage. In the early winter of 1999 he entered the hospital for a bypass operation, which appeared to be successful; however, during recovery he apparently suffered a massive stroke and remained in a coma for several days until his death on December 29, 1999. The funeral was held on December 31, and because of the time factor and location, only about 20 people, mostly his close relatives, attended the graveside service. Weissbach was able

to fly up from Florida and was the only scientific colleague from the past to be present.

Weissbach planned on having a memorial event in Udenfriend's honor for the many scientists whose lives Udenfriend touched. Working with Ashley Carter, the new director of the RISE and Barbara Petrack a RISE member, a half-day symposium was held on May 25, 2000, on the Drew University campus. A scientific lecture was presented by Greengard, and the list of scientific colleagues who made short remarks, in addition to the organizers, included Witkop, Burns, Nirenberg, Axelrod, Spector, Arthur Weissbach, Sjoerdsma, Ron Kuntzman, and Fishman. Aliza, Udenfriend's daughter, was also present.

Udenfriend leaves a scientific legacy that includes close to 500 publications and major contributions to the fields of analytical biochemistry, fluorescence, hydroxylation reactions, serotonin and norepinephrine biosynthesis and metabolism, collagen biochemistry, encephalins, amino acid transport, and protein anchoring to membranes. Although research and not formal teaching was the focus of his career he trained dozens of postdoctoral fellows; through his university appointments at George Washington University, City College, and Columbia University, among others, he trained a large number of graduate students. His role in establishing the Roche Institute was a major accomplishment, but what will be missed most is the enthusiasm and love of science that were an integral part of his being.

Sid Udenfriend is gone but not forgotten.

NOTES

1. Included in this list are Nobel laureates Chris Anfinsen, Julius Axelrod, and Arthur Kornberg. Several scientists from that early permanent staff in Building 3 later were members of the National Academy of Sciences: Bruce Ames, Robert Berliner, Donald Fredrickson,

Leon Heppel, Bernard Horecker, Earl and Theresa Stadtman, Herbert Weissbach, Bernhard Witkop, and James Wyngaarden. Fredrickson and Wyngaarden eventually became directors of NIH. Other outstanding postdoctoral fellows and visiting scientists who worked in Building 3 at that time included Paul Stumpf, Horace Barker, Gerard Hurwitz, Paul Marks, and Arthur Weissbach. The authors realize that this is a partial list and apologize to the many talented scientists who worked in Building 3 but have not been mentioned.

2. A tryptophan research meeting on a regular international basis was eventually organized in 1971, mainly as a result in the growing interest in the role of serotonin in depression and moods and the wider consequences for neurochemistry, psychiatry, cardiovascular studies, and more recently immunobiology and neuro-immunobiology. The acronym for these biannual symposia is ISTRY, or International Study Group for Tryptophan Research.

3. The First Symposium on Arene Oxides in Biochemistry and Metabolism (*Science* 178[1972]:779-81) was held at Roche in April 1972 with Udenfriend presiding and pointing out that as early as 1947, E. Boyland, who was present, had postulated arene oxides as reactive intermediates in the metabolism of polycylic aromatic substrates, an immense area of research for the carcinogenic effects of tobacco smoke and benzopyrene keeping investigators, such as Harry Gelboin (NIH), Allan Conney, (Roche), Don Jerina, (NIH), Charles Heidelberger (University of Wisconsin), and many others busy for years.

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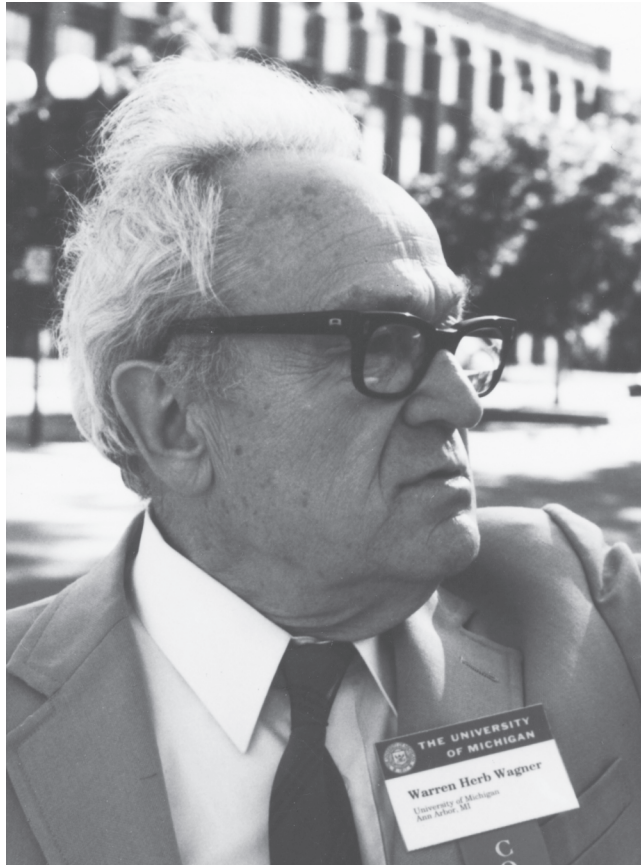
Warren Herbert Wagner

WARREN H. WAGNER, JR.

August 29, 1920–January 8, 2000

BY DONALD R. FARRAR

I N HIS PH.D. RESEARCH Warren ("Herb") Wagner was intro-
duced to classical methods of systematic botany, and found
them wanting. He was disturbed by the frequent absence of
quantitative data and the generally untestable hypotheses
of traditional reconstructions of species' evolutionary rela-
tionships. At the time, the latter was based largely on the
expert's weighing of the evidence and authoritative state-
ment of an opinion that could be argued but not easily
tested. Herb was determined that in his own research
monographing the endemic Hawaiian fern genus *Diellia*,
he would use evidence from all sources and explicitly state
the relative influence of each in an objectively constructed
illustration of phylogenetic relationships. The result was the
birth of his groundplan divergence index, for which he
soon became widely known. Herb's insight and instigation,
coupled in ensuing years with computer-assisted analysis of
comparative data, revolutionized the fundamental methods
and concepts of phylogenetic reconstruction, leading directly
to the burgeoning field of cladistic analysis of evolutionary
relationships among plants. For his seminal contributions
Warren H. Wagner, Jr., is generally considered a founding
father of modern plant systematics.

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Warren Herbert Wagner, Jr., was born on August 29, 1920, and was raised in Washington D.C., the son of Warren Herbert Wagner and Harriet Claflin Wagner. His early interests in natural history took him frequently to the Smithsonian Institution, where he became acquainted with the experts, including the eminent pteridologists William R. Maxon and Conrad V. Morton and lepidopterist Austin Clark. In college at the University of Pennsylvania he became the enthusiastic field companion of Edgar T. Wherry, author of the *The Fern Guide* (paperback, Dover Publications, 1995). Wherry was a mineralogist who became an expert on fern habitats and the first to point out the important associations of epipetric ferns with particular rock types. This undoubtedly nurtured Herb's enthusiasm for mineralogy; later his extended field trips with students often included a day of mineral collecting. When as a student I brought back an unusual form of cliff-brake fern from Missouri, Herb was anxious to visit the site, not so much for the fern as for the barite crystals I had found there. His fascination with butterflies (he authored or coauthored 20 papers on Lepidoptera)—he called them "flying flowers"[1]—dictated that he carry a butterfly net on field excursions, thus presenting the archetypical layman's image of a biology professor. I vividly recall stopping at a fast-food restaurant in the Missouri Ozarks, where after ordering, Herb headed for a nearby field filled with flowers and butterflies. The curiosity of the restaurant staff was definitely aroused by the spectacle of this man running through the field swinging a net at prey invisible to them. After we explained, our waiter walked into the field to shout, "Hey perfesser, your lunch is ready!"

Graduating from the University of Pennsylvania in 1942, Herb entered the U.S. Navy Air Corps, serving first in the Atlantic, then in the Pacific Fleet, where he was a naval air navigator. In the Pacific islands he spent his off-duty hours

collecting ferns and butterflies, later publishing (with David Grether) "Pteridophytes of Guam" as well as articles on the pteridophytes and butterflies of the Admiralty Islands. During this time he also flew into California, taking his specimens to E. B. Copeland, renowned expert on Philippine ferns, at the University of California, Berkeley. This was the beginning of an association that would bring him back to Berkeley for graduate study. While in the Navy, he also began what was to become a lifelong study of the ferns of the Hawaiian Islands.

At Berkeley in 1945 Herb joined an exceptional group of graduate students returning from World War II that formed fertile grounds for growth of new concepts in botany, evolution, and systematics. His student colleagues from 1945 to 1950 included Charles Heiser, Ernest Gifford, Jack Rattenbury, Isabella Abbot, Frank Ranzoni, Verne Grant, Art Krukeberg, and Ed Cantino. Their teachers included Melvin Calvin, Richard Goldschmidt, Curt Stern, G. Ledyard Stebbins, and Herb's major professor, Lincoln Constance. Copeland, though retired, was still active and served on Herb's Ph.D. committee.

Also among Herb's student colleagues was Florence Signaigo, who was studying the systematics of red algae with George Pappenfuss. Herb and Florence were introduced by fellow student Charles Heiser in the elevator of the herbarium. Florence recalls,

Herb and I used to go over to San Francisco, to various bars, where we would order a beer, and after a while Herb would ask the bartender if it was all right if he played the piano. Sometimes the bartender would show up later at the piano with two free beers. Once one had to ask Herb to stop playing a piece because it was making a woman at the bar cry. And once he was offered a job as a piano player.

Herb and Florence were married in 1948. They had two children, Warren Charles Wagner (b. 1953) and Margaret

Frances Wagner (b. 1957). Florence switched her allegiance from algae to ferns and together she and Herb comprised a formidable research team both in the lab and in the field. Their home in Ann Arbor was a busy and warm environment, frequently hosting receptions for visiting botanists and on holidays wonderful dinners for any of his graduate students who were in town. Herb continued to delight audiences in informal gatherings and sometimes at bars with the flamboyant piano playing that reflected his personality. It was always fun to watch the bar manager's expression change from skepticism to astonishment as Herb began to play. Once, after several evenings of this in a hotel bar, Herb was refused permission to play because the house pianist, embarrassed by the contrast with his own lackluster style, was threatening to quit.

Herb actively pursued his research and teaching until just weeks before his death on January 8, 2000, at the age of 79 from sudden cardiac arrest. He had experienced symptoms of heart failure for a few years before his death, but not enough to incapacitate him. Although officially retired, he had continued teaching his courses on woody plants and plant systematics and maintained a rigorous schedule of invited lectures to institutions around the world as well as national and international meetings and symposia. In the summer preceding his death Herb and Florence conducted field work in Alaska and in southwestern Canada, from both places returning with, of course, new species of *Botrychium.*

After receiving his Ph. D. in 1950 Herb spent a year as a Gray Herbarium fellow at Harvard, then moved to the University of Michigan in 1951, where he remained throughout his career. From 1966 to 1971 Herb served as director of the University of Michigan's Matthaei Botanical Garden. He chaired the Department of Botany in the Division of

Biological Sciences from 1974 to 1977, and chaired many additional department and college committees, including the University of Michigan's Tropical Studies Committee from 1983 through 1997. He was chairman or president of nine professional societies, including the American Fern Society, American Society of Plant Taxonomists, and the Botanical Society of America, and council member, trustee, or advisor to dozens of organizations. He was in demand as an external reviewer of departments of biology and botany across the country. He served as an editor for the University of Michigan Press, *The Indian Journal of Pteridology,* and *The Flora of North America* (coediting "Pteridophytes" in volume two [1993]). He reviewed countless journal manuscripts and grant proposals. To these causes and many more he gave freely of his time while continuing to teach and while maintaining a research program that generated over 250 publications. He was elected to the National Academy of Sciences in 1985. His official retirement in 1991 proved to be only a formality, as his research and teaching continued unabated.

