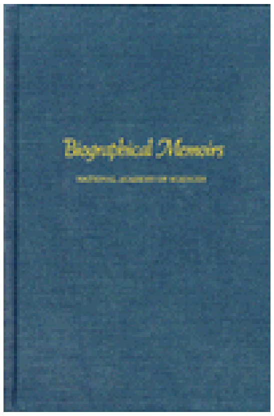

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VOLUME 81

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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
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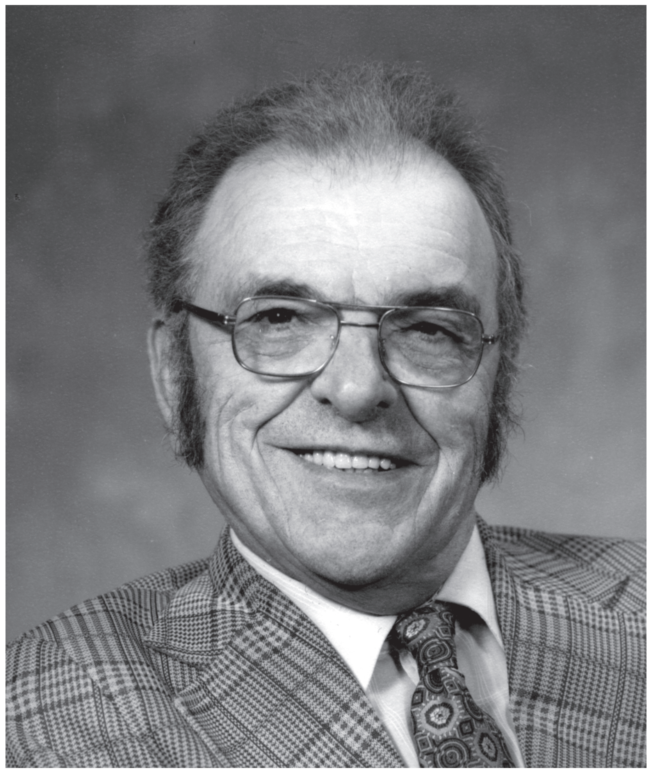

Stanley D Beck

STANLEY D. BECK

October 17, 1919–July 8, 1997

BY JOHN L. WEDBERG, G. MICHAEL CHIPPENDALE, AND JOHN C. REESE

Professor Stanley D. Beck was one of the last of the "Renaissance insect physiologists." A multifaceted researcher and educator, his major interests comprised three quite different areas of insect physiology. He made major contributions to host plant resistance to insects, especially maize resistance to the European corn borer, *Ostrinia nubilalis* (Hübner). With *O. nubilalis* and *Agrotis ipsilon* (Hufnagel) he studied the photoperiodic determination of insect development and diapause, as well as a long-term inquiry focused on particular circadian rhythms. Neither plant resistance nor insect photoperiodism/thermoperiodism could have been investigated in such depth without the foundation he laid years earlier with the development of nutritionally adequate artificial diets for insects. Beck's major scientific treatises included *Animal Photoperiodism* in 1963 and *Insect Photoperiodism* in 1968 (followed by a second edition in 1980), as well as two especially significant reviews on plant resistance and on insect photoperiodism (Beck, 1965; Beck, 1983).

PERSONAL HISTORY

Stan Beck was born on October 17, 1919, in Portland, Oregon. He grew up in several small towns in the state of Washington near Mount Rainier. As a young person he loved to hike and fish in the Cascade Range, and some of his funnier stories dealt with outwitting the wildlife agents in order to hike back to some of the best fishing spots. In an early biology course he became fascinated with insects, an ambition that directed him to Washington State University. He worked at a lumber mill for a year and in the apple orchards of an experiment station at Wenatchee, Washington, for two summers to earn money to attend college. He graduated magna cum laude and as a member of Phi Beta Kappa from Washington State University in 1942. He served as a lieutenant in the U.S. Navy on a minesweeper from 1942 to 1945. Stan started as a research assistant at the University of Wisconsin, Madison, in 1946, served as instructor of entomology from 1948 to 1950, and then as assistant professor of entomology after he received his doctorate in zoology in 1950. In 1952 Stan was stricken with polio, and after a 45-year struggle he succumbed to post-polio syndrome on July 8, 1997. Although polio left him confined to a wheelchair for the remainder of his life, his determination and courage did not allow this confinement to hinder his enjoyment of life.

His incredible list of accomplishments led to Stan's election to the National Academy of Sciences in 1988. He retired from the Department of Entomology, University of Wisconsin, Madison, in 1989. In retirement he was able to fulfill his lifelong dream of writing fiction; he published a novel, *Two in the Game,* about the difficulties of a dual-career family in academic life. He had also completed a draft of a mystery at the time of his death.

Stan is survived by his wife, Isabel, who worked tirelessly to make sure that he was able to travel and work, and to have a loving, caring family. He is also survived by a son, Bruce; two daughters, Diana Beck and Marianne Goins; and five grandchildren. He was preceded in death by a daughter, Karen Beck.

RESEARCH AND TEACHING CONTRIBUTIONS

Stanley D. Beck made enormous contributions to both science and philosophy. He published 138 refereed research papers; several books, including *The Simplicity of Science*, *Animal Photoperiodism*, *Insect Photoperiodism* (two editions), and *Modern Science and Christian Life;* and articles for scientific magazines. As noted by DeFoliart (2000) Beck had many firsts. He was the first to develop an artificial diet on which a phytophagous chewing insect could be reared for successive generations, the first to formulate an artificial diet for a phytophagous piercing-sucking insect, the first to clearly show the roles of various nutritional and allelochemic factors in the establishment and survival of insect larvae, and the first to demonstrate the role of growth-inhibiting allelochemics in plant resistance to insects. These discoveries laid the groundwork for many years of his research and opened the door for many other researchers.

Stan Beck's teaching largely concerned his courses in insect physiology and a proseminar course designed to assist graduate students in their written and oral presentations of scientific information. In this latter course he was known as a witty, cogent, and fluent speaker. He served as advisor for 18 graduate students, as well as a number of postdoctoral fellows, many of whom went on to distinguished careers in research, teaching, and administration. In all facets of his teaching he injected a little philosophy along with a lot of science. No matter how many times he had taught a given topic, he always reviewed his notes one more time just before heading down to the lecture room. He wanted his graduate students in his laboratory to come to him with ideas for experiments, rather than his outlining steps for students to carry out.

"As greater understanding of insect and plant biology, chemistry, and ecology is attained, we will be able to approach the goal of developing agronomic plants that are deliberately and foresightedly designed to be insect-resistant" (Beck, 1965). In that one sentence Beck was able to set the stage not only for many careers worth of research but also for the whole era of biotechnology in crop plants. Transgenic plants like Bt corn are certainly "deliberately and foresightedly designed to be insect resistant."

However, each step in science is built on the foundation of previous work. Before the explosion of work on the chemistry of plant resistance to insects could occur, artificial diets for the bioassay of plant allelochemicals had to be developed. Since then, artificial diets have been used for producing large numbers of insects for screening germ plasm, and have been particularly useful in the bioassay of resistance factors from plants. The advent of artificial diets also made it possible to investigate fundamental aspects of insect nutrition; one putative nutrient at a time could be deleted from experimental diets. In this way, for example, the essentiality of ascorbic acid for a lepidopterous insect was first demonstrated (Chippendale and Beck, 1964).

Bottger (1942) attempted to rear European corn-borer larvae on an artificial diet. Beck and Chippendale (1968) found that the larvae could not grow and develop unless there was microbial contamination. Beck and coworkers were the first researchers to develop an adequate artificial diet for a lepidopterous species, identifying critical components unidentified by previous researchers (Beck et al., 1949; Beck and Stauffer, 1950). The rearing of lepidopterous insects started with the 1949 and 1950 papers on successful artificial diets for rearing the European corn borer. These agar-based diets, incorporating both crude plant materials and specific nutrients, laid the foundation for countless projects. The contribution made by the development of artificial diets for lepidopterous species cannot be overemphasized. This beginning made it possible for the first time to investigate insect nutrition. Many detailed studies were to follow (Beck and Stauffer, 1950; Beck, 1950; Beck, 1951; Beck, 1953; Beck, 1956a; Beck, 1956d; Beck, 1957a; Casida et al., 1957; Scheel et al., 1957; Beck and Kapadia, 1957; Chippendale and Beck, 1965; Chippendale et al., 1965; Beck and Chippendale, 1968; Beck et al., 1968), demonstrating finally the importance of water itself as a nutrient (Reese and Beck, 1978).

Using the European corn-borer diet as a tool, Stan conducted the first systematic studies of the chemical basis of plant resistance (Beck, 1957b; Beck and Smissman, 1960). The availability of an artificial diet made it possible for the first time to assess large numbers of serial extracts and later, pure compounds, one extract or compound at a time. Beck's approach of serially fractionating the resistant plant became the model for systematic investigations. Rather than empirically testing hypothesized resistance factors and generating correlational evidence, cause-and-effect relationships could now be clearly documented. In this way three compounds were isolated from first-generation European corn-borer-resistant corn varieties (Beck and Stauffer, 1957). Originally these factors were designated Resistance Factors A, B, and C, or RFA, RFB, and RFC, respectively. RFA, purified and shown to be deleterious to European corn-borer larvae (Beck and Stauffer, 1957), was subsequently identified as 6-methoxybenzoxazolinone, or MBOA (Loomis et al., 1957; Smissman et al., 1957). RFC was shown to be 2,4-dihydroxy-7-methoxy-1,4-benzoxazine-3-one, or DIMBOA (Beck, 1965). These early successes in isolating and identifying plant allelochemics with biological activities against insects led to significant improvements in the breeding of European corn-borer-resistant genetic lines of maize (Beck and Lilly, 1949; Beck, 1951; Beck, 1956b; Beck, 1956c; Beck, 1957a; Beck, 1957b; Beck and Stauffer, 1957; Beck et al., 1957; Loomis et al., 1957; Smissman and Beck, 1957; Smissman et al., 1957; Wahlroos and Virtanen, 1959; Beck, 1960; Beck and Smissman, 1960; Beck and Smissman, 1961; Smissman et al., 1961; Smissman et al., 1962; Bredenburg et al., 1962; Klun and Brindley, 1966; Klun et al., 1967; Klun and Robinson, 1969; Klun, 1970; Klun et al., 1970; Beck and Reese, 1976; Reese and Beck, 1976a; Reese and Beck, 1976b; Reese and Beck, 1976c; Reese and Beck, 1976d; Guthrie, 1979; Robinson et al., 1982a; Robinson et al., 1982b; Guthrie et al., 1986).

Stan Beck's studies over about 30 years reconciled the key elements of circadian rhythms and photoperiodic responses in insect seasonal time measurement and underscored the unifying principles of the biological clock. He stressed the necessary precision of insect timekeeping and showed that the biological clock regulates physiological processes without feedback that might interfere with its timekeeping function. His pioneering studies into the photoperiodic and thermoperiodic regulation of insect diapause induction and development, cold-hardiness, voltinism, and neuroendocrine regulation culminated in the publication of his dual-system theory of insect time measurement. Beck demonstrated that the integration of information about an insect's physiological, developmental, and behavioral systems, as well as its population ecology, is necessary to understand the temporal regulation and coordination of its life processes (Beck, Beck, 1968a; Beck, 1968b; Beck, 1983).