One of Herb's first endeavors as a young professor at the University of Michigan was probing the origin and relationships of the Appalachian *Aspleniums,* a confusing group of ferns to which he had been introduced years earlier by E. T. Wherry. The keys to solving this puzzle of starkly different species with a seemingly complete array of intermediates lay in (1) examination of chromosome numbers and their pairing behavior in meiosis; (2) relating this chromosome data to spore abortion and intermediate morphologies; and (3) appreciation of the fact that fertility could be restored to "sterile" species hybrids through allopolyploidy, a simple doubling of the basic number of chromosomes (1954). Thus the now well-known Appalachian *Asplenium* triangle was resolved into three diploid species (the corners

of the triangle), three fertile allotetraploid species (originating as hybrids between the three diploids), and numerous backcross hybrids that occurred wherever a tetraploid and diploid species grew together. Subsequently verified through artificial crosses, flavonoid chemistry, and allozymes, this model of reticulate evolution quickly became the basis for making sense of similar species complexes in other fern groups and in seed plants.

Revolutionary in its time, attributing an important role to species hybrids in plant evolution (1968, 1969) contradicted the long-held notion of species hybrids being evolutionary dead-ends. Herb's studies demonstrated that plant species hybrids could in fact be the initial step in the formation, through allopolyploidy, of new species that continued to participate in subsequent evolution of the genus (1980).

Sterile F_1 hybrids also proved to be much more common in plants than in animals, and Herb was on a mission to spread the news. His seminar presentations always worked in a series of hybrids demonstrating wider and wider crosses, ending with a wildly misshapen fern that he proclaimed to be a cross between a wood fern and a red oak! Such exaggerations drove home the point that hybrids were to be expected in nature and recognized as a component of the flora at any given time and place. Although most of these hybrids might be sterile dead-ends, their presence constituted part of the "evolutionary noise" (his term) through which the systematist must trace "signal" lines and processes leading to long-term persistence and divergence (1970).

A part of Herb's diatribe on hybrids was that they were easy to detect, because they were invariably intermediate between their parents. Because development of most morphological traits would be under the control of a set of genes representing a combination of the two parents, not

only could one predict the morphology of hybrids but given a hybrid and one parent, one could also predict the other parent. In the case of allotetraploid species that may have formed in the ancient past, it was possible that one or both of the diploid "parents" might now be extinct. This was Herb's conclusion relative to the wood-fern genus *Dryopteris,* which seemed to lack an extant diploid needed to form two of the allotetraploid species (1970). His naming of this extinct species was hard to accept by many and led to a decade of alternative proposals designed to avoid postulation of a missing species. As with the *Asplenium* triangle, subsequently derived molecular evidence supported Herb's conclusion.

Herb's persistent proclamation of hybrid intermediacy set up a straw man easily knocked down by later studies showing transgressive hybrid morphologies in traits controlled by one of a few genes. This didn't phase Herb. His goal was always to understand and promote the "big picture," the principles that explained most of nature and natural processes. His procedure though was to study the knowable details. Through accumulation of details the big picture would emerge. Thus he produced exhaustive studies of foliar dichotomy (1952), heteroblastic leaf morphologies (1957), paraphyses (1964), spore structure (1974), and vein reticulation (1979). He compiled detailed floristic analysis of the areas in which he worked—the southern Appalachians (1963, 1970), Hawaii (1999)—and distributional analyses of species and genera he studied. From the latter he became convinced that pteridophytes, despite their ease of dispersal by spores, for the most part showed the same distribution limitations as seed plants (1972). Subsequent research demonstrating the general out-breeding nature of ferns provided the explanation—two or more spores germinating in interactive proximity being required for sporophyte production and thus for migration of most diploid species.

Although I had taken Herb's course in plant systematics and had been exposed to his philosophy for several years, I didn't come to appreciate his truly comprehensive knowledge of pteridophytes until 1967, when Herb participated in the offering of a fern course for graduate students in Costa Rica. For two weeks he lectured daily, not only on the morphology and systematics of tropical ferns but also on the ecology, distribution, and occasionally the physiology of the thousand or more species we were likely to encounter, all seemingly without resort to notes. My feeling then and now was that one could hope to contend with Herb's analysis of the big picture only with a similar comprehensive knowledge of the parts.

Though a comprehensive Wagnerian treatment of the pteridophytes was not produced during his lifetime, Herb's influence on pteridology in the last half of the twentieth century was enormous, through his own studies and those of his students and their students. He was coeditor of the "Pteridophyte" volume of *The Flora of North America* (1993) and author or coauthor of treatments on Ophioglossaceae, Lycopodiaceae, Schizeaceae, Aspleniaceae, and *Dryopteris*. At the time of his death Herb and Florence Wagner had largely finished "The Pteridophyte Flora of Hawaii" (it is now being completed by Florence Wagner). That flora, in its treatment of the remarkable evolutionary patterns of Hawaiian pteridophytes, will reflect their lifetime accumulation of knowledge of pteridophyte biology.

Herb had a passion for studying the small. In 1963 with Aaron J. Sharp he published a paper in *Science* describing "a remarkably reduced vascular plant"—the fingernail-size gametophyte of the fern genus *Vittaria*. The reduction to which the paper referred was not the size of the gametophyte plant itself but its failure to ever produce a sporophyte, the larger and more familiar phase of the fern life cycle. Though

well documented in bryophytes, indefinite persistence of
the supposedly ephemeral gametophyte phase through
vegetative reproduction was an unheard of phenomenon in
ferns. Furthermore, these independent gametophytes were
very common in the southeastern United States, covering
square meters of moist cliff surfaces much the same as bryo-
phytes. The paper in its initial submission was titled "The
Most Reduced Vascular Plant," but the reviewers cautioned
that still greater reduction might be found. True to this
prediction Wagner and Robert Evers shortly thereafter
described from the canyons of southern Illinois the gameto-
phyte of *Trichomanes*—another independent gametophyte,
this one reduced to a mere branching filament of cells.

I arrived in Ann Arbor just at the time of these discoveries
and was fascinated to find, on my first trip with the Wagners
to southern Ohio and Kentucky, both genera of independent
gametophytes growing in luxuriant abundance. With Herb's
enthusiastic encouragement and my own love of exploring
cliffs and rockhouses, I was powerless to resist a lifelong
enchantment with the evolution and ecology of these plants.
The existence of independent fern gametophytes is now
well documented in North America, Hawaii, and Europe
and probably occurs worldwide as a natural result of the
preadaptation of certain tropical species for vegetative
reproduction and dispersal in the gametophyte stage, a habit
evolved to promote cross-fertilization in epiphytic habitats.

The other small plants to attract a disproportionate
amount of Herb's attention were the moonworts, diminutive
plants of the genus and subgenus *Botrychium*. Generally
less than 10 cm tall, these plants produce but one leaf per
year of very simple (reduced) morphology, usually well hidden
among associated vegetation. When Herb first turned his
attention to this group, six species were recognized world-
wide, five in North America. With Florence's expertise in

cytology and their combined ability to coax hoards of students and amateurs to crawl through meadow vegetation on hands and knees they began detection of a much larger complex of species than ever imagined.[2] Their uncanny ability to discern subtle morphological differences revealed a diversity of diploid, tetraploid, and hexaploid species now totaling 30[3] and illustrating as well as any organisms the concepts of cryptic speciation (1983).

Of Herb Wagner's many contributions to plant systematics, he is most widely known for his early conceptual contributions to cladistic methods of analysis and representation of phylogenetic relationships, now the method of choice for research into evolutionary relationships among organisms. After first conceiving and applying his groundplan divergence index method in his dissertation work,[4] Herb spent the next two decades analyzing, perfecting, and promoting it, while applying it to more and more complex systematic problems (1964, 1969). Ultimately he convinced most of his colleagues that his objective and testable methods yielded results more satisfying than the subjective judgments of experts, and with their adoption by the new breed of computer-savvy systematists, "cladistics" was off and running. Later reflecting on the struggles of this period, he commented that "most active taxonomists are so busy that they have little time to contemplate the philosophical foundations of their calling. They are too preoccupied with the act of classification to be burdened with the ideas behind it or to devote themselves to developing a consistent theory" (1969).

Asked to review his development of the groundplan divergence index (1969, 1980), Herb acknowledged that no one part was new and that his thinking was initially influenced by the writings of Benedictus Danser[5] regarding detection of the ancestral form or "groundplan" of phylo-

genetic groups. Herb's contribution was putting philosophy and method together to yield a diagrammatic depiction of phylogenetic relationships based on explicit data and assumptions. Herb's method consisted of five steps: (1) identifying the taxa to be considered; (2) selecting characters that showed evolutionary trends; (3) determining the ancestral state for each character; (4) finding the degree of advancement of each taxon; and (5) connecting taxa by their degree of shared derived characters. Each of these steps required careful objective analysis with no *a priori* assumptions. "Homology is a conclusion and not a datum. . . . Only trends and patterns shown by the data themselves can be applied" (1969). Most basic was the use of in-group and out-group comparisons to objectively determine ancestral character states and the Occam's razor principle of assuming an overall diagram (tree) requiring the fewest character changes (steps) as being the most likely. Herb's method was soon computerized to produce "Wagner trees" as they became known.[6,7] With many subsequent modifications and increasing sophistication, Wagner trees continue to appear in systematic literature. Along with the awards for Herb's many contributions to systematic botany (Willi Hennig fellow, National Academy of Sciences, American Academy of Arts and Sciences fellow, Asa Gray Award of the American Society of Plant Taxonomists), the Wagner tree inscription appropriately recognizes his profound influence on modern phylogenetic reconstruction.

Herb emphasized that a major goal of his groundplan divergence index was to teach concepts in systematic botany. It "forces us to investigate the nature of character states and to evaluate all of the available characters." He admonished that "the systematist should not simply 'plug in' his data set and allow the computer to come up with the cladogram. He should think it out himself, and this, scien-

tifically, may be one of the most useful rewards of following each of the procedures of the Groundplan-divergence Method" (1980). He did more. He *created* an entirely new family of plants, the Dendrogramaceae (also known as the Wagneraceae), to teach the principles involved. The species (illustrated on 5×7 cards) demonstrated evolution from normal to fleshy stems, simple to compound leaves, free to fused petals (or possibly the reverse of all of these) as well as other variations. In the classroom these "plants" stimulated hours of discussion (sometimes fierce arguments) over the direction and pattern of their evolution and which was the most parsimonious solution. The exercise proved so effective that through the 1960s new species of Dendrogramaceae continued to be discovered (as well as fossil ancestors). They also reproduced vigorously and dispersed, ultimately achieving much the same distribution as Herb's students and grand-students. Publications appeared analyzing their systematic relationships using an array of computerized methods. They became as well recognized and as important in systematic lore as real plant families.

Such was Herb Wagner's talent for getting students immersed in systematics and plant science in general. He had little sympathy for those who complained of the difficulties of academia or who did not pursue their studies with a strong, honest effort. For students displaying genuine interest in their research discoveries he quickly multiplied that interest through his own. His clear excitement over discoveries large and small was the genius of his inspirational leadership. He could make hard work not only palatable but also fun. My recollection of lunchtime discussions among Herb and us students is that always there was the sense of examining breaking news at the forefront of scientific discovery. Importantly, it was the science behind those discoveries, rather than the people, that was the focus. He

cultivated the attitude that all research was worthwhile and that the goal was advancement of knowledge, not personal glory. He applied this philosophy to encourage reluctant students to publish their work, saying that they "owed it to science" to communicate their findings. This particular ploy worked to keep me in school when I was contemplating taking time out for a stint in the Peace Corps.

Herb received well-deserved awards for and acknowledgements of his gift for teaching both inside and outside the classroom, but his influence certainly was not limited to the classroom. In addition to numerous research field trips, Herb seldom made a seminar visit to a new or botanically interesting area without insisting on an accompanying field trip. These trips invariably included a retinue of local amateur botanists as well as students and academic professionals. From their "Wagner experience" hundreds of students, professionals, and amateurs became hooked on science, not because they wanted to please Herb, although that was always fun, but because they became genuinely infused with the excitement of scientific discovery. Herb's ability to inspire others through his interest in their studies and their knowledge not only fostered independent research but also created a legion of professionals and amateurs eager to contribute data to Herb's projects as well. The total productivity of this synergism, though unquantifiable, remains hugely visible.

Herb's distinguished career at the University of Michigan included chairmanship or cochairmanship of over 45 doctoral committees and membership on more than 235. He taught a variety of courses, including systematic botany and biology of woody plants, both of which he continued to co-teach after "retirement" in 1991 through the fall of 1999. Teaching was as much a joy to Herb as it was to the students who continued to pack his courses. His outrageous performances and exaggerations delighted his audiences. It was always of

great interest to his teaching assistants to see who among the students did and who didn't believe that *Rafflesia* was pollinated by elephants, *Wolffia* by mosquitoes, and *Podophyllum* by turtles. Herb's public lectures and seminars were equally popular. Few biologists have been in such demand as a visiting speaker. His curriculum vitae list of invited lectures totaled 169—after retirement!

Warren H. Wagner, Jr., will be remembered as a wonderful teacher and inspirational leader whose legacy lives on in hundreds of individuals whose lives he touched. His command of the principal subjects of his research, his beloved ferns, was excelled by none. He used intimate knowledge of detail to synthesize big-picture principles that withstood the scrutiny his flamboyant style invited. His contribution to plant systematics and evolution and to the biology of ferns profoundly influenced the direction of these fields into the twenty-first century.

Additional biographic information on W. H. Wagner, Jr., with more complete bibliographies has appeared in obituary publications in *Taxon* (49[2000]:585-592) and *American Fern Journal* 92[2000]:39-49). The photograph and information on early years were graciously provided by Florence Wagner. Factual information is taken from Herb Wagner's 1999 curriculum vitae. Other anecdotes and observations extend from my long association with the Wagners, as a graduate student in Ann Arbor and in many subsequent field trips and discussions of plants, people, and philosophy.

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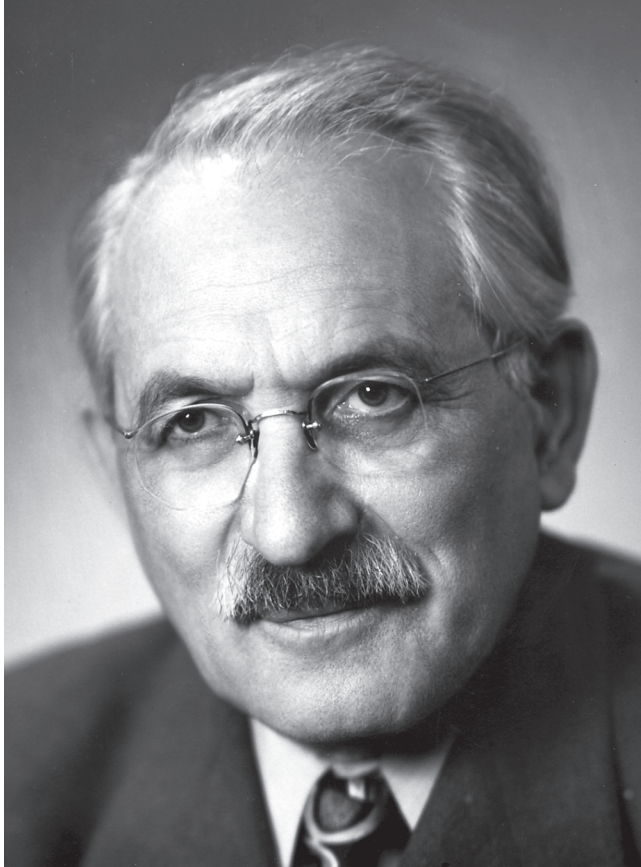
Selman A. Waksman

SELMAN ABRAHAM WAKSMAN

July 22, 1888–August 16, 1973

BY ROLLIN D. HOTCHKISS

M ANY GIFTS HAVE COME to humanity from Selman Waksman's energy, enthusiasm, and passion for science. These came about through the development of valuable antibiotic substances discovered in his systematic researches on microbial components of the soil. With extraordinary humanism and philanthropy he used the royalties that resulted from the commercial development of these "miracle medicines" as further contributions to society. He donated a major part of them to create institutes and endow foundations that continue to support international fellowships and grants beneficial to science and medicine. All of this without having the advantage so many scholars have had: early family or local role models demonstrating the qualities and traditions of academic science and research.

Selman Abraham Waksman was born and raised in the rural Ukrainian town of Novaya Priluka. Remaining in that remote town on the steppes until age 20, he certainly could not have dreamed of the triumphs and obstacles that lay ahead. His father made a modest living tending and renting some small houses he owned. His mother was a capable manager of her own dry goods business, developed while the father was away on years of military service. The youngest of eight intelligent and pious sisters, she energetically strove

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to lead a rational and useful life in the fine Jewish tradition. Starting with an impressive and accomplished grandmother, this matriarchy was clearly proud of the stirring ambitions of young Selman. As an only surviving child, he was loved and supported in his tendency to outdo, rather than rebel against, the standards of his community. Probably their backing was responsible for the easy, confident way he approached personal relationships and decisions later in his career.

Intellectual stimulation of a general sort there was; Waksman for some years studied the Bible and Talmud and the history of the pious Jewish people and their enthusiasm for learning. From the age of 10 he was continually involved in tutoring other less able students in their academic weak spots. Simultaneously he availed himself of tutors to speed his own advance. His autobiography (Waksman, 1954) gives us a proud and nostalgic recollection of the influences in his youth that moved him toward a career in the study of life processes. The rich black soil of his native town and the surrounding villages supported a teeming agricultural life that he could not have missed. He may not have done much practical work in it, but he was perceptive in developing an early, incompletely formulated curiosity about such chemistry as goes on in the fertile soil.

Probably his family expected that he would become a *malamed*, teacher of local youth, but his tutors and his father were aware of a big world outside, with larger projects. By the age of 20, after his mother's death, he surrendered his legacy in his father's modest house properties and moved to the larger centers, Zhitomir and Odessa. He passed several examinations for more advanced study, then following the example of some of his relatives, migrated to the United States in 1910.

Received in New York by a cousin, a chicken farmer in New Jersey, he was installed in their home and for a few

years performed useful work on the family farm. He soon
enrolled at nearby Rutgers College, where he came under
the influence of Jacob Lipman and Byron Halsted. The former
advised an agricultural course rather than one in medicine,
and proceeding on this line, Waksman took accelerated course
work, spending the fourth year in research. Asked to assay
the bacteria in culture samples from successive soil layers,
he became drawn to fungi and eventually some regularly
appearing pleomorphic, filamentous bacteria, the actino-
mycetes. These became an abiding interest and the focus of
his master's degree thesis, which he received in 1916, and
in his doctorate with H. Brailsford Robertson at the University
of California, Berkeley. The little investigated actinomycetes
continued as a subject in which he would become a major
expert.

In 1916 he became a naturalized U.S. citizen. The move
to California was also a wedding trip following his marriage
to Deborah Mitnik, an accomplished vocalist and artist from
his hometown who was affectionately known in the family
as Bobili. She became a guide and spur for his cultural
advances in the United States and internationally. Their
devoted partnership remained steadfast and enriched the
remainder of their lives.

It was necessary to supplement his graduate fellowship
stipend, so he started to work for an industrial medical
organization, Cutter Laboratories, which would set a pattern
that proved useful later on.

Back at Rutgers Agricultural Bacteriology Department
in 1918 his position was at first precarious. Needing to
augment a meager income, he developed a comfortable
cooperative association with the local industrial Takamine
laboratory. Continuing research on the soil microflora, he
described new thiobacilli (1922) that oxidize elemental sulfur.
Exploring vigorously the actinomycetes and fungi, he analyzed

and reported systematically the life to be found in several soil environments of the New World (1916). In time he would redefine the bacteriology department as one of soil microbiology. Eventually his interest in natural chemical processes led him to studies of some modifications an investigator could impose on those soil processes.

In these still strenuous years a son was born in September 1919 and was loyally named Byron Halsted Waksman, after one of Selman's inspiring mentors. After some infant health difficulties the child would go on to become an active and capable student himself, and eventually an accomplished immunologist, carrying on the family tradition of service to medical science and to the public.

In 1924 after several years devoted to soil research the Waksmans traveled in Europe for six months. While there, Selman visited many important laboratories and institutes in France, Italy, Germany, and Scandinavia, discussing methods and research with many workers in soil biology and chemistry close to his field. His diary reported (Waksman, 1954, pp. 123-55) that while he met some impressive soil biologists, among them Sergei Winogradsky, then resident in France, others were not living up to that field's possibilities. He also briefly visited some important European biochemists. The Waksmans were welcomed in their native Ukraine, but found a depressing decay in conditions there. His wife, Deborah, having introduced Selman to a broader cultural life in New York, made sure that they visited important museums and concert halls in Europe. He returned to the United States both exhausted and stimulated by new possibilities he envisioned.

On the returning steamship he found young French biologist Rene Dubos, who was immigrating to the United States, and soon offered him a place in the Rutgers laboratory. This encounter was ultimately significant for both men.

The laboratory had now grown to be a rather popular training ground. In teaching the lore of soil microbiology Waksman had occasion to describe to the students the inhibitory interactions between organisms in the soil, probably presenting them as examples of "environmental" influence, complex and variable. Dubos became, by his nature, a thoughtful student in this field and began soon to look upon them more as discrete biochemical interactions. In any case, by 1927 the student was pursuing one-on-one effects of soil organisms in decomposing cellulose and was beginning an approach that would lead to modern antibiotics. Other steps had to be made, however.

Dubos, traveling to New York City especially to consult his countryman Alexis Carrel, was referred to Oswald Avery. The latter, at the Rockefeller Institute Hospital, was searching for something that would attack the capsular polysaccharide of a special line of pneumococcus (*Streptococcus pneumoniae*, Type III) that he had isolated. Hearing of the problem, Dubos immediately proposed that a soil bacterium could be found for the purpose. Hired by Avery for this study, he did succeed at Rockefeller in finding in soil such a culture. For a time this seemed of possible therapeutic use.