In the 1950s Stan Beck and his colleague, Jim Apple, were geographically well located in Wisconsin to study the voltinism of the European corn borer. The borer entered the United States around 1917 in Massachusetts and initially was univoltine. By the late 1930s a bivoltine population appeared in the east and north-central states. The ecotype with two generations per year reached Wisconsin around 1940. By the 1950s Beck and Apple were able to study geographical variation in the photoperiodic and temperature responses of this insect.

In 1961 Beck and Apple published a landmark paper on voltinism in the European corn borer in the *Journal of Economic Entomology* (Beck and Apple, 1961). They tested the hypothesis that the adaptation of the borer to particular local conditions involved changes in the frequencies of genetic factors controlling its photoperiodic responses. They plotted seasonal temperature accumulations against day length for three geographical populations of the corn borer in Illinois and Wisconsin and demonstrated that different geographical populations, exposed to different day lengths and temperatures, had different incidences of diapause. The practical significance of these findings provided the impetus for a North Central Regional Project (NC 20) to study geographical differences in the behavior and seasonal development of the European corn borer. This project is still active under a new number, NC 205.

Building on his early voltinism studies and continuing to use the European corn borer as his model insect, Stan Beck focused on gaining an increased understanding of the underlying mechanisms of insect seasonal time measurement. In his 1962 presentation at the twenty-third annual biology colloquium at Oregon State University in Corvallis, he commented: "The regular annual cycle of photoperiods forms the most precise basis known for the setting of the 'physiological clocks' by which biological events may be timed and synchronized. And, as might be expected, insects have taken full advantage of this possibility in their exploitation of evolutionary pathways" (Beck, 1963).

Stan Beck studied the interaction of day length and temperature on diapause induction and development. A photoperiodic response curve was obtained by plotting the incidence of diapause against the photoperiods under which European corn-borer larvae were reared. Diapause was induced only by a narrow range of photoperiods between 10 and 14 hours of light per day. The critical photoperiod (50-percent diapause) for a Wisconsin population of corn borers was between 15 and 15.5 hours of light per day. Subsequently, he expanded his photoperiodic studies to examine more closely the relationship between the light and dark phases in the daily photoperiod. The dark phase was shown to be the most effective in inducing diapause in the European corn borer (Beck and Hanec, 1960; Beck, 1962; Beck, 1988).

Stan Beck and his coworkers (Beck and Alexander, 1964; Beck et al., 1965) investigated whether a hormone produced by the proctodaeum of the European corn borer plays a role in diapause development. Beck named this hormone proctodone and concluded that the ileal epithelium is an endocrine center secreting proctodone in response to photoperiodic signals. In turn, the released proctodone was considered to control the activity of the cerebral neurosecretory system of diapause larvae. Beck used a two-oscillator model to explain the interaction between the secretion of proctodone and the secretion of prothoracicotropic hormone from the cerebral neurosecretory system. He postulated that an eight-hour subcircadian proctodone secretory rhythm is phase set by the onset of darkness, and that an eight-hour cerebral neurosecretory rhythm is phase set by the onset of illumination. Under long days the rhythms are in phase, but under short days the rhythms are out of phase. The conclusion was that proctodone activates the neurosecretory system under long days, when the two rhythms are in phase, but this does not occur under short days, when the two rhythms are out of phase (Beck, 1964).

The period from 1974 to 1985 can be called the integrative phase of Stan Beck's photoperiodic research. He developed a model to account for circadian and developmental photoperiodism (Beck, 1974a; Beck, 1974b; Beck, 1975; Beck, 1976; Beck, 1977; Beck, 1985). His dual-system theory of photoperiodic time measurement made the following assumptions:

- Different species share a common fundamental time-measuring mechanism.
- Photoperiodic determination of diapause or polymorphism involves gating in a manner identical to the gating of circadian rhythms.
- Two biochemical systems interact. Photoperiodic signals regulate the kinetics of these two systems: One system functions as a circadian pacemaker and as a determinative rhythm and the second system functions as a gating system.

Stan Beck developed this unifying theory when there were no corroborating molecular data to provide the underpinnings of the biological clock. It was an important stepping-stone to move the field forward.

Toward the end of his research career Stan Beck was convinced that interactions between day length and temperature cycles held the key to understanding how insect seasonal cycles are regulated. This quote from his 1983 *Annual Review of Entomology* article captures this point: "It is now becoming increasingly apparent that there are exceedingly significant biological responses to daily temperature cycles, with important interactions between photoperiodic and thermoperiodic adaptations. This promising facet of insect bionomics demands detailed investigation; it can no longer be ignored in our pursuit of the knowledge required to understand the fundamental characteristics of insect development and ecological strategies and to manage economically important insect populations."

SERVICE TO HIS PROFESSION AND REFLECTIONS ON HIS LIFE

Stan Beck was a member of the Entomological Society of America and served as its president and was a member of its Governing Board and Executive Committee, as well as other committees. He presented papers in national and international conferences and served on numerous task forces addressing ethical and disability issues. The society established in his honor the Stanley D. Beck Fellowship, a fund for disabled or disadvantaged students.

Those of us who shared Stan's professional life will never forget the sheer force of his will, determination, and intellect. He was paralyzed after contracting polio in 1952. In the ensuing decades he struggled valiantly against this disease. He ultimately was able to hold a pencil in one hand, to write, and could type with one finger. His hospital room looked like a college office with books and notes strewn all around the bed. The university loaned him a dictating machine to assist his efforts. Between therapy sessions and naps he continued to meet with graduate students and conduct other business. His mental processes remained unimpaired, and with his wide-ranging intellect he wrote and published classical scientific findings; books on scientific, theological, and fictional subjects; and countless articles for general scientific magazines. DeFoliart (2000) quoted Reginald H. Painter, the founder of the discipline of plant resistance to insects, as stating, "Ever since he [Beck] went back to his research [after being stricken with polio], with its outstanding contributions, I have considered that . . . he is one of the heroes of the human spirit. . . ."

One of us (J.C.R.) will never forget the day that Stan rolled out of his office announcing that he had just re-read a 1971 paper by Jim Truman and that he thought he had a new way of attacking insect photoperiodism. He immediately started to work on a mathematical model for the production and subsequent breakdown of two purely hypothetical substances. The math quickly outgrew his 128-step programmable calculator. He took a course in FORTRAN and was, we think, the first faculty member at the University of Wisconsin, Madison, to connect to the mainframe computer from his office. This work led to a series of publications on what he called the dual system theory (Beck, 1974a; Beck, 1974b; Beck, 1975; Beck, 1976; Beck, 1977), including another major review (Beck, 1983).

Stan also had a lifelong interest in the philosophy of science and devoted much effort to the communication of science to nonscientists (Chippendale and Reese, 1998). His first book *The Simplicity of Science* published in 1959 was nontechnical and written after he came home from the hospital. He believed that scientists should vigorously counter anti-science and anti-intellectual groups, which were becoming increasingly vocal in society (Chippendale and Reese, 1998). This concern for academic and scientific freedom was again manifested during his 1982 term as president of the Entomological Society of America. His presidential address, *Science and Politics* (Beck, 1983), addressed the problem of legislative and partisan political interference in science.

An anecdote provided by one of his former graduate students summarizes well how Stan conducted his career as a biologist with far-flung interests. He became interested in the phenomenon of retrogression, or the condition of certain species of beetle larvae getting smaller with each molt. In this project he weighed *Trogoderma* larvae and adults. He did this himself instead of asking his technician to do it, and in spite of his physical limitations. His explanation was that he needed a project of his own so that he would not "bug" his students too much about all the details of their projects. This indomitable spirit was summarized by Wallace Wikoff, writer for the Madison-published newspaper, *Wisconsin State Journal*, when he quoted Stan as follows: "Once you have adjusted yourself to the realization that you are—slightly incapacitated, then the road back is less difficult. For, sooner or later, you wake up to the realization that there are not many alternatives. You either must readjust your life or give up completely."

In an unpublished "Tribute to Stanley D. Beck" presented at the 1997 Entomological Society of America meetings in Nashville, Tennessee, Reese stated: "Dr. Beck used to talk about the bionomics of ideas and how a good idea or hypothesis may not last long, but will give rise to other ideas. In the same way, although he would probably like knowing that he is missed, it would please him far more to know that his contributions to his family, his science, and his professional society, have stimulated others to continue to make these kinds of contributions. These continuing contributions may be the greatest tribute we can pay to the memory of Stanley D. Beck."

IN CONCLUSION

We quote here from Chippendale and Reese (1998): "It is difficult to capture the multifaceted contributions of this remarkable scientist and man. For those who knew Dr. Beck, his legacy extends far beyond the written record of his accomplishments, his cutting edge research, and his exemplary teaching. He taught us a lot about life and how to persist in the face of seemingly insurmountable difficulties. In 1980 he wrote: 'Research may be characterized as the process of opening an infinite regression of black boxes.' He helped those around him to open their eyes to the full potential life has to offer. We were fortunate to be advised by Dr. Beck in our doctoral programs . . . and learned much of lasting value from observing his analytical approach to research problems, his skill in formulating hypotheses, designing and interpreting experiments, and from his philosophy of life."

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REFERENCES

Beck, S. D. 1950. Nutrition of the European corn borer, *Pyrausta nubilalis* (Hubn.). II. Some effects of diet on larval growth characteristics. *Physiol. Zool.* 23:353-61.

Beck, S. D. 1951. Nutritional aspects of host plant resistance to the European corn borer. *Proc. 6th Ann. Mtg. North Central Branch Am. Assoc. Econ. Entomol.,* p. 58.

Beck, S. D. 1956a. A bimodal response to dietary sugars by an insect. *Biol. Bull.* 110:219-28.

Beck, S. D. 1956b. The European corn borer, *Pyrausta nubilalis* (Hubn.), and its principal host plant. I. Orientation and feeding behavior of the larva on the corn plant. *Ann. Entomol. Soc. Am.* 49:552-58.

Beck, S. D. 1956c. The European corn borer and its principal host plant. II. The influence of nutritional factors on larval establishment and development on the corn plant. *Ann. Entomol. Soc. Am.* 49:582-88.

Beck, S. D. 1956d. Nutrition of the European corn borer, *Pyrausta nubilalis* (Hubn.). IV. Feeding reactions of first-instar larvae. *Ann. Entomol. Soc. Am.* 49:399-405.

Beck, S. D. 1957a. The European corn borer, *Pyrausta nubilalis* (Hübn.), and its principal host plant. IV. Larval saccharotrophism and host plant resistance. *Ann. Entomol. Soc. Am.* 50:247-50.

Beck, S. D. 1957b. The European corn borer, *Pyrausta nubilalis* (Hübn.), and its principal host plant. VI. Host plant resistance to larval establishment. *J. Insect Physiol.* 1:158-77.

Beck, S. D. 1962. Photoperiodic induction of diapause in an insect. *Biol. Bull.* 122:1-12.

Beck, S. D. 1963. *Animal Photoperiodism.* New York: Holt, Rinehart, and Winston.

Beck, S. D. 1964. Time-measurement in insect photoperiodism. *Am. Natur.* 98:329-46.

Beck, S. D. 1968a. *Insect Photoperiodism.* New York: Academic Press.

Beck, S. D. 1968b. Environmental photoperiod and the programming of insect development. In *Evolution and Environment,* ed. E. T. Drake, pp. 279-96. New Haven: Yale University Press.

Beck, S. D. 1974a. Photoperiodic determination of insect development and diapause. I. Oscillators, hourglasses, and a determination model. *J. Comp. Physiol.* 90:275-95.

Beck, S. D. 1974b. Photoperiodic determination of insect development and diapause. II. The determination gate in a theoretical model. *J. Comp. Physiol.* 90:297-310.

Beck, S. D. 1975. Photoperiodic determination of insect development and diapause. III. Effects of nondiel photoperiods. *J. Comp. Physiol.* 103:227-45.

Beck, S. D. 1980. *Insect Photoperiodism.* 2nd ed. New York: Academic Press.

Beck, S. D. 1983. Science and politics. ESA presidential address. *Bull. Entomol. Soc. Am.* 29:21-24.

Beck, S. D. 1988. Resonance in photoperiodic regulation of larval diapause in *Ostrinia nubilalis*. *J. Insect Physiol.* 34:929-33.

Beck, S. D., and G. M. Chippendale. 1968a. Environmental and behavioral aspects of the mass rearing of plant-feeding lepidopterans. In *Radiation, Radioisotopes and Rearing Methods in the Control of Insect Pests.* Proceedings Panel Organized by Joint FAO/IAES Division of Atomic Energy in Food and Agriculture. IAEA Panel Proc. Series, pp. 19-30.

Beck, S. D., and J. H. Lilly. 1949. Report on European corn borer resistance investigations. *Iowa State College J. Sci.* 23:249-59.

Beck, S. D., and E. E. Smissman. 1960. The European corn borer, *Pyrausta nubilalis*, and its principal host plant. VIII. Laboratory evaluation of host resistance to larval growth and survival. *Ann. Entomol. Soc. Am.* 53:755-62.

Beck, S. D., and J. F. Stauffer. 1957. The European corn borer, *Pyrausta nubilalis* (Hubn.), and its principal host plant. III. Toxic factors influencing larval establishment. *Ann. Entomol. Soc. Am.* 50:166-70.

Beck, S. D., G. M. Chippendale, and D. E. Swinton. 1968. Nutrition of the European corn borer, *Pyrausta nubilalis* (Hubn.). VI. A larval rearing medium without crude plant fractions. *Ann. Entomol. Soc. Am.* 61:459-62.

Beck, S. D., I. B. Colvin, and D. E. Swinton. 1965. Photoperiodic control of a physiological rhythm. *Biol. Bull.* 128:177-88.

Beck, S. D., J. L. Shane, and I. B. Colvin. 1965. Proctodone production in the European corn borer, *Pyrausta nubilalis* (Hubn.). *J. Insect Physiol.* 11:297-303.

Bottger, G. T. 1942. Development of synthetic food media for use in nutrition of the European corn borer. *J. Agric. Res.* 65:493-500.

Bredenburg, J. B., E. Honkanen, and A. I. Virtanen. 1962. The kinetics and mechanism of the decomposition of 2,4-dihydroxy-1,4-benzoxazin-3-one. *Acta Chem. Scand.* 16:135-41.

Casida, J. E., S. D. Beck, and M. J. Coles. 1957. Sterol metabolism in the American cockroach. *J. Biol. Chem.* 224:365-71.

Chippendale, G. M., and S. D. Beck. 1965. A method for rearing the cabbage looper, *Trichoplusia ni,* on a meridic diet. *J. Econ Entomol.* 58:377-78.

Chippendale, M., and J. Reese. 1998. Obituary, Stanley D. Beck (1919-1997). *J. Insect Physiol.* 44:361-63.

DeFoliart, G. R. 2000. Professor Stanley D. Beck: Outstanding scientist and hero of the human spirit. *Am. Entomol.* 46:141-45.

Guthrie, W. D. 1979. Breeding for resistance to insects in corn. In *Biology and Breeding for Resistance to Arthropods and Pathogens in Agricultural Plants,* ed. M. K. Harris, pp. 290-302. College Station, Tex.: Texas A&M.

Guthrie, W. D., R. L. Wilson, J. R. Coats, J. C. Robbins, C. T. Tseng, J. L. Jarvis, and W. A. Russell. 1986. European corn borer leaf-feeding resistance and DIMBOA content in inbred lines of dent maize grown under field versus greenhouse conditions. *J. Econ. Entomol.* 79:1492-96.

Klun, J. A. 1970. Relation of chemical analysis for DIMBOA and visual resistance rating for first-brood corn borer. *Proc. Twenty-fourth Corn and Sorghum Res. Conf.* 24:55-60.

Klun, J. A., and T. A. Brindley. 1966. Role of 6-methoxybenzoxazolinone in inbred resistance of host plant (maize) to first-brood larvae of European corn borer. *J. Econ. Entomol.* 59:711-18.

Klun, J. A., and J. F. Robinson. 1969. Concentration of two 1,4-benzoxazinones in dent corn at various stages of development of the plant and its relation to resistance of the host plant to the European corn borer. *J. Econ. Entomol.* 62:214-20.

Klun, J. A., C. L. Tipton, and T. A. Brindley. 1967. 2,4-Dihydroxy-7-methoxy-1,4-benzoxazin-3-one (DIMBOA), an active agent in the resistance of maize to the European corn borer. *J. Econ. Entomol.* 60:1529-33.

Klun, J. A., W. D. Guthrie, A. R. Hallauer, and W. A. Russell. 1970. Genetic nature of the concentration of 2,4-dihydroxy-7-methoxy(2H)-1,4-benzoxazin-3(4H)-one and resistance to the European corn borer in a diallel set of eleven maize inbreds. *Crop Sci.* 10:87-90.

Loomis, R. S., S. D. Beck, and J. F. Stauffer. 1957. The European corn borer, *Pyrausta nubilalis* (Hubn.), and its principal host plant. V. A chemical study of host plant resistance. *Plant Physiol.* 32:379-85.

Reese, J. C., and S. D. Beck. 1976a. Effects of allelochemics on the black cutworm, *Agrotis ipsilon*; effects of p-benzoquinone, hydroquinone, and duroquinone on larval growth, development, and utilization of food. *Ann. Entomol. Soc. Am.* 69:59-67.

Reese, J. C., and S. D. Beck. 1976b. Effects of allelochemics on the black cutworm, *Agrotis ipsilon*; effects of catechol, L-dopa, dopamine, and chlorogenic acid on larval growth, development, and utilization of food. *Ann. Entomol. Soc. Am.* 69:68-72.

Reese, J. C., and S. D. Beck. 1976c. Effects of allelochemics on the black cutworm, *Agrotis ipsilon*; effects of resorcinol, phloroglucinol, and gallic acid on larval growth, development, and utilization of food. *Ann. Entomol. Soc. Am.* 69:999-1003.

Reese, J. C., and S. D. Beck. 1976d. Effects of certain allelochemics on the growth and development of the black cutworm. *Symp. Biol. Hung.* 16:217-21.

Robinson, J. F., J. A. Klun, W. D. Guthrie, and T. A. Brindley. 1982a. European corn borer (Lepidoptera: Pyralidae) leaf feeding resistance: DIMBOA bioassays. *J. Kansas Entomol. Soc.* 55:357-64.

Robinson, J. F., J. A. Klun, W. D. Guthrie, and T. A. Brindley. 1982b. European corn borer leaf feeding resistance: A simplified technique for determining relative differences in concentrations of 6-methoxybenzoxazolinone (Lepidoptera: Pyralidae). *J. Kansas Entomol. Soc.* 55:297-301.

Scheel, C. A., S. D. Beck, and J. T. Medler. 1957. Nutrition of a plant-sucking Hemiptera. *Science* 125:444-45.

Smissman, E. E., S. D. Beck, and M. R. Boots. 1961. Growth inhibition of insects and a fungus byindole-3-acetonitrile. *Science* 133:462.

Smissman, E. E., J. B. LaPidus, and S. D. Beck. 1957. Isolation and synthesis of an insect resistance factor from corn plants. *J. Am. Chem. Soc.* 79:4697-98.

Wahlroos, O., and A. I. Virtanen. 1959. The precursors of 6-MBOA in maize and wheat plants, their isolation and some of their properties. *Acta Chem. Scand.* 13:1906-1908.

Wedberg, J. L. 1998. Stanley D. Beck. *Am. Entomol.* 44:127.

Wikoff, W. 1953. The Becks: Heroes without medals. *Wisconsin State Journal,* June 7, 1953.

SELECTED BIBLIOGRAPHY

1949

With J. H. Lilly and J. F. Stauffer. Nutrition of the European corn borer, *Pyrausta nubilalis* (Hbn.). I. Development of a satisfactory purified diet for larval growth. *Ann. Entomol. Soc. Am.* 42:483-96.

1950

With J. F. Stauffer. An aseptic method for rearing European corn borer larvae. *J. Econ. Entomol.* 43:4-6.

1953

Nutrition of the European corn borer, *Pyrausta nubilalis* (Hubn.). III. An unidentified dietary factor required for larval growth. *J. Gen. Physiol.* 36:317-25.

1957

With G. Kapadia. Insect nutrition and metabolism of sterols. *Science* 126:258-59.

With E. T. Kaske and E. E. Smissman. Quantitative estimation of the resistance factor, 6-methoxybenzoxazolinone, in corn plant tissue. *J. Agric. Food Chem.* 5:933-35.

1958

With W. Hanec. Effect of amino acids on feeding behavior of the European corn borer, *Pyrausta nubilalis* (Hubn.). *J. Insect Physiol.* 2:85-96.

1960

The European corn borer, *Pyrausta nubilalis* (Hubn.), and its principal host plant. VII. Larval feeding behavior and host plant resistance. *Ann. Entomol. Soc. Am.* 53:206-12.

With W. Hanec. Diapause in the European corn borer, *Pyrausta nubilalis* (Hubn.). *J. Insect Physiol.* 4:304-18.

1961

With J. W. Apple. Effects of temperature and photoperiod on voltinism of geographical populations of the European corn borer, *Pyrausta nubilalis* (Hubn.). *J. Econ. Entomol.* 54:550-58.

With E. E. Smissman. The European corn borer, *Pyrausta nubilalis*, and its principal host plant. IX. Biological activity of chemical analogs of corn Resistance Factor A (6-methoxybenzoxazolinone). *Ann. Entomol. Soc. Am.* 54:53-61.

1962

With E. E. Smissman and O. Kristiansen. Presence of 6-methoxybenzoxazolinone in uninjured corn tissue. *J. Pharm. Sci.* 51:292.

1963

With D. G. R. McLeod. Photoperiodic termination of diapause in an insect. *Biol. Bull.* 124:84-96.

1964

With N. Alexander. Hormonal activation of the insect brain. *Science* 143:478-79.

With G. M. Chippendale. Nutrition of the European corn borer, *Ostrinia nubilalis* (Hübn.) V. Ascorbic acid as the corn leaf factor. *Entomol. Exp. Appl.* 7:241-48.

1965

Resistance of plants to insects. *Ann. Rev. Entomol.* 10:207-32.

With G. M. Chippendale and F. M. Strong. Nutrition of the cabbage looper, *Trichoplusia ni* (Hübn.). I. Some requirements for larval growth and wing development. *J. Insect Physiol.* 11:211-23.