In later steps Dubos with Avery developed the concept of a Gram-positive core antigen of pneumococcus to be attacked. Again Dubos set out with *live* bacteria and soil samples to look for enriched growth of something destroying the pneumococci. Such an agent was eventually isolated (Dubos, 1939) and pursued as a wartime project. He identified the culture as *Bacillus brevis*. Joining the project, I isolated from the crude agent, tyrothricin, two crystalline polypeptides, tyrocidine and gramicidin, with different antibacterial properties. These were the first highly purified substances produced from a deliberate search for bacteria that inhibited growth of other bacteria.

It must be realized that there was an "unorthodox" feature in this finding: Ever since the time of Koch and Lister much emphasis in infectious disease had been placed on the necessity of avoiding contamination of infections by soil or other non-sterile matter. It was an escape from this categorical thinking to consider *using* a soil-derived culture to combat an infectious process! The careful medical investigators had not ventured that implicit step. Moreover, the unsystematic use of mudpacks in whimsical folk practice could never have led to it.

The excitement produced by this purposeful search by his former student gave Selman Waksman a clear stimulus to seek more examples. He soon organized an energetic search for preexisting antibacterial organisms in soil samples that was to continue for years with the help of dozens of collaborators. So was overcome a paralysis that had set in following the earlier somewhat analogous discovery by Alexander Fleming of an accidental contamination of bacterial cultures by an airborne inhibitory mold (producing penicillin). Although it had also been considered for therapeutic use, penicillin had not been produced in a stable useful form until wartime 1940.

The Waksman group did their screening by looking for growth inhibition zones around single colonies of a series of systematically isolated soil microbes on agar plates, growing under a variety of culture conditions (1940). Now they tested the inhibition on specifically targeted pathogenic bacteria, as Dubos had done. Government support for this work was sought but not granted, however through the help of A. N. Richards, support was obtained from the Commonwealth Fund. The group in the next few years described more than 20 new natural inhibitory substances, mainly from actinomycetes. Among them were streptomycin, neomycin, and actinomycin. Waksman proposed the now standard term

"antibiotics" for this class of natural growth inhibitors. In time countless more examples came from the commercial industries that sprang up, extending the searches. The roster continues to grow to the present day.

For Waksman the discovery of streptomycin in 1944 and its effect on the tubercle bacillus accomplished with the collaboration of A. Schatz and confirmation by E. Bugie was a rich and satisfying fulfillment of many of his personal and altruistic aims. Ever practical, he established effective and congenial relations with Merck and Company, which developed liquid culture methods for production of bulk quantities of the microbial products during World War II. Patenting and licensing the promising ones, notably streptomycin, provided funds, 80 percent of which was assigned to Rutgers University to support research and eventually an associated Institute of Microbiology. He also soon arranged to have animal tests and clinical trials carried out at the Mayo Clinic to expedite the possible use in treating tuberculosis. Of the 20 percent of license funds accruing in his own name, one-half was later consigned to a foundation for research support.

Throughout the 1930s Waksman had been acutely aware of the growth of fascism and anti-Semitism under Hitler. As one response he resigned from editorships in German journals. In addition he embarked on a study of marine bacteriology and did useful service in the study of fouling of oceangoing vessel bottoms for the U.S. Navy and Coast Guard. This was done through a connection with the Woods Hole Oceanographic Institution, which became a lasting link for him and his family in Woods Hole, Massachusetts. His work on humus conversion into peat in this period also served to give the United States an independent source of this interesting material.

In recognition of his energetic studies and analyses of soil microorganisms, he was elected to membership in the

National Academy of Sciences at the very outset of the anti-biotic searches in 1942.

A postwar European trip of five months in 1946 brought a series of opportunities to convey serious reports on the values of antibiotic treatments to eager and grateful medical audiences. It also provided a chance to visit son, Byron, who was on Army medical service in Germany. In addition he revisited the Soviet Union, where he established influential relations and gave well-received lectures in Moscow. However, after the ravages of war only a few of the old friends and relatives remained from his native Priluka. Near Paris he visited Serge Winogradsky, by then 90 years old, and began a process to secure the publication of that pioneer's collected works. It would eventually involve him in further financial support. Briefer repeats of this kind of triumphal visit would occur as he received something like 13 medals and awards from European countries within the next six years. Among them was the Emil Christian Hansen Award in Denmark and appointments to the French Academy of Science and the Legion of Honor.

In the United States he received many awards, including a Passano Foundation Award and a Lasker Award, a notable honorary degree ceremony at Princeton, as well as numerous medals from pharmaceutical and other societies. A more complete list of some 66 awards and 22 honorary degrees appears in the volume (Woodruff, 1968) organized by Waksman colleagues in Rutgers to honor his eightieth birthday.

Already in 1949 he had proposed to establish an Institute of Microbiology in association with Rutgers (Waksman, 1954, p. 277). This was formally achieved in 1951 and completed in 1954 with a dedication and symposium in which many eminent microbiologists participated. The institute was endowed and supported by the 80-percent assignment

of streptomycin patent royalties to Rutgers and has had a productive history through the years. Successive directors have been Selman Waksman, 1954-58; J. Oliver Lampen, 1958-80; David Pramer, 1980-88; and Joachim Messing, 1988 to the present. Each director redefined the mission policy and organization of what was renamed the Waksman Institute of Microbiology after the founder's death in 1973. As other endowed institutions have done, it has had to develop gradually more of its support from government sources during later years.

Although I was appointed for a term on the institute's Board of Advisors, the administration at that time did not have occasion to call upon us for more than official mail votes. My experience with the institute was accordingly by way of attending most of its symposia and conferences and observing from outside its stepwise movement toward a center for molecular biology and genetics.

INTERNATIONAL RECOGNITION—AND SHARING REWARDS

The great practical promise of streptomycin for tuberculosis and other infections led to the award of a Nobel Prize in physiology or medicine in 1952. There was much acclaim for the effort and patience expended in the development of the antibiotic treatments, and it inspired others to similar allied work. A broad public response to this award brought many additional honors, such as the Japanese Order of Merit of the Rising Sun and invitations from and contacts with colleagues in Europe and Asia.

The Nobel Prize did not diminish Waksman's conscientious effort to convey the knowledge and insight of careful scientific work. In the pre-Nobel period he published 16 books and monographs and in the two decades after almost as many more, most of them under his sole authorship. These were well-documented works, thoroughly covering the history

and essential science of their subjects. Whatever clerical help he may have had, it is clear that he had an ability to digest and assemble straightforward information from the published literature. In the later period several of his books were grateful biographies of his personal heroes, Sergei Winogradsky (Waksman, 1953), Jacob Lipman (who had advised him to enter agricultural and soil science rather than medicine) (Waksman, 1966), and the tragic Waldemar Haffkine (Waksman, 1964).

His papers on antibiotics continued unabated, although the pattern changed. Before the prize three-fourths of them were with coauthors; but after the prize a large number of historical reports and addresses were composed under sole authorship and delivered with inspiring enthusiasm and a considerable degree of pride. A similar pride, delivered nevertheless with sober modesty, characterizes his autobiography (Waksman, 1954), appearing in 1954 in the United States and later in translations in several other countries.

Now the honors and awards were coming at an increased rate. More details of these than can be accommodated here can be found in the jubilee volume prepared on Waksman's eightieth birthday (Woodruff, 1968). Royalty fees were also accumulating and largely donated in support of research. Merck and Company was always appreciative of Waksman and his associates' rights and they too proved public spirited in sharing commercial privileges at a time when the United States was at war.

I have worked with several of Waksman's associates, including Julius Marmur, Dorris Hutchinson, and Jack Fresco, and have known several others. Uniformly they displayed a warm respect, even admiration for the hard work and dependable good will of the "professor." There was also my lifetime of association with Rene Dubos, who differed considerably from Waksman in temperament. Yet never as we talked about

antibiotics did he more than suggest that the systematic repetition of empirical searches was not for him. Perhaps some other scientists of the intuitive type felt that Waksman's productive career was more characterized by systematic development of a few ideas than by "exciting" formulation of new ones.

There was one unfriendly legal action, brought by former coworker Albert Schatz, who declined to surrender some of the rights in streptomycin development to Waksman, demanding personal payment for his participation. Let us suppose the case originated within familiar bounds: the pride of an able young associate having overcome technical obstacles and successfully maneuvered part of the routes to solution. This was a time when the contributions of young associates were just beginning to get more recognition. In such situations the contributions of the experienced senior advisor, which can include the underlying planning and facilities for the project, its initiation, timing, and quite likely a substantial part of the special methodology, all can be disregarded by lawyers conducting a "nuisance" claim. That was an element of this case; it gave Waksman great distress and was only "settled" by a costly and practical compromise (Waksman, 1954, pp. 279-85). In consequence he felt that justice obliged him to use still more of the royalties to give unsought bonuses to his entire staff and coworkers. This gesture in turn earned even more of their general loyalty and goodwill.

How may we evaluate Selman Waksman's scientific career? It seems to me that his most outstanding trait was his patient, driving energy directed toward altruistic goals. His personal skills in the realms of morphology and nutrition of a wide range of microorganisms were put at the service of an active curiosity and a retentive memory. He accomplished much in looking into the natural biological processes going on in the soil. In most of this work he remained close to nature:

to constructs and theories that emphasized interactive and ecological relationships. In the laboratory he sought the findings from *organisms in a context* that were the intellectual product of a naturalistic outlook. He maintained a lively interest and goodwill toward his coworkers and behaved as a benevolent sponsor and guide to them. With tireless energy and insight he was an early and successful innovator of what is now called technology transfer.

Another vector for growth was always active; in spite of some limitations in his biochemical background he sought, supported, and learned from chemically skilled coworkers. He consciously strove for analysis and understanding of chemical and physiological descriptions of soil processes, but his most notable successes were in finding and describing valuable microorganisms. That may be because most of his projects began with a broadly framed naturalistic question.

In fact, he acted as a sponsor not only for microbiology but almost as much for microbial biochemistry. He was impressed by the scientific work of Cornelius Van Niel, which (like Kluyver's and Winogradsky's) took account of chemical processes going on in populations within a complex environment. So far as I know, his main contact with Van Niel's concepts came from the literature and through coworkers who followed that interest, Robert Starkey and Jackson Foster. He clearly wanted to encourage advances in this field. Such a motivation showed strongly in his grant efforts as well as in membership proposals for the National Academy of Sciences.

What stands out above all else is that coming from a modest rural background, Selman Waksman felt grateful and with great humanity wanted to repay society by thoughtful and constructive contributions to science and health and, furthermore, by freely reporting them to the public.

A FAMILY—MANAGED BENEVOLENCE

In 1951, as royalty income accumulated, Waksman established the Foundation for Microbiology by assigning half of his 20-percent personal royalties over for its support of research efforts to benefit society and humanity. Rene Dubos and Harry Eagle were invited to join as cofounders. Later he arranged the formation of Waksman foundations in France, Italy, and Japan that could expend patent income from the world areas where it accrued for the support of scientific work in or near those areas.

Asked to serve as a trustee of the U.S. Foundation for Microbiology when Rene Dubos withdrew in 1959, I was fortunate to see firsthand some of the impulses and insights that Selman Waksman applied in science administration. One soon realized that although he proudly allowed his name to be associated with some of his benevolent actions, that pride was accompanied by a realistic self-appraisal and true modesty.