1976

Photoperiodic determination of insect development and diapause. V. Diapause, circadian rhythms, and phase response curves, according to the Dual System Theory. *J. Comp. Physiol.* 107:97-111.

With J. C. Reese. Insect-plant interactions: Nutrition and metabolism. *Rec. Adv. Phytochem.* 10:41-92.

1977

Dual system theory of the biological clock: Effects of photoperiod, temperature, and thermoperiod on the determination of diapause. *J. Insect Physiol.* 23:1363-72.

1978

With J. C. Reese. Interrelationships of nutritional indices and dietary moisture in the black cutworm (*Agrotis ipsilon*) digestive efficiency. *J. Insect Physiol.* 24:473-79.

1983

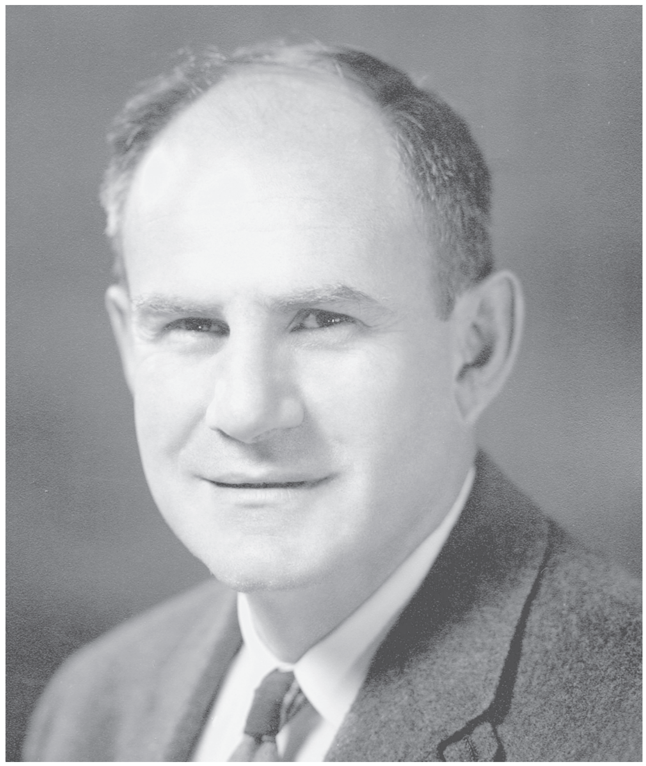
Insect thermoperiodism. *Ann. Rev. Entomol.* 28:91-108.

1985

Dual system theory of the biological clock. *J. Theor. Biol.* 113:93-115.

1989

Factors influencing the intensity of larval diapause in *Ostrinia nubilalis*. *J. Insect Physiol.* 35:75-79.



EARL PHILIP BENDITT

April 15, 1916–May 27, 1996

BY DAVID LAGUNOFF AND GEORGE M. MARTIN

EARL PHILIP BENDITT, a preeminent twentieth-century experimental pathologist, was born in Philadelphia 16 years after the start of the century and died the width of the country away in Seattle 4 years before the century's end. Benditt maintained a lifelong enthusiasm for the methodologies the century provided for the assessment of biologic form and function and for the statistical modes useable to assess the acquired numbers. For his studies of disease processes he exploited quantitative histochemistry and electron microscopy, utilized biochemical techniques, and in the late 1980s turned increasingly to the tools of molecular biology for his experiments. From electrophoresis using the Tiselius apparatus to acrylamide gels to in situ hybridization, he mastered procedures as he needed them. The propensity to embrace any discipline that might help to elucidate the natural history of disease was a central feature of Benditt's commitment to experimental pathology.

Benditt was raised in Philadelphia through the Depression in a large Jewish family; his father worked in the family tobacco business begun by his grandfather, a German-Jewish cigar maker. Benditt's father went to great lengths to provide him with adventures in the widening world. When

Benditt was 14 it was arranged through an uncle for Benditt to accompany an itinerant professor from Berkeley on a motorcycle trip from Philadelphia to California. The professor, who according to Benditt's postcards home, must have taken a secret vow of silence at least for the term of the trip and was not too familiar with the workings of the vehicle; so it fell to Benditt, who rode in the sidecar, to make the necessary emergency repairs en route. Benditt's return home was by bus.

Intelligence and diligence assured Benditt's success in high school but not acceptance to Haverford College. He was rejected there because, as the admissions director wrote his father, "for upwards of a year it has been impossible for us to accept any more applicants from Jewish patrons." Swarthmore, a Quaker-founded, liberal arts college with an outstanding record of graduates who became scientists or physicians and sometimes, as in Benditt's case, both, had room for him, and he whas admitted in 1933. He did extremely well in the educational program invested as it was with a spirit of inquiry by the college president, Frank Aydelotte, soon to become the director of the Institute for Advanced Studies at Princeton University. Christian Anfinsen, another member of the National Academy of Sciences and a Nobel-prize winner, was a classmate and friend. Benditt graduated from Swarthmore in 1937, Phi Beta Kappa, with highest honors in mathematics and biology, as well as a varsity letter in swimming. Family legend has it that Benditt aspired to be an engineer but was redirected to medicine by his mother, aided and abetted by a general practitioner uncle. Benditt maintained a great respect for the skills and achievements of caring practitioners of medicine spanning the generations from his influential uncle to his son Joshua.

Benditt's record at Swarthmore earned him a coveted place at Harvard Medical School then, like Haverford, an institution with a quota for Jews. He found the traditional approach to education at Harvard stultifying after his experience at Swarthmore and often escaped in the afternoons and on weekends to the art museums of Boston or to art classes. There is in the family's possession a competent bust of his friend Ward Fowler, a graduate of Swarthmore and a classmate at Harvard, as well as other pieces that Benditt sculpted during that period. He later wrote that teaching medical students as "apprentices by example after example becomes a dreadfully time consuming process in an area so large as the field of medicine." "It accounts," he continued, "for the narrower and narrower specialization . . . [and] . . . leads to the problem of the blind men and the elephant." "Medicine as it is taught today," he observed, "is an appalling and frustrating thing to the medical student." Benditt's boredom under the educational system at Harvard was relieved at the end of his second year by an invitation from Lawrence Irving, the chair of biology at Swarthmore, to join with Peter Morrison in a summer research expedition to Gaspé in Quebec to study the decrease in oxygen capacity of blood in Atlantic salmon as the fish moved from brackish to fresh water during their journey to spawn. Years later when Irving and Morrison had migrated to Alaska's Institute for Arctic Research and Benditt had reached Seattle, a project developed to look at the blood vessels of aging Pacific salmon returning up river.

At Harvard Benditt's interest in research found expression his senior year in work on thiamine pyrophosphate in A. Baird Hastings's laboratory. On graduation Benditt returned to Philadelphia's General Hospital for two years of clinical internship and residency. With the entry of the United States into World War II in December 1941, Benditt anticipated joining the Air Force, but the discovery of a small, tuberculous pulmonary lesion kept him out of the service permanently and in bed at a sanitarium for a cure accelerated by the urgent need for residents at the hospital. Benditt was able to complete his two years of clinical training by December 1943 and was ready to move on to the University of Chicago for a residency in pathology. Just before leaving Philadelphia, he met Marcella Wexler who would marry him in 1945 after a year of long-distance courting.

The University of Chicago under Robert M. Hutchins, was a perfect fit for Benditt with its aggressive intellectualism, a medical school embedded in a Division of Biological Sciences, and a Department of Pathology with a Ph.D. program and a tradition of providing residents with ample opportunities for research. A number of Benditt's peers in the program had similarly been attracted by the research orientation of the department, notably Robert Wissler, Clarence Lushbaugh, Olaf Skinsnes, and Frank Johnson. Faculty at the University of Chicago in 1943 who were to influence him included Paul Cannon, the chairman; Paul Steiner, a fastidious and highly knowledgeable anatomic pathologist (it was purported that Steiner on occasion would perform an autopsy in black tie and tux—white gloves were optional); and Eleanor Humphreys, a consummate surgical pathologist with wide interests in biology. Benditt recalled receiving an urgent message in 1953 from the surgical pathology lab to look at a hot new paper by Watson and Crick. Cannon was successor to H. Gideon Wells, a seminal figure in pathology in the United States and author of an influential book *Chemical Pathology; Being a Discussion of General Pathology from the Standpoint of the Chemical Processes Involved.* Cannon, like Wells before him and Benditt after him, was elected to membership in the National Academy of Sciences. George Gomori was another faculty member at Chicago who had a significant impact on Benditt's career. Gomori, a pathologist by training with an appointment in the Department of Medicine, was a brilliant, innovative investigator and the acknowledged originator of enzyme histochemistry.

A large part of the pathology department's research effort throughout the war was devoted to studies of protein malnutrition under Cannon's direction. Benditt participated in these studies from his early days in the residency program. Between a 1944 paper with Wissler and Cannon on surgical infection in the presence of protein deficiency and a 1950 paper with Wissler and Jaffe on the arrest of dietary cirrhosis by feeding methionine and choline, he published 13 papers on a range of aspects of protein malnutrition in rats. A separate scientific venture was the examination of serum protein profiles using a Tiselius apparatus. Together with Sheldon Walker, he looked at serum from patients with syphilis, scleroderma, and diverse other connective tissue diseases. During this period one of Benditt's talents that he would use to good advantage throughout his career was manifested: the ability to attract bright medical students and residents into his orbit. Don Rowley was the first of a line of scientific acolytes to join Benditt at the University of Chicago and the University of Washington. Rowley and Benditt shared a love of sailing that was to bring them not only to own a "Star" but also to assemble a dinghy in the morgue in the basement of Billings Hospital, using the pathology department's tools for the job. They were discovered *delicto flagrante* by Cannon, who according to Rowley, told them simply but firmly to "get the dinghy out of there!" Benditt as a chairman was equally forgiving in the face of a graver indiscretion by one of his junior faculty members. A luncheon party had been arranged in the lab by a visiting postdoc at which the main course was delicately fried, breaded legs from rats sacrificed for their mast cells. Benditt, who had come upon the feast unknowingly, tried a leg proffered to him as chicken. He questioned the size of the chicken from which the diminutive legs had come and the lingering flavor of ether before politely taking his leave.

In 1949 an interest in inflammation led to a series of experiments with Al Dorfman on the "spreading factor" present in hyaluronidase preparations. When Benditt was able to prove that the active factor was not hyaluronidase, he turned to an examination of other edemogenic factors. Studies of ovomucoid, a protein present in egg whites, confirmed the dependence of its effects on mast cell degranulation, thereby launching a series of studies on these tissue cells of inflammation that was to extend over the next 10 years. With Rowley he established that rat mast cells, in addition to the previously identified histamine, contained and released serotonin. With David Lagunoff, another medical student recruit at the University of Chicago, he isolated rat peritoneal mast cells and demonstrated the presence of 5-hydroxytryptophan decarboxylase in the cells to account for their serotonin content. Using an ingenious semiquantitative method for studying competitive enzyme inhibition histochemically, he and Margaret Arase, a talented and devoted technologist, identified a mast cell esterase with an inhibitor profile closely paralleling that of chymotrypsin. The histochemical reagent they used for these studies was one Gomori had originally synthesized as a potential substrate for acetylcholinesterase that instead was selectively hydrolyzed by unknown enzymes in neutrophils and mast cells. At the University of Washington, the mast cell enzyme was isolated, characterized as a protease, sequenced by Rick Woodbury in Neurath's laboratory, and found to be a protease distinct from any of the known forms of chymotrypsin. The identification of serotonin as an inflammatory mediator synthesized by mast cells led to studies with Ruth Wong of the enterochromaffin cell, another storage site for serotonin.