The charter program obliged us to expend most of the annual income from the patents for streptomycin and neomycin in support of scientific endeavor. Our board of about five or six microbiologists usually met at Essex House on Central Park South in New York City for a congenial dinner and work session. At a typical trustee meeting the colleagues would be joined by a few associates, such as for several years A. Dudley Watson, Waksman's financial advisor (followed by Max H. Schwartz), and perhaps some secretarial help, besides the board secretary. The group met in a short cocktail session at which members greeted and exchanged news with one another. Waksman, however eager he may have been to get on with the serious work of the foundation, always provided a good dinner with sumptuous choices. Afterward, as the conversations began to move into a con-

vivial mode, he would call for the business session. He tried the experiment of conducting part of the business before the dinner, but modern life schedules made that almost impossible.

A courteous and patient taskmaster, Waksman as president took the chair, handing out the requests we were to consider. He would not indicate his personal judgments until all committee members had expressed theirs. Then he gave his own opinion and we would move toward a group decision. On those occasions when the other trustees disapproved of an application he might show a generous inclination to offer a small token payment as a "consolation" award. So sometimes we would have to insist that this was "sending the wrong signal" and only inviting a new modified request, although at other times that was exactly what we wanted to get.

The foundation handled scores of small grants, especially those providing funds for purposes likely to be limited or omitted from government research grants. It could help in funding small conferences on specialized topics, or for young scientists to travel to conferences. An abiding problem in Waksman's own experience had been the wish to present high-quality photographs of fungi and ascomycetes, etc. Therefore, he always noticed when the researches involved little known organisms. A subsidy for biological illustrations in color could often be raised, even and especially for little known microorganisms. Part of our funds might be assigned to the Cold Spring Harbor Laboratory, the National Academy of Sciences, and sometimes to the Weizmann or Technion institutes in Israel for distribution in support of programs they conducted. Support was also given for a Waksman Lectureship in microbiology, administered by the National Academy of Sciences. For years we supported fellowship

programs and Latin-American professorships given by the American Society for Microbiology.

Of course, a favorite intention of most donors is to give "catalytic" support to a project that seems just to be emerging from obscurity. I think this was at times accomplished by influential efforts of such members of the Board of Trustees as Harry Eagle, Kenneth Thimann, or Harlyn Halvorson to ferret out such opportunities.

The Foundation for Microbiology throughout its history always maintained a strong family involvement. Selman Waksman remained president for its first 19 years, retiring in 1969. Byron Waksman was a trustee from 1968 and president from 1970 for thirty years before Frederick Neidhardt took charge in 2001. In the meantime Deborah Waksman served as trustee from 1957 until her death, respectful of the science but naturally paying more attention to the social and educational aspects of the research supported. At later points the grandchildren have become trustees and officers of the Foundation. The trustees have also been augmented by one or two in number and in scope by appointment of distinguished microbiologists and biologists. I believe it has continued to serve the principles of its founder in a most enlightened way.

It deserves mention that Deborah Waksman not only encouraged the scientific supports that her husband bestowed but also in her own name made donations on behalf of the arts. For a number of years she offered music fellowships at Douglass College, a women's branch of Rutgers, and made donations to Albert Einstein College of Medicine, Brandeis, and Hadassah. She arranged musicales in their family home for several years, and a high honor came when she sang for the Schola Cantorum.

SOME PERSONAL REMINISCENCES

On one occasion I happened to arrive at a Foundation meeting well ahead of the out-of-town members, so Waksman and I conversed a while, then at the window I looked out upon Central Park in the growing dusk. Seeing the Wollmann Skating Rink, a small lighted rectangle, several blocks north, lighted up with its evening crowd of enthusiastic skaters, I remarked that the Wollmanns had "done a great thing for New York City folks" in establishing the concession. Waksman seemed excited by my remark and asked me to point it out to him—then subsided into thoughtful reverie, peering long at the sight. I feel confident in claiming that he was, for long moments, impulsively thinking something like, "I'm fond of New York, too; how could I do something like that?" That conception of his blend of emotional and practical generosity is based on long acquaintance with his humanity.

His wife, Deborah, was largely responsible for his affection for New York and its culture. Her awareness of his position in science assured her commitment to dignity in their audiences with several heads of state and royalty and other attentions of society. Nevertheless, on one occasion this cause seemed to be threatened. At the Nobel ceremony in Stockholm's Town Hall, in 1952, seated between the Swedish King and his brother, her formal gown got caught up on the King's chair and he sat down on a fold of her skirt. Discomfited—up on a dais!—she could hardly converse with Prince Wilhelm about poetry until he, observing her nervousness, asked what was troubling her. She confessed to him her difficulty. With a laugh he proceeded to speak quietly to his brother, the King. The latter then laughed, discreetly released her skirt and said quietly to her, "Why didn't you poke me in the ribs?" Then he quickly charmed her by extolling the praises of the Nara shrines in Japan,

where the Waksmans were about to travel. This memoir from Deborah's own notes (D. Waksman, 1952) of the great ceremony suggests to me that the King's disarming humanity reassured her with regard to her husband's similar disregard of his own eminence.

Selman often told a story about quizzing a pharmacist from whom he, unrecognized, had purchased some bandages treated with tyrothricin (Dubos's antibiotic mixture), asking what that medication was. Receiving the answer, "Some sort of coal-tar derivative," and amused, he came back with, "Is that so?" To this, the self-important response was, "This must be quite over your head!"

On a number of occasions around the time of his retirement in 1958 and after Selman phoned from New Jersey to my laboratory in New York, inviting me to join him for a drink and dinner. When I could accept, the two of us would meet at an open cafe or bar in the Rockefeller Center or Times Square regions, start conversing, and then walk or taxi to another of his favorite midtown spots. I suppose these occasions were at times when his wife was away or otherwise occupied. Our relaxed and congenial conversations over a cocktail, rarely two, covered several topics in microbiology and what some of our colleagues were doing in science. I might express some enthusiastic opinions about research topics and such work as I was familiar with at Cold Spring Harbor, but probably typically tentative and cautious ones about people. Neither of us had much capacity for "small talk." Nor do I think he had an agenda, such as sounding me out for a post in his institute, since I made no secret of my satisfaction with my role at Rockefeller Institute at that time. Rather, I believe, he was moving out of his specialty toward the chemistry that he always admired. Usually he would propose with obvious pleasure a dinner, perhaps at Lindy's on Broadway. Often he would reminisce there in

a serious, logical, and unromantic way about his past. At such times one could see clearly how straightforwardly and sensibly he viewed his own life and science.

Such logical "down-to-earth" expression was characteristic of most of Waksman's scientific exchange. He gave the impression that what mattered were the practical ways and means of experiment and what could in fact be achieved. Some interpreted this as a sign that he did not care or perhaps know much about theory. This was not true, but microbiology at that time was almost necessarily an empirical science.

A memorial and symposium in honor of Selman Waksman was held at the Institute of Microbiology at Rutgers on October 13, 1973, following his death on August 16th. Byron Waksman opened the session with brief messages from absent friends and recollections of the quiet ironic natural humor of his father. Oliver Lampen, director of the institute, testified warmly of the generous management modes exerted by the great teacher. So did Max Tishler of Merck and Company, admiring the combination of idealism and great practical sense that had enabled Waksman to develop the effective interaction with industry that brought out the fruits of the scientific work. Sir Ernest Chain, chemist of the penicillin Nobel Prize winners, expressed a passionate European's recognition of the arduous career that had produced so much.

Honoring the hundredth anniversary of Selman Waksman's birth in the humble lost village in the steppes, a celebratory symposium was held in 1988 at Rutgers, at which several distinguished colleagues spoke on their perspectives of the status of microbiology, and his influence upon it.

Selman Waksman was buried in the cemetery at Woods Hole, Massachusetts, after a more private ceremony. I treasure the message his loved and devoted Bobili wrote me from

the depths of her loss, in thanks for my comments about Selman in a letter to her at this time. She followed him only about a year later.

It is a comforting thought that the contributions of this great and pragmatic humanist and student of nature will endure for a long time in a changing world. They will do so, because they were based on assiduous work on something as universal as the soil, and because he erected from it a technology that in his and other hands has given us so many of our magic medicines. Moreover, as a generous discoverer, he was able to inspire associates and to implant his ideas and vision to a talented family that clearly is continuing his altruistic traditions of serving the common good into the twenty-first century.

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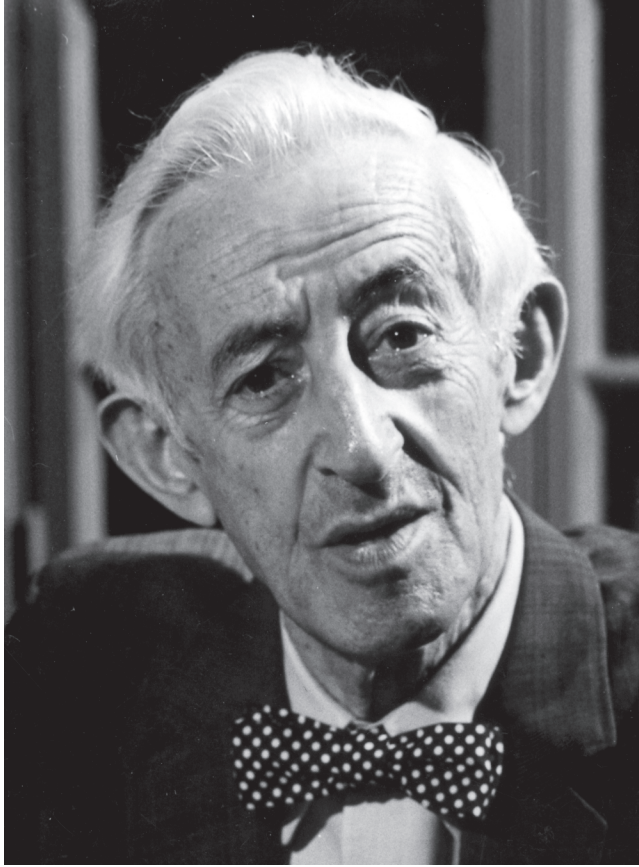
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ABEL WOLMAN

June 10, 1892–February 22, 1989

BY M. GORDON WOLMAN

I N THEIR PAPER PUBLISHED in 1919 Abel Wolman and Linn Enslow, employees of the Maryland Department of Public Health, demonstrated a method for controlled chlorination of drinking water supplies that transformed water treatment, providing safe drinking water throughout the world. A founding member of the Water Pollution Control Federation (now the Water Environment Federation), president of the American Water Works Association, and president of the American Public Health Association, Abel Wolman was a major contributor not only in the science and engineering of sanitation, pollution control, and water resources but also in policy formulation in the broad area of natural resources. His contributions in public health ranged from provision of water and wastewater treatment and urban and regional planning to protection of the public in the production of atomic power, and in the use of radioactive materials in medicine and industrial processes. As a professor of sanitary engineering and founder of departments in engineering and in the School of Public Health at Johns Hopkins University, Wolman taught a host of graduate and undergraduate students from around the world. He served as a consultant on water supply and water resource manage-

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ment throughout the United States and the developing world with the World Health Organization and independently with countries in the Middle East, Latin America, and Asia. An engineer and professor, he was equally comfortable with and similarly a teacher of students, plumbers, and politicians.

My friendship with my father, that I can recall, began when I was about four. Some months before he died he reminded me as we watched Charles Street traffic from his home that we used to "count cars" together from the third-floor window at Eutaw Place and Whitelock street in a row house in Baltimore. We counted separately Packards, LaSalles, Chevys, Pierce Arrows, and others. Then too we walked— and talked—to Druid Park Lake Drive and back. The talk did not stop until he died on February 22, 1989. My father and I worked together, traveled together, and reviewed each other's manuscripts. Perhaps the best-organized person I've ever known, he was not rushed and had plenty of time for me and the full life he and my mother shared. It is in part from this vantage point that I write this memoir.

Abel Wolman was born in Baltimore, Maryland, on June 10, 1892. His parents, Louis and Rose (Wachsman) Wolman, and his eldest brother had emigrated from Poland and settled in the ghetto of east Baltimore. He and his five siblings were educated in the public schools. Wolman, a pre-med major, received his B.A. degree from Johns Hopkins University in 1913. In that year the university announced the opening of the Engineering School, and he joined the first class in civil engineering, receiving his bachelor's degree in engineering in 1915. The story has it that his mother declared that he should become an engineer, inasmuch as there was already one doctor in the family, his oldest brother Samuel. He married Anna Gordon in 1919, and they had one child.

Wolman's professional career began as a sanitary engineer with the Maryland State Department of Public Health in 1914 after one year with the U.S. Public Health Service sampling water in a study of water quality on the Potomac River. The position with the health department primarily involved inspection of water and wastewater treatment plants. Nonetheless, under the tutelage of his boss, Robert B. Morse, he was encouraged to pursue research and publication. A singular bulletin of the department (Morse, 1921) includes 10 papers reprinted from journals published between 1919 and 1921; all are authored or coauthored by Abel Wolman. One of these papers (1919), coauthored with Linn Enslow, a chemist in the department, developed a test for chlorine absorption, which established a controlled method for chlorination of municipal water supplies. The method, assuring safe drinking water, was adopted worldwide, perhaps the most important contribution to public health in the twentieth century.

Focusing on a combination of engineering science and practice, Wolman published on the principles of rapid sand filtration, on the probabilistic approaches to the assessment of drinking-water supply quality, and on all phases of the behavior of water and wastewater systems from raw water quality to the financing of infrastructure. In addition to publishing over several hundred papers, he edited the *Journal of the American Water Works Association* (1921-37) and was associate editor of the *American Journal of Public Health* (1923-27) and editor of *Municipal Sanitation* (1929-35). Although a contemporary colleague of some, Wolman was among the second generation of engineers in the "sanitary revolution" that began in the nineteenth century, succeeding major figures in the United States such as Sedgwick, Fuller, Winslow, Whipple, and Hazen.

In 1922 he became chief engineer of the Maryland State Department of Health. In maintaining the close association of sanitary engineering and public health and in the development of his career he was aided by Dr. William H. Welch, one of the four leading figures in the establishment of the Johns Hopkins Medical School and founder of the School of Hygiene and Public Health. During the same period he worked very closely with George W. Fuller, at one time director of the Lawrence Experiment Station, site of original work on filtration, chlorination, and water quality. Fuller was perhaps the leading consulting sanitary engineer in the field at the time. Wolman's association with him included a trip to review water and wastewater practices and research in leading centers in Europe. Responsible for environmental regulation of the waters of Maryland, Wolman helped to develop water quality standards, and, reflecting his interest in water resources planning and management, he was instrumental in establishing regional water and wastewater systems as well as the Interstate Commission on the Potomac River in the Washington and Baltimore metropolitan regions. Early on, much of his job required convincing cities and towns to install water treatment and wastewater systems, a task he said was initially made easier by the extraordinarily high typhoid fever rates experienced early in the century. Growing evidence that provision of clean water remarkably reduced the incidence of typhoid fever and convinced legislators to appropriate funds for water and wastewater treatment plants.

While he grew impatient with what he considered misguided and sometimes excessive regulatory zeal in the last quarter of the century—"the bulk of my criticism is of speed and ignorance" (Hollander, 1981, p. 633)—he was a strong administrator who did not blanch at forcing an industry desiring to locate a plant in Maryland during the depth of the depression to meet attainable ambient water-quality

standards even at the risk of losing jobs should the industry choose to locate elsewhere. The industry complied.

First as a government officer and later as a consultant, Wolman served every mayor of Baltimore (nine in all) from 1914 until he died in 1989. Beginning in 1931 and until his death he was a consulting engineer on water supply, sewerage, refuse disposal, and management to the Baltimore City Department of Public Works. The municipal building in Baltimore is named the Abel Wolman Building. The building is about five blocks from the east Baltimore "ghetto" in which he grew up, a fact he noted during the dedication ceremony.

Over time Wolman's work in planning and development encompassed not only water and sewerage but also solid waste, transportation, and natural resources. He served as chairman of the Maryland State Planning Commission and was the author of many studies dealing with management of natural resources and urban infrastructure.

Wolman become chairman of the Water Resources Planning Committee of the National Resources Planning Board (1935-41) during the Roosevelt era. In addition to overseeing the preparation of planning studies for the major river basins in the United States, the committee exercised some oversight over water projects proposed by the Corps of Engineers and the Bureau of Reclamation. Although the chief of engineers of the corps declared that prioritizing their projects as proposed by the committee was impossible, at the committee's insistence the corps complied. The committee initiated a number of studies of specialized topics involving hydrology, hydraulics, and public works. Of particular significance was the beginning of studies that led to the first procedure for benefit-cost analysis of water projects competed in 1950 by a different body.

In his role as chairman of the Water Resources Planning Committee and spokesman for engineers and health pro-

fessionals in national organizations Wolman became increasingly involved in national policy issues. As his published papers indicate he espoused the importance of the development of a national water policy. Described as a pragmatist, he was also a planner who grew leery of grand plans. This transformation is captured in several observations: "Well, I did it, and it doesn't work" (Hollander, 1981, p. 439), and more comprehensively: "Does our country want a planning agency at the Federal level? The answer throughout our history . . . is that it does not want such an agency" (*op. cit.* p. 435).

Abel Wolman was among the first to call attention to public health issues associated with the development of atomic energy. Against the initial opposition of distinguished members of the atomic energy fraternity descended from the Manhattan Project, he insisted that public health officers in the states and the broader community of public health professionals become involved in the debate over development of atomic energy and the location of nuclear power plants. Although not an opponent of nuclear power development— he became a member of the first Reactor Safeguards Committee—he pushed for recognition of the importance of the disposal of atomic wastes. He also stressed the necessity for thorough characterization of the geologic, hydrologic, meteorologic, and demographic conditions of prospective sites for nuclear power plants. In helping to bring into the decision-making process a broad spectrum of professionals from beyond the federal perspective—from the Manhattan Project and the early Atomic Energy Commission—Wolman was part of an emerging movement expanding both the number and the professionalism of diverse interests involved in making public decisions (Balogh, 1991).

Wolman was an active participant in the international scene. Simultaneously with the establishment of the State

of Israel he began service as chairman of the consulting committee on the development of the water system for the State of Israel (in 1945), remaining in that position until his death. He was an advisor to nations in Southeast Asia, including India, Ceylon, and Thailand, to many countries in Latin America and Africa, in all to about 50 foreign nations. As a member of the first U.S. delegation to the world assembly at the founding of the World Health Organization, he led the effort to include within WHO a program focused upon water supply and wastewater, a mission omitted from the initial design that focused on the role of medicine in achieving health. He returned regularly to Geneva as an advisor to the program to urge development of urban water systems, early on insisting that even the very poor in villages would pay for good water, a view then much contested but now accepted.

Abel Wolman had a particularly long and close relationship with colleagues in Latin America and in the Pan American Health Organization. He was a founder and honorary president of AIDIS, the Interamerican Association of Sanitary Engineering and Environmental Sciences, an organization devoted to the education of sanitary engineers through provision of texts, development of educational programs, and encouragement of students and faculty in the field. Many of the participants were former students. A new headquarters established in 1998 in São Paulo, Brazil, was named for him when AIDIS celebrated its fiftieth anniversary.

Charles ReVelle (1997), a colleague of Wolman's on the faculty in environmental engineering, notes that "in a speech to a lay audience in 1983, he explained his personal goals for WHO in water supply. 'I want water for people to drink and water for people to wash and children that survive. Too many children are still dying.'" His commitment and pleasure in seeing occasional success in the developing world was

evident in a large well-known WHO photograph of a young girl in Africa using her hands to drink from a tap. The picture hung on the wall in the entrance hall to his home.

Wolman's work abroad with mayors, governors, or heads of state mirrored his interest and style in this country. He stressed what he called the "M's": motivation, money, management, and manpower, maintaining a conviction that people would do much for themselves if given the opportunity. "I know of no people who given the opportunity would not wash themselves" (ReVelle, 1997). He placed reliance upon elected officials and civil servants and was unenthusiastic about hyperbole in public rhetoric and hysteria in public decision. At the same time, he participated in many a public brouhaha, including an appearance before a hostile Kansas state legislature, following a devastating flood, defending a plan of the consulting board of which he was a member; the plan included construction of a number of reservoirs, one of which would flood an old cemetery. Similarly he enjoyed recounting how he attempted to defend a proposed private leasing of oyster beds to a group of oystermen on the eastern shore of Maryland while preparing an escape through a window when the crowd grew unruly. A lifelong student of politics and participant in public decision making, my father enjoyed the company of politicians, observing, "I have always been an amateur student of political relationships" (Hollander, 1981, p. 963).

This aspect of my father's career is captured by Gilbert White (1969, p. x), who observed,

Probably Wolman's most pervasive influence is in the genre of thought and presentation that shines only partly on the printed page. Rare is the national organization or conference touching on water and environmental engineering that has not felt the charm of his analysis of an issue of policy and responsibility. Usually extemporaneous, always felicitous in expression, and punctuated with gentle wit and a soft-spoken sarcasm, the typical Wolman

talk sums up the problems in a lucid framework and sends his audience away smiling, a bit puzzled by some of the generalizations, and refreshed by a train a thought that leads to a new perspective. A gift for asking the pertinent but disarming question and for illuminating it in a sharp and faintly ludicrous light has given both direction and relief to countless administrative sessions, and has enlivened seminars and consulting boards. Technical precision and insight blend with cultured urbanity.

Indefatigable, he returned to urge passage of legislation on bond issues in support of public works, sometimes a decade after initial proposals had been rejected. Not one to joust at windmills, he remained both an optimist and a realist, remarking on one occasion that one of the things he liked about working in India was that "graft included provision for those who swept the floor as well as those at successive levels to the top."

Throughout his life my father was a teacher. Beginning in 1922 he taught part-time in the Johns Hopkins School of Engineering and in the School of Hygiene and Public Health, and in 1937 he became chairman of the Department of Sanitary Engineering in the engineering school and chair of the Department of Environmental Health Engineering in the School of Hygiene and Public Health. The joint appointment reflected his view that the environmental engineer should have a deep understanding of the field of public health that encompassed fields such as epidemiology, toxicology, and microbiology. Many in engineering do not accept this view, but in the history of the School of Public Health, Fee (1987, p. 151) concludes that at the university Wolman successfully pushed a reluctant faculty in the School of Hygiene and Public Health to accept engineers in their courses and physicians and health professionals were subjcted to engineering courses in water supply and wastewater, with salutary results..

A popular lecturer to large classes at the School of Public Health, in addition to graduate courses in sanitary engi-

neering, Wolman taught a course on the social, economic, and financial aspects of engineering each year to senior civil engineers; the course perhaps best reflected his view of the broad role and responsibility of an engineer. He formally retired as professor at Johns Hopkins in 1965, but maintained his office at the university, continuing in his professional activities and periodically giving lectures and seminars. He had been scheduled to give a seminar two days after he died. Because of his faithful attendance at the department's weekly seminars into his ninety-sixth year, outside speakers occasionally found, as they were criticizing a work done 60 years before, that the author was not only still alive but was sitting in the room prepared to offer a question. Professor ReVelle again captured his role as a teacher (1997): "He assisted and advised students for over half a century. He always made himself available for career counsel and for encouragement. . . . To see him required only a knock on the door. Although he was incisive and critical in technical matters, I cannot recall his offering personal criticism of anyone."