By 1957, when Benditt was recruited to the University of Washington to build an academic pathology department, he had risen to the rank of associate professor, he had passed his boards in anatomic pathology, and the Benditt family had increased to include three boys: John, Allen, and Joshua. A fourth son, Charles, was born in Seattle. On his return from his first visit to the Pacific northwest, Benditt wrote Gomori, who had moved to southern California, "Despite the fact that it rained the three days that I was in Seattle, it looked much less bleak than Chicago under similar circumstances and less bleak than Chicago has looked for the last two days with the temperature in the low 20s and the gray skies and the grime." Needless to say, it was not the climate, not the clean streets, not the rather miserly salary the university was offering that attracted Benditt to the University of Washington. It was the opportunity to build a department capable of carrying out an "investigative approach to the study of disease using new concepts and new tools," working "with people like H. Stanley Bennett in Anatomy, . . . Hans Neurath in Biochemistry, . . . Ruch in Physiology, Evans in Microbiology, Williams in Medicine and Harkins in Surgery, all explorers in medicine and biology." After Benditt joined this group he was vigorous in his defense of the complete set of basic science departments. When the Department of Pharmacology was threatened with extinction, he insisted on its continuation, resulting eventually in the recruitment of Ed Krebs back to the University of Washington.

Benditt brought with him to Seattle two graduating residents from the Chicago program, Bob Priest and George Martin, together with a modest National Institutes of Health grant to jump-start research in the department. Lagunoff arrived from an internship to be a postdoctoral fellow the following year. In rapid succession Russell Ross, Edward Smuckler, and Oscar Iseri joined the group as graduate students and Ben Trump moved over from the anatomy department soon after. Ross, originally trained as a dentist, was the department's first Ph.D., Smuckler the second. Within five years Benditt had created a full-fledged academic department virtually from the ground up and acquired an impressively expanded renewal of his Reaction to Injury grant (a grant that was the first million-dollar award to the University of Washington, one that has lived on and is at this writing in its forty-sixth year). New faculty he recruited in the early years included Rich Prehn, Buster Alvord, Bernie Wagner, and Karle Mottet. In 1962 Benditt turned down the possibility of a chair at a prestigious East Coast medical school in favor of the potential he saw at the University of Washington for continuing to build a department that would excel in research, while, as Cannon had advised on Benditt's taking leave of Chicago, keeping "experimental pathology in balance with the urgent needs of practical pathology." Benditt was well aware of the conflict between the "need for action in treating disease and the slow deliberate search for etiology." Even before Benditt arrived at the University of Washington he had agreed to relinquish the future clinical laboratories in spite of the projected loss of income this entailed. Benditt viewed the clinical labs as a distraction from his central goals but helped ensure that the laboratories were in capable hands.

The restructured department rose rapidly to compete with older established programs in the country. It was a department imbued from the start with Benditt's vision of pathology as the basis of a "rational and dynamic conception of disease processes," built with knowledge from biochemistry, biophysics, and morphology, combining these to create pathology's own discipline. In his early years in Seattle Benditt was involved in virtually every project in the department: the biochemistry of liver injury with Smuckler; wound healing with Ross; the morphology of renal disease with Trump and subsequently Gary Striker; studies of mast cell structure and function with Lagunoff; the influence of basement membrane on tissue regeneration with Ruddy Vracko; abnormalities of collagen cross-linking with Roy Page; catecholamine injury to myocardium with Denny Reichenbach; and serum oxidases with Martin. If Archilochus's dichotomy of the hedgehog that knows one big thing and the fox that knows many things can be applied to scientists in the sense Isaiah Berlin applied it to nineteenth-century Russian writers, Benditt was a consummate fox.

As the young investigators he had recruited to his projects matured they gradually assumed control of their own work, and Benditt's research focused increasingly on amyloidosis and atherosclerosis. Although he retained an interest in the studies of his students as they moved out of his orbit, he invariably encouraged their independence and supported them without reservation when they chose to leave the department.

As early as 1950 Benditt had been interested in the nature of amyloid. He conjectured then on the determinants of the insolubility of the deposits, wondered if hyaluronidase could dissolve the amyloid, and considered the possibility that oxidative cross-linking analogous to insect cuticle hardening might account for its stability. At the University of Chicago he maintained a colony of flour beetles, and at the University of Washington he had the histology lab process cuticles from wild cockroaches captured late evenings in the halls of the medical school wing by a willing if not enthusiastic assistant professor. Initial attempts in Seattle to reproducibly generate mouse amyloid failed. Then in 1962 a patient with ulcerative colitis presented with signs of renal failure and extensive amyloid in her renal biopsy. Although amyloid frequently occurs in the presence of chronic inflammation, ulcerative colitis is a peculiar exception. Exceptions aside, the death of the patient provided ample amyloid to support Benditt's initial studies. He and Lagunoff planned the first experiments using the fragile criteria of an elevated tryptophan content of amyloid, indicated by a histochemical reaction, and the fibrillar character of the deposits as seen with the electron microscope to instruct the isolation. Nils Eriksen undertook the definitive extractions, which depended on removing as much soluble protein as possible and then solubilizing the amyloid with high molar concentrations of urea. Eriksen, a biochemist, had started working with Benditt at the time Benditt arrived in Seattle and was a major participant throughout the studies on amyloid. His finding of a characteristic low-molecular-weight electrophoretic band in the extracts provided a robust basis for isolation of the protein from additional human cases, Pekin duck, and monkey liver. With the help of Mark Hermodson and Lowell Ericksson in Ken Walsh's sequencing lab in the Biochemistry Department, N-terminal sequences were obtained and then the complete sequence of the monkey amyloid. A premature claim by George Glenner that all amyloids consisted of N-terminal portions of immunoglobulin light chains was readily shown to be mistaken by Benditt and Eriksen, who were able to divide amyloids into two groups, A and those that were not A, which they termed B and included Glenner's light chain amyloid. The amyloid A isolated by Benditt and his collaborators and independently by Mordechai Pras, Ed Franklin, and Dorothy Zucker-Franklin was later termed AA, and it together with the immunoglobulin light chain amyloid, AL, turned out to be the first of a long list of amyloids formed from distinct proteins. Benditt and Eriksen went on to identify the circulating protein from which the amyloid A protein derived as an apolipoprotein, apoSAA, associated with HDL particles. Together with Eriksen, Joseph Hoffman, Rick Meek, and Ron Hansen, Benditt continued his amyloid studies as the field burgeoned, identifying cells of the monocyte/macrophage lineage as a potential local source of apoSAA to augment that derived from hepatocytes as an acute phase protein and probing the significance of the multiple genetic variants of apoSAA.

The other major focus of Benditt's research from the late 1960s on was atherosclerosis. In the course of a renewal of his Reaction to Injury grant, which had by then expanded into a program project, Benditt made a deliberate decision to open a new line of investigation, extending his previous studies of the pathology of the microvasculature to the examination of elastic and muscular arteries involved in atherosclerosis and hypertension. He and Ned Moss, a resident and then a fellow, carried out initial studies on the spontaneous, nonfatty, atherosclerotic lesions of chickens and subsequent studies on lesions aggravated by feeding the chickens cholesterol. John Poole, a visiting professor from Oxford, examined with Benditt the ultrastructural aspects of the response of rat aorta to injury induced by a suture through its wall. These studies added to the growing evidence for a key role of smooth muscle cells in the pathogenesis of atherosclerosis. Stephen Schwartz, after his pathology residency, began work with Benditt on the intima of the rat aorta. Their studies explored the development of the intima, and they designed cell kinetic methods to study replication of endothelial and vascular smooth muscle cells.

In 1965 Stan Gartler, a member of the Genetics Department and a close friend of Benditt's, carried out a clever experiment with Dave Linder, a pathologist from Oregon. They used the early random inactivation of one of the two X chromosomes in women and the resulting mosaicism to prove that leiomyomas of the uterus consisted of individual clonal growths. The experimental design depended on the derivation of the tumors from African American women heterozygous for the glucose-6-phosphate dehydrogenase locus on the X chromosome. The presence of multiple atheromatous plaques in aortas and coronary arteries led Benditt to consider that these proliferative lesions could be benign tumors of vascular smooth muscle analogous to leiomyomas of the uterus; Gartler's experimental system provided an elegant first test of the hypothesis. If atheromas were smooth muscle tumors, then they too should be monotypic. Benditt recruited his eldest son, John, to join him for extended times in the cold-room dissecting plaques and then separating the isoforms of glucose-6-phosphate dehydrogenase by starch gel electrophoresis. The results were highly consistent with the hypothesis. A clear majority of small noncoalescent lesions predominantly contained a single enzyme isoform, and there was no strong bias for either isoform. He also showed that some very small samples, 0.1-0.3mm^3, of media beneath the plaques and of normal vessel wall were not monotypic.

Ross, following a sabbatical at the Strangeways Research Laboratory in Cambridge, began to culture vascular smooth muscle cells and with Michael Stemerman induced intimal smooth muscle proliferative lesions in femoral arteries of nonhuman primates by removing the endothelium with a balloon catheter. In 1973 Ross and Glomsett published an influential review in *Science* proposing that the smooth muscle proliferation in atherosclerosis was a response to endothelial injury, unfortunately neglecting Benditt's work and the evidence for monoclonality. Meanwhile George Martin had turned his attention to cellular aspects of aging and proposed that atherosclerotic lesions might be related to manifestations of cell senescence.

Thus, in the department three divergent views on the pathogenesis of atherosclerosis were simultaneously being promulgated. Schwartz was soon to join the controversy as an independent investigator. Tensions were inevitable, but they were largely held in check and the department survived in part because of the intellectual debt each of the others owed Benditt and in part because of Benditt's magnanimity. In 1981, with Benditt's support, Ross succeeded him as department chair; Martin and Schwartz stayed on in the department to build their own research dynasties in aging and vascular biology, respectively. Trump, Smuckler, and Lagunoff by that time had become chairmen elsewhere. Other chairs of pathology departments who were influenced by their experience in Benditt's department include Don Thrush, Tom Norris, and Mary Lipscomb.

Benditt pursued the possibility that analogously to neoplasms, atherosclerotic plaques could be initiated by somatic mutation in a single cell. A series of papers with Mark Majesky, a graduate student, and Mont Juchau in the department of pharmacology explored the possibility that chemical mutagens could be factors in the induction of atherosclerosis. Repeating previous work by others, they induced intimal smooth muscle lesions in chicken abdominal aorta after prolonged treatment with benz(a)pyrene or 7,12-dimethylbenzanthracene. When several doses of the latter carcinogen were followed by chronic treatment with methoxamine, a putative tumor promoter, lesions occurred in the thoracic aorta. Benditt also stimulated interest in the possibility of virally induced mutations in smooth muscle cells but played only a small personal role in such studies.

Although the observation of monotypic plaques was confirmed by several laboratories, the significance of the finding for the generation of plaques was questioned over the years by several investigators, including Martin, who based his concerns on evidence for clonal attenuation and succession in proliferating cultures of normal diploid human skin fibroblasts. Beginning in 1995 Charles Murry, working with Schwartz, revisited the question of monoclonality with a different X-chromosome probe suggested by Benditt. Using methylation in the first exon of the androgen receptor gene to examine X-chromosome inactivation in samples from thick sections of vessel wall, Murry confirmed the monotypia of atherosclerotic plaques but found evidence that monotypic patch size in the media beneath either plaques or diffuse intimal thickening, although usually smaller than that of plaques, was in contrast to Benditt's original findings, of a size that could reasonably be expected to give rise to plaques from division of more than a single progenitor cell. Benditt participated at the onset of these experiments and was, according to Schwartz, prepared to accept the early evidence from these experiments, but unfortunately Benditt's terminal illness prevented his review of the completed work. While he was in the hospital Martin brought him the news that the mutation responsible for Werner's syndrome, a progeroid syndrome with accelerated development of atherosclerosis, was a member of a family of DNA helicases. Benditt was delighted and lifted a knowing finger accompanied by "Aha, DNA repair!" Whatever the ultimate understanding of the genesis of the atherosclerotic plaque, there is no gainsaying the fact that Benditt's study of plaque clonality initiated a new and crucial phase in the study of atherosclerosis

For his fiftieth Swarthmore reunion Benditt observed of pathology, "It occurs to me we must be sharing the excitement felt by those physicians and investigators who in the second half of the nineteenth century participated in the advances in histology, physiology, and microbiology that began to unravel the mysteries of pathology . . .” In a more personal vein he reported, “I can survey with considerable pleasure the Department’s growth from ground zero to its present status” and continued, referring to his relinquishing the chairmanship, “Retirement marked an end to a happy phase of my career.” When Benditt assumed an emeritus professorship in 1986, his published papers numbered 218. In the next 10 years he published an additional 33 papers. The publications during this latter period remained concentrated on amyloid and atherosclerosis. Two additional papers from Steve Schwartz’s lab bearing Benditt’s name were published posthumously.

Benditt was not known, particularly by medical students, as a great lecturer. Students at the University of Chicago were reputed to re-enact a Benditt lecture by turning to the blackboard, writing with chalk so that no one could see what they were writing, meanwhile conversing with the board. It was not that he was not able to present a clear, concise, didactic lecture, as he proved on many occasions. The problems arose in the course of a lecture when, seemingly forgetting his audience, he would become engaged in an ongoing critical review of the information he was conveying, requiring frequent caveats, corrections, and revisions as he proceeded.

Social gatherings at the Benditts’ home were always interesting: the food was good, Benditt could be counted on to cook a perfect salmon, and conversation centered variously on Benditt’s interests in Kuhn’s theories on scientific progress, Tycho Brahe’s data on the motion of the planets, or the state of pathology and Marcella’s interests in the arts, but Benditt was sometimes a bit lax when it came to social amenities. At a dinner party he hosted for a prospective faculty member, a lack of proper introductions left the recruit and his spouse puzzled by the presence of an unidentified and largely silent member of the party, only to be told on inquiry of the host at the end of the evening that the tall, taciturn character in question was the dean of the medical school. Benditt's wry sense of humor was not to be underestimated. While serving as a consultant to a major drug company, he was subjected to a detailed harangue, economically justifying the inadvisability of undertaking the development of an HIV vaccine. At the conclusion of the presentation, Benditt offered his agreement with the conclusion on the condition that the company remove from its logo the word "ethical."

Benditt had little patience with bad experiments or unsupported conclusions. He was adept at demolishing an opponent in a scientific polemic but always had the time to listen attentively to someone's latest results and the insight to propose at least five cogent alternative experiments to anyone who approached him with a scientific problem, often before the supplicant could finish a description of the problem. Benditt's sheer enthusiasm for research was able to counteract even the most disastrous of outcomes of experiments by neophytes. In Lipscomb's case she was finishing her residency with six months in research with Benditt. He proposed that she test the possibility that amyloid in Pekin ducks was transmissible. Lipscomb carefully raised a group of ducks from eggs and injected her amyloid-free domestic ducks with liver extracts from a group of Chinese ducks with amyloid. The next morning every one of the injected domestic ducks was dead in the pond. Benditt was ready to immediately begin planning the follow-up experiment, and Lipscomb went on, inspired, to a successful career as an experimental pathologist.

Benditt derived great satisfaction from his family and was proud of their accomplishments. Marcella was a writer, an editor, and a community activist; their sons established successful careers in their own spheres, John as a science writer and editor, Alan as a New York actor, Joshua as an academic pulmonologist, and Charles as an architectural designer.

In addition to his work as a scientist, a teacher, and an administrator, Benditt was active in a variety of university and public undertakings. He was elected to membership in the National Academy of Sciences in 1975. He served on numerous committees, local, national, and international. He was the elected president of the Histochemical Society and of the American Society for Investigative Pathology, when it was still the American Association of Pathologists; he served on National Institutes of Health study sections and the Board of Scientific Counselors of the National Institute of Environmental Health Sciences; and he participated in two politically sensitive reviews of the effects of dioxin exposure on the health of veterans of the war in Viet Nam conducted by the Institute of Medicine and the Food and Drug Administration. His scientific work was recognized by an array of honors. He was Dammin lecturer at Harvard, Lichtfeld lecturer at Oxford, MacArthur lecturer at Edinburgh, Wellcome Foundation lecturer at Cornell, and Veterans Administration Distinguished Physician. In 1980 the American Society for Investigative Pathology bestowed on Benditt the Rous-Whipple Award and four years later the Gold Headed Cane.

Inside Benditt the empirical scientist there was a natural philosopher fighting to assert himself. The laws of thermodynamics, Bernard's concept of homeostasis, Weissmann's idea of continuity of the species through the "germ plasma," Darwin's exposition of natural selection as the force driving evolution, and Virchow's emphasis on cells as the site of disease processes were recurring themes in his explorations into the philosophic basis of pathology. At the University of Chicago he found a kindred, wide-ranging mind in Heinrich Klüver, a reclusive, well-read experimental psychologist best known for his description with Paul Bucy of the temporal lobe syndrome but also as the developer of the useful Luxol fast blue stain for myelin sheaths. The two kept in touch for many years after Benditt left Chicago.

Although Benditt's long-running National Institutes of Health grant was entitled "Reaction to Injury," he rejected the popular idea that disease could be defined simply as a response to adverse circumstances. His earliest philosophical efforts were directed toward a thermodynamic definition of normality of biological function in terms of maximum energetic efficiency and a corresponding definition of disease as a deviation from optimal function, rather than from average function. Later he came to view disease less rigidly as a "failure of organizational regulation and of proper interaction with the environment of the several parts of an organism." In 1971, returning to the roots of the word itself, he defined disease as "a distortion of the operations and/or the structures of the body beyond the ordinary comfortable limits of the living state." While snippets of his efforts at developing a logical, self-consistent philosophic basis for pathology appeared in print, Benditt never published an extended exposition of his ideas, perhaps because he was never quite satisfied with his formulations and was repeatedly revising them in the belief, held by many of us, that there would always be time enough tomorrow and the next day to find the ideal words to express his vision. Sadly his life was ended too soon by complications following surgery for an abdominal aortic aneurysm. There is among Benditt's papers a curious 1971 letter from Klüver quoting

Harvey Cushing's advice: "Learn to live forever; live as to die tomorrow."

Benditt obviously enjoyed the roles of department chairman, public figure, and acknowledged seer, but he was from the time of his first studies of salmon blood to the end of his life a laboratory scientist planning the next experiment, expectantly awaiting the results, analyzing the data, rethinking the problem, re-doing the experiment, and finally writing the paper. He had little patience with idle research driven by a need to generate publications. One of his favorite cartoons was Abner Dean's drawing of "Bright Young Men" busily, mindlessly, contentedly extending a massive complex of useless, endless plumbing. He believed that experiments should be designed to rigorously test meaningful hypotheses. Benditt's scientific contributions are unarguably substantial, but of equal or perhaps even greater importance is the legacy inherited by his students of a spirit and practice of intense inquiry into the nature of disease that they in turn will surely pass on to their students.

WE ARE GRATEFUL first and foremost to Marcella Benditt for her help in recollecting Earl's life. We also wish to thank Robert Wissler, Stephen Schwartz, Lawrence Loeb, Mary Lipscomb, and Charles Murry for their willingness to share their memories of Earl with us. We of course absolve them of responsibility for any inadvertent misrepresentations that they may find in the biography. Finally, we apologize to all of those who worked with Earl over the years whom we have failed to mention in this too brief, incomplete biography but who were important to him and affected by him: Tom Barrett, John French, Victor Gould, Alan Gown, Thomas Grayston, Ray Haines, Henry Harris, John McDougall, Johsel Namkung, Sigurd Normann, to name but a few among many.

SELECTED BIBLIOGRAPHY

1941

With P. Morrison and L. Irving. The blood of the Atlantic salmon during migration. *Biol. Bull.* 80:429-40.

1947

With E. M. Humphreys, R. L. Straube, R. W. Wissler, and C. H. Steffee. Studies in amino acid utilization. II. Essential amino acids as a source of plasma protein and erythrocytes in the hypoproteinemic rat. *J. Nutr.* 33:85-94.

1953

With J. E. French. Histochemistry of connective tissue. I. The use of enzymes as specific histochemical reagents. *J. Histochem.* 1:315-20.

1955

With R. L. Wong, M. Arase, and E. Roeper. 5-Hydroxytryptamine in mast cells. *Proc. Soc. Exp. Biol. Med.* 90:303-304.

1956

With D. A. Rowley. 5-Hydroxytryptamine and histamine as mediators of the vascular injury produced by agents which damage mast cells in rats. *J. Exp. Med.* 103:399-412.

1958

With M. Arase. Enzyme kinetics in a histochemical system. *J. Histochem. Cytochem.* 6:431-34.

1961

With R. McAlister and G. M. Martin. Evidence for multiple caeruloplasmin components in human serum. *Nature* 190:927-29.

With R. Ross. Wound healing and collagen formation. I. Sequential changes in components of guinea pig skin wounds observed in the electron microscope. *J. Biophys. Biochem. Cytol.* 11:677-700.

1962

With D. Lagunoff, N. Eriksen, and O. A. Iseri. Amyloid. Extraction and preliminary characterization of some proteins. *Arch. Pathol.* 74:323-30.

With R. E. Priest and S. J. Normann. Diet-induced myocardial infarction in rat. *Arch. Pathol.* 74:375-80.

With E. A. Smuckler and O. A. Iseri. An intracellular defect in protein synthesis induced by carbon tetrachloride. *J. Exp. Med.* 116:55-72.

1966

With N. Eriksen. Amyloid. III. A protein related to the subunit structure of human amyloid fibrils. *Proc. Natl. Acad. Sci. U. S. A.* 55:308-16.

With R. C. Page. Molecular diseases of connective and vascular tissues. I. The source of lathyritic collagen. *Lab. Invest.* 15:1643-51.

1970

With N. S. Moss. The ultrastructure of spontaneous and experimentally induced arterial lesions. II. The spontaneous plaque in the chicken. *Lab. Invest.* 23:231-45.

With R. Vracko. Capillary basal lamina thickening. Its relationship to endothelial cell death and replacement. *J. Cell Biol.* 47:281-85.

1971

With J. C. F. Poole and S. B. Cromwell. Behavior of smooth muscle cells and formation of extracellular structures in the reaction of arterial walls to injury. *Am. J. Pathol.* 62:391-414.