In 1968 the departments of geography and of environmental engineering science joined to become the Department of Geography and Environmental Engineering. I became chairman of the new department in 1970, thereby making my father a faculty member in my department. The following exchange of letters reveals a sense of humor not captured in the recitation of accomplishments and awards.

September 24, 1976
Dean Owen
Homewood House

My Dear Dean Owen:

The new circular of the Johns Hopkins University dated June 1976 indicates on page 320 that Abel Wolman D. Eng. is Professor Emeritus of Mathematics, and Sanitary Engineering and Water Resources. While it is important for the University to recognize the contributions of distinguished faculty, as a member of the Academic Council over a period of years, I do not recall having approved the appointment of Dr. Abel Wolman as Professor of Mathematics (Emeritus or otherwise).

No doubt Dr. Wolman's contributions in Mathematics are not inconsiderable. However, I find no Teval records of his teaching performance in Calculus 1, nor record of current student evaluations of his teaching at the time of his appointment as Professor Emeritus of Mathematics. May I ask, have the procedural requirements been met in this case?

Inflation of the apparent number of full Professors in the Department of Mathematics at an earlier time could of course provide the basis for a claim of restitution. Is the Department of Mathematics interested in Sanitary Mathematics?

Thanks for your consideration.

Very truly yours,

M. Gordon Wolman
B. Howell Griswold
Professor of Geography

September 27, 1976

Dr. M. Gordon Wolman
B. Howell Griswold, Jr. Professor of
Geography and International Affairs
The Johns Hopkins University
513 Ames Hall
Baltimore, MD 21218

Dear Sir:

I have a copy of your strange letter to Dean Owen on my qualifications as Professor Emeritus of Mathematics and other exotic subjects.

I have at last realized how King Lear must have felt when his children turned upon him – "sharper than a serpent's tooth" or something like that!

In any event, the appointment gives me much gratification, when I have just about mastered calculating with a slide rule.

The typesetter, who made this appointment, had an unusual awareness that Johnny Hoskins U. could well stand a couple of professors who know nothing about their subjects. He has a surprising acquaintance with the modern "free university".

It would be expecting too much, I suppose, to have you make a public retraction of your complaint, especially so close to the November election.

Sadly, your one-time father

Abel Wolman
Professor Emeritus of Too Many Things

A member of the National Academy of Sciences and the National Academy of Engineering, Wolman was the recipient of numerous awards including the Sedgwick Medal of the American Public Health Association, a special award of the Lasker Foundation, the Tyler Ecology Prize, the Health for All Medal of WHO, the Horton Medal of the American

Geophysical Union, and the U.S. Medal of Science. They reflect his scientific and engineering contributions as well as his leadership in a lifelong effort to satisfy the aspirations of human societies while protecting and enhancing the environment on which society depends. At the turn of the twenty-first century the *Baltimore Sun* newspaper declared Abel Wolman to be the Marylander of the Century.

On the day my father died the university was holding its commemoration day exercises at which I was to present a candidate, a former student of his, for an honorary doctorate. After a brief early morning conversation he said to me, "Go do what you have to do!" I did see him again but at the moment neither he nor I knew I would.

I AM indebted to Walter Hollander, Jr., now deceased, author of the oral history of Abel Wolman; to Gilbert F. White, editor of selected papers of Abel Wolman; and to professors John Boland and Charles ReVelle for help in preparing this memoir.

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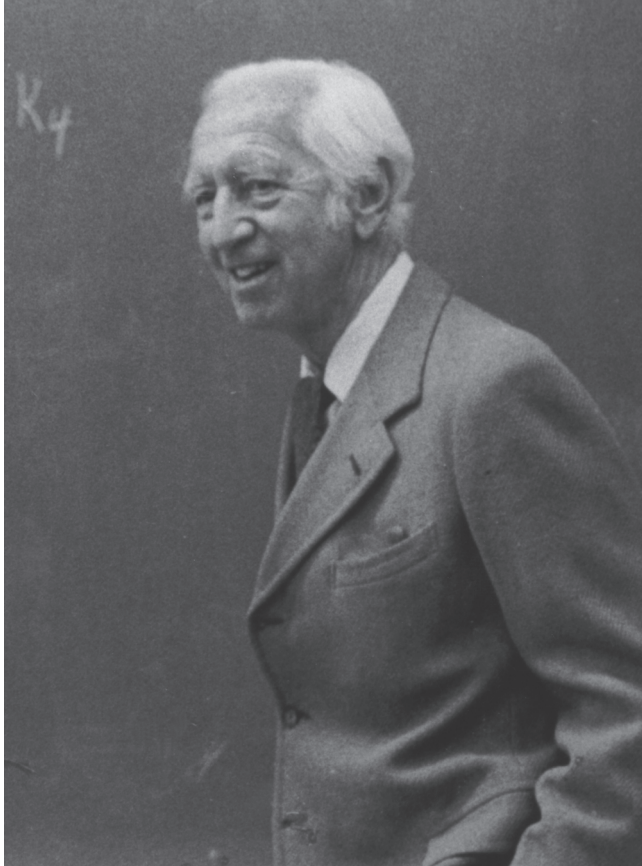
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JEFFRIES WYMAN

June 21, 1901–November 4, 1995

BY ROBERT A. ALBERTY AND ENRICO DI CERA

J EFFRIES WYMAN WILL LONG be remembered for his contribu-
tions to our understanding of the binding of oxygen by
hemoglobin and the linkage of this process with the binding
of hydrogen ions and other species in the solution. In thinking
about these complicated interactions, the internal changes
in the hemoglobin molecule, and its dissociation, Jeffries
brought a deep understanding of thermodynamics and math-
ematics. In his 50 years of research on these remarkable
phenomena, which are also involved in enzyme catalysis,
Jeffries's approach became increasingly sophisticated and
general. He showed how the concept of the binding poten-
tial unified the treatment of all the equilibrium properties
of these complicated systems, contributing greatly to our
understanding of cooperativity, linked functions, allostery,
and internal changes in proteins. He showed how these
concepts could be extended to treating systems in steady
states. During his life he was honored by membership in
the National Academy of Sciences (1969), American Academy
of Arts and Sciences, and the Italian Accademia dei Lincei,
but the important thing was that he was sought out by bio-
chemists around the world for advice and collaboration.

Jeffries Wyman was born June 21, 1901, in West Newton,
Massachusetts. His ancestors were New Englanders and he

was the third in successive generations to bear that name. The first Jeffries Wyman (1814-74) was a great comparative anatomist and the first director of the Peabody Museum of American Archeology and Ethnology at Harvard. He was one of the founding members of the National Academy of Sciences in 1863. The second Jeffries Wyman was an officer in the Bell Telephone Company. When the third Jeffries entered Harvard College in 1919, he majored in philosophy. He graduated with highest honors in philosophy and with high honors in biology. During these years he developed an interest in mathematics and physics and took P. W. Bridgman's famous course in advanced thermodynamics. Jeffries's research career indicates that he had a solid foundation in thermodynamics and a remarkable aptitude for it. Jeffries Wyman and John T. Edsall entered Harvard at the same time and by their third year had developed a close friendship that lasted over 75 years. John Edsall's descriptions of Jeffries's life are wonderful sources of information about their interacting lives.[1,2]

After graduation Jeffries spent 1923-24 in Harvard Graduate School taking advanced courses in physics and chemistry. In June 1924 Jeffries Wyman and John Edsall went abroad together on a slow steamer with 700 cattle and 200 human passengers to work in the newly established Department of Biochemistry in Cambridge, England, headed by Sir Frederick Hopkins ("Hoppy"). The reader was J. B. S. Haldane, who at that time was writing his book *Enzymes* on the basis of the course he was teaching. This was just at the time at Cambridge when G. S. Adair was establishing for the first time the molar mass of hemoglobin and was formulating the basic equation for the binding of oxygen and other ligands to hemoglobin. At the end of one term Jeffries moved to London because he became interested in the work on the dynamics of muscle that was being carried out by A. V.

Hill. In 1926 Jeffries received a Ph.D. from University College for his thesis on the viscoelastic properties of muscle and the thermodynamics of muscle contraction.

Jeffries became a member of the Biology Department at Harvard in 1927 and continued his teaching and research there until 1951. In his first years at Harvard Jeffries spent a large part of his time in the Laboratory of Physical Chemistry, which E. J. Cohn had established at the medical school. His first research there was on the viscosities of protein solutions and on the dielectric constants of solutions of dipolar ions. He showed that the dielectric increment was 23 for α-amino acids, 71 for dipeptides, and 115 for tripeptides. Edsall[2] writes that Jeffries's data on polar liquids stimulated Lars Onsager to produce the first adequate theory of the dielectric properties of polar liquids.

Jeffries married Anne Cabot in 1928, and they had two children: Anne Cabot (1929) and Jeffries, Jr. (1930). When his wife died of Hodgkins lymphoma in 1943, Jeffries was devastated. He married Rosamond Forbes in 1948, but that marriage lasted only 18 months.

In June 1950 Jeffries was en route to Korea to give scientific lectures, but the Korean war broke out when he reached Japan, and so instead he spent six months in General Douglas MacArthur's postwar Japan. Within a couple of days Jeffries was invited to visit the emperor, who was interested in biology and collected invertebrate animals near his summer palace. His daughter's book[3] contains the letters he sent to Anne and Jeff.

B. German and J. Wyman (1937) studied the acid-base titration of deoxy- and oxyhemoglobin and confirmed and extended earlier work that had shown that oxygenation of hemoglobin results in the release of hydrogen ions. J. B. S. Haldane and L. J. Henderson had already pointed out the reciprocal relations involved, but German and Wyman pro-

vided a more mathematical treatment of the data by show-
ing that it is possible to calculate the oxygen affinity as a
function of pH from these titration curves by an integra-
tion. They gave a general treatment of the fact that the
effect of oxygenation in increasing the acid dissociation
constant of hemoglobin in the alkaline loop implies a
reciprocal effect involving a decrease of oxygen affinity with
hydrogen ion concentration in the same region. These effects
are reversed in the acid loop.

In 1939 Jeffries wrote a classic paper that dealt with the
heat of oxygenation of hemoglobin, which varies with the
pH over the range 3 to 11. He discovered the important
fact that the heat is the same for each stage of the oxygen-
ation process, as is the shift in the amount of base bound at
constant pH. Jeffries also made oxidation-reduction measure-
ments (1941). They derived the relation between the binding
polynomial and the average number of ligands bound by a
protein, which was a totally new result. This relation played
an important role in future theoretical treatments of ligand
binding. They showed that this same treatment could be
applied to oxidation-reduction equilibria. In 1944-45 Jeffries
Wyman was away from Harvard working for the Navy on
problems of sonar and smoke screens.

In 1948 Jeffries published a very complete review of all
aspects of the knowledge about heme proteins. It contains
a deep analysis of the nature of linked functions as applied
to a highly integrated system such as blood. Only a small
part of this review is on the quantitative thermodynamics of
the linked functions of these molecules. In the section on
linked functions Wyman showed his sophistication in math-
ematics and thermodynamics; he used calculus to discuss
the variation of the heat of oxygenation with pH.