With N. Eriksen, M. A. Hermodson, and L. H. Ericsson. The major proteins of human and monkey amyloid substance. Common properties including unusual N-terminal amino acid sequences. *FEBS Lett.* 19:169-73.

With N. Eriksen. Chemical classes of amyloid substance. *Am. J. Pathol.* 65:231-52.

1973

With J. M. Benditt. Evidence for a monoclonal origin of human atherosclerotic plaques. *Proc. Natl. Acad. Sci. U. S. A.* 70:1753-56.

1977

With S. M. Schwartz. Aortic endothelial cell replication. I. Effects of age and hypertension in the rat. *Circ. Res.* 41:248-55.

1980

With N. Eriksen. Isolation and characterization of the amyloid-related apoprotein (SAA) from human high density lipoprotein. *Proc. Natl. Acad. Sci. U. S. A.* 77:6860-64.

1983

With T. B. Barrett, P. Sampson, G. K. Owens, and S. M. Schwartz. Polyploid nuclei in human artery wall smooth muscle cells. *Proc. Natl. Acad. Sci. U. S. A.* 80:882-85.

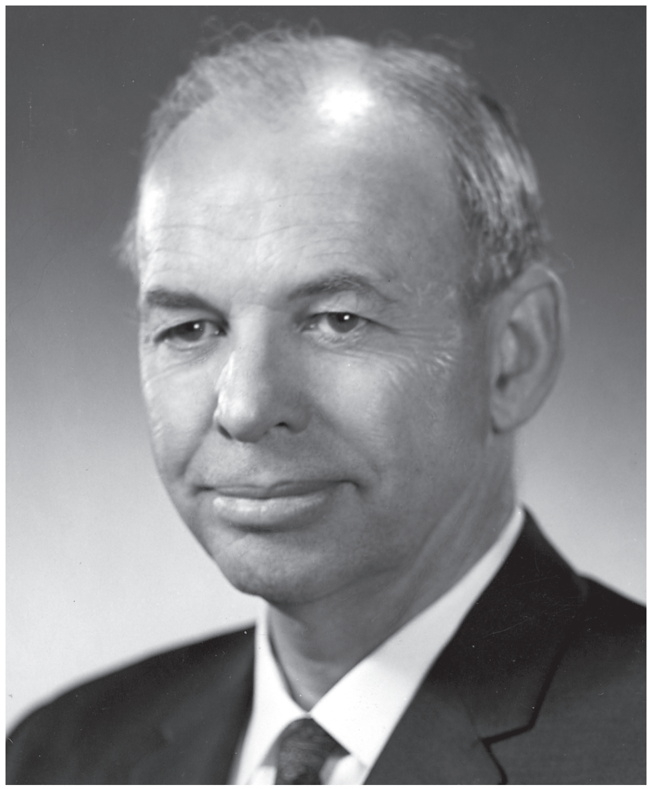
With T. Barrett and J. K. McDougall. Viruses in the etiology of atherosclerosis. *Proc. Natl. Acad. Sci. U. S. A.* 80:6386-89.

1990

With D. Gordon, M. A. Reidy, and S. M. Schwartz. Cell proliferation in human coronary arteries. *Proc. Natl. Acad. Sci. U. S. A.* 87:4600-4604.

1992

With R. L. Meek and N. Eriksen. Murine apoSAA3 is an HDL apoprotein and is secreted by macrophages. *Proc. Natl. Acad. Sci. U. S. A.* 89:7949-52.



Courtesy of the University of Wisconsin, Madison.

R. H. BING

October 20, 1914–April 28, 1986

BY MICHAEL STARBIRD

R. H. BING LOVED TO work on problems in topology, perhaps because he was consummately successful at solving them. He was a mathematician of international renown, having written seminal research papers in general and geometric topology. The Bing-Nagata-Smirnov metrization theorem is a fundamental result in general topology that provides a characterization of which topological spaces are generated by a metric. His work and the methods he used in the study of the geometric topology of 3-dimensional space were so seminal and distinctive that that area of investigation is often referred to as Bing-type topology. His leadership both in research and in teaching resulted in his serving as president both of the American Mathematical Society and the Mathematical Association of America. However, we who knew him personally remember him most for his zest for life that infected everyone around him with a contagious enthusiasm and good humor. So this paper celebrates a life well lived, a life whose joy came partly from significant contributions to topology and partly from an overflowing *joie de vivre.*

A VIGNETTE ON BING'S DEVOTION TO MATHEMATICS

It was a dark and stormy night, so R. H. Bing volunteered to drive some stranded mathematicians from the fogged-in Madison airport to Chicago. Freezing rain pelted the windscreen and iced the roadway as Bing drove on—concentrating deeply on the mathematical theorem he was explaining. Soon the windshield was fogged from the energetic explanation. The passengers too had beaded brows, but their sweat arose from fear. As the mathematical description got brighter, the visibility got dimmer. Finally, the conferees felt a trace of hope for their survival when Bing reached forward—apparently to wipe off the moisture from the windshield. Their hope turned to horror when, instead, Bing drew a figure with his finger on the foggy pane and continued his proof—embellishing the illustration with arrows and helpful labels as needed for the demonstration.

Two of Bing's mathematical colleagues Steve Armentrout and C. E. Burgess independently recalled versions of this memorable evening. Those of us who knew Bing well avoided raising mathematical questions when he was driving.

R. H. Bing started and ended in Texas. He was born on October 20, 1914, in Oakwood, Texas, and there he learned the best of the distinctively Texas outlook and values. What he learned in Oakwood guided him clearly throughout his life. He had a strong Texas drawl, which became more pronounced proportionate to his distance from Texas; and he spoke a little louder than was absolutely necessary for hearing alone. He might be called boisterous with the youthful vigor and playful curiosity that he exuded throughout his life. He was outgoing and friendly and continually found ways to make what he did fun. You could hear him from down the hall laughing with his TA's while grading calculus exams or doing other work that deadens most people. He did not sleep well and when he woke at 4:00 a.m., he would get up and work. He especially enjoyed working on things requiring loud hammering at that hour on the grounds that if you are going to be up at 4, the family should know about it. He practiced the traditional Texas value of exercising independent judgment, both in general matters and in matters mathematical. He treated people kindly and gently—unless he knew them, in which case it was more apt to be kindly and boisterously.

Both of Bing's parents were involved in education. His mother was a primary teacher and his father was the superintendent of the Oakwood School District. Bing's father died when R. H. was five, so Bing most remembered his mother's impact on his character and interests. Bing attributed his love for mathematics to his mother's influence. He recalled that she taught him to do mental arithmetic quickly and accurately and to enjoy competition both physical and mental.

After high school Bing enrolled in Southwest Texas State Teachers College in San Marcos (now Southwest Texas State University) and received his B.A. degree in 1935 after two and a half years there. Later in life Bing was named as the second distinguished alumnus of Southwest Texas State University. The first person so honored was Lyndon Baines Johnson. Bing's college education had prepared him as a high-school mathematics teacher. He also was a high-jumper on the track team and could jump his own height—which was over 6 feet.

Bing's final academic position was as the Mildred Caldwell and Blaine Perkins Kerr Centennial Professor in Mathematics at the University of Texas at Austin, but his first academic appointment was as teacher at Palestine High School in Palestine, Texas. There his duties included coaching the football and track teams, teaching mathematics classes, and teaching a variety of other classes, one of which was typing. His method of touch-typing involved anchoring his position over the keys by keeping some constant pressure on his little fingers. This habit was hard to break, apparently, because later he said that when he used an electric typewriter or computer keyboard (neither of which he did often) he tended to produce large numbers of extraneous "a's."

Nowadays one frequently hears complaints about a school system that gives the football coach the added assignment of teaching a mathematics class. One wonders if those football boosters of a bygone day in Palestine complained to the local school board about a real mathematics teacher coaching the football team.

In an effort to improve public school education in the 1930s, the Texas legislature approved a policy whereby a teacher with a master's degree would receive more pay than a teacher with a bachelor's degree. So, many teachers saved and scrimped during the nine-month session and went to summer school during the three summer months in an effort to upgrade their talents and their salaries. Bing was among them.

R. H. began public school teaching in 1935 and began taking summer school courses at the University of Texas at Austin. There he met Mary Blanche Hobbs, whom he married in 1938. R. H. and Mary enjoyed a long and happy marriage. They had four children: Robert Hobbs Bing, 1939; Susan Elizabeth Bing, 1948; Virginia Gay Bing, 1949; and Mary Pat Bing, 1952. His wife, Mary, all their children, their children's spouses, and their grandchildren still have fond memories of Bing.

The same year as his marriage he earned a master of education degree from UT. During one summer there Bing took a course under the late Professor R. L. Moore, also a member of the National Academy of Sciences. Moore was inclined to deprecate the efforts of an older student such as Bing was, so Bing had to prove himself. But he was equal to the task.

Bing continued to take some summer courses while teaching in the high schools. In 1942 Moore was able to get Bing a teaching position at the university, which allowed him to continue graduate study to work toward a doctorate and to try his hand at research.

An unofficial rating scheme sometimes used by R. L. Moore and his colleagues went something like this: You could expect a student with Brown's talents and abilities every year; you could expect a student with Lewis's talents and abilities once every 4 years; but a student with Smith's talents and abilities came along only once in 12 years. Bing's talents and abilities threw him in the 12-year class, or in an even higher class, since he was one of the most distinguished mathematicians ever to have received his degree from the University of Texas at Austin. Several of Moore's later graduate students have written that in the days after Bing, Moore used to judge his students by comparing them with Bing—not to their advantage.

Bing received his Ph.D. in 1945, writing his dissertation on planar webs. Planar webs are topological objects now relegated to the arcana of historical topological obscurity. The results from his dissertation appeared in one of his earliest papers (1946) in the *Transactions of the American Mathematical Society*. He told us that the *Transactions* had sent him 50 reprints at the time and if we were interested we could have some because he still had 49 or so left.

But Bing did not have long to wait for recognition of his mathematical talent. He received his Ph.D. degree in May 1945, and in June 1945 he proved a famous, longstanding unsolved problem of the day known as the Kline sphere characterization problem (1946). This conjecture states that a metric continuum in which every simple closed curve separates but for which no pair of points separates the space is homeomorphic to the 2-sphere.

When word spread that an unknown young mathematician had settled this old conjecture, some people were skeptical. Moore had not checked Bing's proof since it was his policy to cease to review the work of his students after they finished their degrees. Moore believed that such review might tend to show a lack of confidence in their ability to check the work themselves. So when a famous professor wired Moore asking whether any first-class mathematician had checked the proof, Moore replied, "Yes, Bing had."

Primarily because of the renown among mathematicians generated by his having solved a famous conjecture, Bing was offered positions at Princeton University and at the University of Wisconsin, Madison. Moore naturally wrote letters of recommendation. One comment he made was that, although the Kline sphere characterization problem was a much better known topic than that of planar webs, Moore felt that it was Bing's work on planar webs that demonstrated that Bing had the mathematical strength to be an outstanding mathematician.

One of the leading topologists of the time was at Princeton, but Bing did not wish to follow in anyone's footsteps, so in 1947 he accepted a position at Wisconsin. He remained at Wisconsin for 26 years except for leaves: one at the University of Virginia (1949-50), three at the Institute for Advanced Study in Princeton (1957-58, 1962-63, 1967), one at the University of Texas at Austin (1971-72), and brief teaching appointments elsewhere. He returned to the University of Texas at Austin in 1973; but it was during his tenure at the University of Wisconsin, Madison, that his most important mathematical work was done and his prominent position in the mathematical community established.