In 1951 Wyman and D. W. Allen began the process of
explaining the oxygen equilibrium of hemoglobin and the

Bohr effect in terms of structural effects. They concluded that the interaction is due to entropy effects, because the heat effect is the same for each stage of the four-step oxygenation process, whereas the free energy change due to the heme interactions certainly differs markedly from one step to the next. They suggested that configuration effects involving entropy changes could provide an explanation of heme-heme interactions and the Bohr effect. This paper was revolutionary in its proposal that cooperative interactions among the subunits of hemoglobin could be mediated indirectly by conformational transitions. Wyman and Allen had de facto discovered allostery many years before Jacques Monod and Francois Jacob of the Pasteur Institute in Paris formulated and publicized the concept as we know it today. Remarkably, the paper was denied publication in several other journals before it finally appeared in the *Journal of Polymer Sciences*. Even today, very few biophysicists and biochemists are fully aware of the contribution that this seminal work had in the development of allosteric theory.

Jeffries resigned from Harvard in 1951 to be science attaché in the U.S. Embassy in Paris from 1952 to 1955. He traveled widely in France visiting scientific laboratories. This was a difficult time for international scientific relations. Because of the reckless accusations of Senator Joseph McCarthy about Communist infiltration, it was difficult for foreign scientists to visit the United States during this period. Jeffries worked on behalf of a number of French colleagues. In 1954 Jeffries married Olga Lodigenski, and they moved to Cairo in 1955. Jeffries was one of the first science attachés in a U.S. embassy. In 1955-58 Jeffries was director of one of the four regional science offices of UNESCO. His headquarters were in Cairo, but his responsibilities extended from Morocco to Pakistan.

Jeffries was a great walker and was quite adventurous. On a vacation trip to western Pakistan he walked into a part of Afghanistan that was closed to foreigners. The local chieftain decided that Jeffries must return to Pakistan, and so, accompanied by a bodyguard, he rode a yak to the border.

During the time he was carrying out these administrative responsibilities, Jeffries continued to collaborate with John Edsall by mail, by visits to Cambridge, and by John's trips to Europe as they wrote their book *Biophysical Chemistry* (1958). This book had its origins in the course they had taught together in the Biology Department. It was the first book in an emerging field and really defined a discipline that remains a centerpiece of modern macromolecular sciences. The plan was to write a second volume, but that was never completed because John became the editor of the *Journal of Biological Chemistry* and Jeffries went to Rome.

When Jeffries completed his service to UNESCO, John Kendrew, then director of studies at Peterhouse, invited him to Cambridge for the fall term of 1959-60. Eraldo Antonini, from the University of Rome's Biochemical Institute and the Istituto Regina Elena, lectured at Cambridge and invited Jeffries to visit his department, which was headed by Alessandro Rossi Fanelli. When they offered Jeffries a position as guest scientist, he accepted for a "trial period" that lasted 25 years.

While in Rome, Jeffries developed fully the theory of linked functions and reciprocal effects in his landmark 1964 paper in *Advances in Protein Chemistry*. Using straightforward thermodynamic principles embodied by the first and second laws, Jeffries showed that the responses of a macromolecular system to chemical and physical variables like chemical potentials, pHs, and temperature, are mutually dependent. Linkage relations, formally equivalent to those developed by James Clerk Maxwell in electromagnetism and by Bridgman

in his general thermodynamic tables, emerged from consideration of the nature of the binding polynomial developed in early studies. Never before had the power of thermodynamics, as applied to biology, been so eloquently and elegantly presented to the scientific community. The effects of temperature and pH on the oxygenation properties of hemoglobin became intuitively obvious when looked at through the powerful formalism of linkage thermodynamics.

In 1965 Wyman linked the binding polynomial to the concept of the binding potential as a useful tool for the study of ligand binding by a polyfunctional macromolecule. This article starts out with,

> In the course of reading over the other day, at a window by the sea, the page proof of an article on linkage I was suddenly struck by the realization that in all the years I had been thinking about the matter I had consistently failed to recognize one significant general concept, although it is clearly implicit in almost every earlier discussion and stands out unmistakably once it catches the eye. This is the concept of what may be called the binding potential.

Wyman used the Russian L for the binding potential to avoid confusion with symbols current for the other more familiar thermodynamic potentials U, S, H, A, and G. (Later Alberty[4] used G' for a similar thermodynamic potential at specified pH and pMg, and Di Cera[5] showed that the binding potential is the same as the chemical potential of the reference system.) This was a very important step because it connected Wyman's previous work more closely with the formulation of the rest of thermodynamics of reaction systems. He pointed out that thermodynamic potentials "are not accessible to measurement but are known only in terms of their changes." He further noted that "every ligand may be expected to exert some influence on every other; in other words, that, at the highest level of approximation the ligands all form a single linkage group. The breaking up of this

group at a lower level of approximation depends on the factorability of the polynomial."

In 1985 John Edsall[1] wrote, "Certainly in modern times it is most unusual, if not unprecedented, for a scientist to leave research for as long as eight years, becoming deeply involved in other responsibilities, and then return to science, and make his most important research contributions in the years that followed. Yet that is, in fact, what Jeffries achieved." During his time in Rome Jeffries further developed the concept of allosteric linkage, introduced Legendre transforms and binding potentials to the field, and discussed polysteric and polyphasic linkage.

Jeffries had become well acquainted with Jacques Monod while he was in Paris in 1952-55. Now Monod and his group were working on regulatory aspects of metabolism, and especially feedback inhibition of metabolic pathways. Monod and Jacob had introduced the term "allosteric" in 1961 to describe enzymes that can bind effector molecules at sites quite distinct from the catalytic site. The binding of the effector induces conformational changes that promote or inhibit catalytic activity. When Jeffries visited Paris in 1964, Jacques Monod invited him to give a seminar on his views about the effects of conformation changes in hemoglobin on ligand binding and their relation to cooperativity and effectors. These discussions led to the famous paper by Monod, Wyman, and Changeux (1965) proposing that allosteric proteins are oligomers, composed of several subunits (protomers), the oligomer being capable of existing in two distinct conformations, denoted as T and R, which differ in their affinity for ligands and effectors. Homotropic interactions are always cooperative, and heterotropic interactions, which are caused by displacement of the R/T equilibrium by the effector, can involve either activation or inhibition at the catalytic site for an enzyme or at the

ligand-binding site for hemoglobin. Later Jeffries wrote a tribute to Jacques Monod (1979) that describes the writing of this paper, which was such a stimulus to the field.

In 1967 Jeffries wrote a paper for the *Journal of the American Chemical Society* that presented a detailed discussion of the equations involved. In this paper Wyman uses the term "allosteric binding potential." Wyman used the term to describe regulatory effects due to conformation changes in a macromolecule induced by the binding of a ligand. Allosteric equilibria always lead to positive homotropic interactions. This paper discusses in detail the many equations involved.

In 1968 Wyman wrote a complete review of regulation and control in macromolecules. In his concluding remarks Jeffries raises the questions, "Why is it, from a molecular point of view, that the different conformations should have different ligand affinities, and why is it that the uptake of ligand should lead to a conformation change?" He concludes his review with the comment that "these and other problems of structure and function lie in the Biophysics and Biology of tomorrow." In 1975 he wrote a mathematical paper showing that the binding of ligands by a macromolecule can be described by an Abelian group of thermodynamic potentials. Each member of the group corresponds to a particular set of experimental conditions: system open to some, closed to others of the ligands. The group of thermodynamic potentials provides all possible linkage relations, and various thermodynamic potentials can be derived from each other by Legendre transforms. Here Wyman provides a clear description of how different choices yield different information, and he also introduces the distinction between true and pseudolinkage This was an important generalization of the underlying theory.

In 1981 Jeffries wrote "The Cybernetics of Biological

Molecules," which dealt with ligand-induced association, dissociation, or phase changes, so-called polysteric reactions. This provides a broad overview of the thermodynamics of binding and of linkage mechanisms. Linkage under steady state conditions and free energy transduction are discussed. In 1984 Careri and Wyman wrote a paper entitled "Soliton-Assisted Unidirectional Circulation in a Biochemical Cycle."

Beginning in 1964 while Jeffries was in Rome he was involved in the establishment of the European Molecular Biology Organization (EMBO). He was the first secretary-general, a member of the Council, and at some time or other a member of almost every committee established by the Council. EMBO established the European Laboratory of Molecular Biology, which was headed by John Kendrew.

After about 1975 Jeffries made yearly trips to Stanley Gill's laboratory at the University of Colorado. When they started writing a book together in 1979, Jeffries was suffering increasingly from Parkinsons' disease. In 1980 they published together on sickle cell hemoglobin. Because this hemoglobin has a tendency to precipitate out of solution, they had to develop polyphasic linkage. While Jeffries was going back and forth between Rome and Boulder, he was working on a long paper on linkage graphs, which appeared in 1984. In this important article he acknowledged many discussions with Stanley Gill, and P. E. Phillipson (Physics Department, University of Colorado) and expressed his appreciation to Eraldo Antonini, whose recent untimely death had left such a gap. In 1985 Gill, Richey, Bishop, and Wyman emphasized the use of the binding partition function in generalizing binding phenomena in an allosteric macromolecule. In 1987 Robert, Decker, Richey, Gill, and Wyman generalized the allosteric model that incorporates a hierarchy of conformational equilibria. In 1988 Di Cera, Gill, and

Wyman published their canonical formulation of linkage thermodynamics.

In 1990 Wyman and Gill brought all this together in their book *Binding and Linkage: Functional Chemistry of Biological Macromolecules.* Their idea was to bring together in one place concepts and procedures applicable to ligand binding by biological macromolecules and to show from what minimum set of general physical and mathematical principles they arise. This book remains a cornerstone of modern biophysical chemistry and is widely used in graduate courses in biochemistry and biophysics.

In his paper on linkage graphs (1984), Jeffries looked to the future when rate processes and quantum mechanics would have to receive more attention in understanding binding phenomena. He then commented that his emphasis on thermodynamics had been due to "the commanding role of thermodynamics as a limitation to which all natural processes are subject, a common background shared by all dynamical phenomena." He also quoted Emilio Segre[6] who wrote,

Thermodynamics has the same degree of certainty as its postulates. Reasoning in thermodynamics is often subtle, but it is absolutely solid and conclusive. We shall see how Planck and Einstein built on it with absolute trust and how they considered thermodynamics the only absolutely firm foundation on which to build a physical theory. Whenever they were confronted by formidable obstacles, they turned to it.

When Jeffries was 83 this magnificent paper was published, and so some philosophical comments were certainly justified. Jeffries once told one of us (E.D.C.), "Never yield to temptation, unless it persists." Thermodynamics was his lifelong temptation and Wyman's monumental contribution was to bring the rigor of thermodynamics to biochemistry.

In 1986 Jeffries and Olga moved to Paris and lived in the Paris flat that Olga's parents bought in 1945. In Paris

Jeffries continued his scientific work and published on nesting in 1987 and the canonical formulation of linkage thermodynamics in 1988. Jeffries and Olga had a summer place near Sens, where Jeffries would enjoy hour-long afternoon walks in the countryside. Olga died in 1990. Jeffries died in his sleep on November 4, 1995. His funeral was held in the Russian Orthodox Church at Saint Genieve en Bois outside Paris. There was a memorial service for him at the Bigelow Chapel at the Mount Auburn Cemetery, Cambridge, Massachusetts, on December 11, 1995.

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NOTES

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