Bing's early mathematical work primarily concerned topics in general topology and continua theory. He proved theorems about continua that are surprising and still central to the field. Among these results is Bing's characterization of the pseudo arc as a homogeneous indecomposable, chainable continuum (1948). The result that the pseudo arc is homogeneous contradicted most people's intuition about the pseudo arc and directly contradicted a published but erroneous "proof" to the contrary. Bing continued to do some work in continua theory throughout his career—including directing a Ph.D. dissertation in the subject at UT in 1977.

Around 1950 one of the great unsolved problems in general topology was the problem of giving a topological characterization of the metrizability of spaces. In 1951 Bing gave such a characterization in his paper "Metrization of Topological Spaces" in the *Canadian Journal of Mathematics* (1951). Nagata and Smirnov proved similar, independent results at about the same time, so now the result is referred to as the Bing-Nagata-Smirnov metrization theorem. That 1951 paper of Bing's has probably been referred to in more papers than any other of his papers, even though he later was identified with an altogether different branch of topology. Bing's paper enfolds in a manner consistent with an important strategy he practiced in doing mathematics. He always explored the limits of any theorem he proposed to prove or understand. Consequently, he would habitually construct counterexamples to demonstrate the necessity of each hypothesis of a theorem. In this paper Bing proved theorems numbered 1 to 14 interspersed with examples labeled A through H. The impact of this paper came both from his theorems and from his counterexamples. Bing's metrization theorems describe spaces with bases formed from countable collections of coverings or spaces where open covers have refinements consisting of countable collections of sets. He defined and discussed screenable spaces, strongly screenable spaces, and perfectly screenable spaces—terms that have been largely replaced by new terminology. He proved in this paper that regular spaces are metrizable if and only if they are perfectly screenable. (The term perfectly screenable means that the space has an ω_0-discrete basis.)

His metrization theorems hinged strongly on his understanding of a strong form of normality, and certainly one of the legacies of this paper is his definition of and initial exploration of collectionwise normality. This paper contains the theorem that a Moore space is metrizable if and only if it is collectionwise normal. After identifying this important property of collectionwise normality he explored its limits by constructing an example of a normal space that is not collectionwise normal. Bing was known for his imaginative naming of spaces and concepts, but this example enjoys its enduring fame under the mundane moniker of "Example G." Immediately following his description of Example G, Bing included the following paragraph that formed the basis of countless hours of future mathematicians' labors:

> One might wonder if Example G could be modified so as to obtain a normal developable space which is not metrizable. A developable space could be obtained by introducing more neighborhoods into the space [Example G]. However a difficulty might arise in introducing enough neighborhoods to make the resulting space developable but not enough to make it collectionwise normal.

Nowadays if you refer to Bing-type topology, you are referring to a certain style of geometric analysis of Euclidean 3-space that came to be associated with Bing because of the fundamental work he did in the area and the distinctive style with which he approached it. The first paper Bing wrote in this area was titled "A Homeomorphism Between the 3-Sphere and the Sum of Two Solid Horned Spheres" and appeared in the *Annals of Mathematics* in 1952. It contains one of Bing's best-known results, namely that there are wild involutions of the 3-sphere, that is, it is possible to reflect 3-space through a mirror that is not topologically embedded in the same manner as a flat plane. The result in this paper hinges on a method of shrinking geometric objects in unexpected ways. When Bing first worked on the question considered in this 1952 paper, he naturally did not know whether it was true or false. He claimed that he worked two hours trying to prove it was true, then two hours trying to prove it was false. When he originally worked on this problem, he used collections of rubber bands tangled together in a certain fashion to help him visualize the problem. The mathematics that Bing did is abstract, but he claimed to get ideas about these abstruse problems from everyday objects.

A final note about this problem involves a paper that Bing wrote in 1984 containing one of his last results. If one shrinks the rubber bands in the manner described in Bing's 1952 paper, each rubber band becomes small in diameter but very long. It became interesting to know whether one could do a similar shrinking without lengthening the bands—in other words, could you do the same thing with string as Bing had proved could be done with rubber. Bing's original procedure had been studied by numerous graduate students and research mathematicians for more than 30 years and yet no one had been able to significantly improve Bing's shrinking method. It was left for Bing himself to prove that "Shrinking Without Lengthening" (the title of this final paper) (1988) is possible.

Bing's results in topology grew in number and quality. He proved several landmark theorems and then raised lots of related questions. Because of his habit of raising questions many other mathematicians and students were able to prove good theorems in the areas of mathematics that he pioneered. He emphasized the importance of raising questions in one's papers and encouraged his students and colleagues to do so. He felt that mathematicians who read a paper are often more interested in what remains unknown than they are interested in what has been proved.

The period from 1950 until the mid-1960s was Bing's most productive period of research. He published about 115 papers in his lifetime, most during this period at the University of Wisconsin, Madison. In 1957 alone three of his papers appeared in the *Annals of Mathematics*. These papers concerned decompositions of Euclidean 3-space and the theorem that surfaces embedded in Euclidean 3-space can be approximated by polyhedral surfaces. Later, that result was extended to show that the polyhedral approximation can be constructed to lie "mostly" on one side of the surface being approximated (1963). In a 1958 *Annals* paper he proved that a compact 3-manifold is homeomorphic to S^3 if and only if every simple closed curve is contained in a ball. This theorem was a partial result in an attempt to settle the still unresolved Poincaré conjecture in dimension 3. In the next year the *Annals* published his independent proof of the theorem that 3-manifolds can be triangulated (1959), a result that had recently been proved in a more complicated way by Edwin Moise.

These theorems and many others he proved about tame and wild surfaces in Euclidean 3-space developed the foundations of the investigation of the geometric topology of 3-space. Bing stated and proved basic facts about 3-space and how surfaces can lie in it. He proved that a surface is tame if it can be approximated entirely from the side (1959). He proved that every surface in 3-space contains tame arcs (1962) and every surface in 3-space can be pierced by a tame arc (1962).

Along the way Bing produced many intriguing examples, many with memorable nicknames: "The Bing Sling"—a simple closed curve that pierces no disk (1956); "Bing's Sticky Foot Topology"—a connected countable Hausdorff space (1953); "Bing's Hooked Rug"—a wild 2-sphere in 3-space that contains no wild arc (1961). These examples helped show the limits of what is true.

His research success brought him honors, awards, and responsibilities. He was quickly promoted through the ranks at the University of Wisconsin, becoming a Rudolph E. Langer Research Professor there in 1964. He was a visiting lecturer of the Mathematical Association of America (1952-53, 1961-62) and the Hedrick lecturer for the Mathematical Association of America (1961). He was chairman of the Wisconsin Mathematics Department from 1958 to 1960, but administrative work was not his favorite. He was president of the Mathematical Association of America (1963-64).

In 1965 he was elected to membership in the National Academy of Sciences. He was chairman of the Conference Board of Mathematical Sciences (1966-67) and a U.S. delegate to the International Mathematical Union (1966, 1978). He was on the President's Committee on the National Medal of Science (1966-67, 1974-76), chairman of the Division of Mathematics of the National Research Council (1967-69), member of the National Science Board (1968-75), chairman of the Mathematics Section of the National Academy of Sciences (1970-73), on the Council of the National Academy of Sciences (1977-80), and on the Governing Board of the National Research Council (1977-80). He was a colloquium lecturer of the American Mathematical Society in 1970. In 1974 he received the Distinguished Service to Mathematics Award from the Mathematical Association of America. He was president of the American Mathematical Society in 1977-78. He retired from the University of Texas at Austin in 1985 as the Mildred Caldwell and Blaine Perkins Kerr Centennial Professor in Mathematics. He received many other honors and served in many other responsible positions throughout his career. He lectured in more than 200 colleges and universities in 49 states and in 17 foreign countries.

Bing believed that mathematics should be fun. He was opposed to the idea of forcing students to endure mathematical lectures that they did not understand or enjoy. He liked to work mathematics out for himself and thought that students should be given the opportunity to work problems and prove theorems for themselves. During his years in Wisconsin Bing directed a very effective training program for future topologists. The first-year graduate topology class, which he often taught there, would sometimes number 40 or more students. He directed the Ph.D. dissertations of 35 students and influenced many others during participation in seminars and research discussions.

Bing enjoyed teaching and felt that experiments in teaching were usually successful—not because the new method was necessarily better but because doing an experiment showed an interest in the students, which they appreciated and responded to. Here are a couple of the experiments he tried while teaching at UT. Bing thought that a person who could solve a problem quickly deserved more credit than a person who solved it slowly. He would say that an employer would rather have an employee who could solve two problems in as much time as it took for someone else to solve one. So in some of his undergraduate classes he introduced speed points. For a 50-minute test he gave an extra point for each minute the test was submitted early. He noticed that often the people who did the work the quickest also were the most accurate. Speed points were somewhat popular and sometimes he would let the class vote on whether speed points would be used on a test. Another experiment in test giving was not popular. One day Bing prepared a calculus test that he realized was too long. Instead of deleting some questions, however, he decided to go ahead and give the test, but as he phrased it, "Let everyone dance to the tune of their own drummer." That is, each person could do as many or as few of the problems as he or she wished and would be graded on the accuracy of the problems submitted. The class was quite angry when the highest score was obtained by a person who had attempted only one problem.

In the 1971-72 school year Bing accepted an offer to visit the Department of Mathematics at the University of Texas at Austin. In 1973 the mathematics department persuaded Bing to accept a permanent position at UT. Bing believed that part of the fun of life was to take on a variety of challenges. When he accepted the position at UT, he came with the idea of building the mathematics department into one of the top 10 state university mathematics departments in the country. While he was at Texas from 1973 until his death in 1986, he helped to improve the research standing of the department by recruiting new faculty and by helping to change the attitudes and orientation of the existing faculty. Raising research standards was the watchword of that period and is the guiding principle for the mathematics department now. Bing was chairman of the department from 1975 to 1977, but he used his international prominence for recruiting purposes throughout his stay at UT. The Department of Mathematics was considered one of the most improved departments over the period of Bing's tenure. The 1983 report of the Conference Board of Associated Research Councils listed Texas as the second most improved mathematics department in research standing during the period 1977-82, ranking it number 14 among state university mathematics departments at that time. The strategy of research improvement has continued in the UT

Department of Mathematics through the present day, and Bing would certainly be proud to see the department's continued improvement in its research stature.

Bing accomplished much during his life and left us with many ideas, personal and mathematical, to consider and enjoy. He left topologists a treasure-trove of theorems and techniques and left the UT Department of Mathematics with a goal and 13 years of good progress toward it. He was a man of strong character and integrity who liked to understand things for himself. For example, he never claimed to understand a theorem unless he personally knew a proof of it. He made decisions based on his own experience, relying on his independent judgment of a person or a cause whenever possible rather than averaging the opinions of others. He was a kind man and respected people for their own merits rather than measuring them on a single scale.

R. H. Bing died on April 28, 1986. He suffered from cancer and heart trouble during his last years, but he never complained about his health problems nor did he allow discomfort to dampen his enthusiasm and good spirits. He was an exemplary person. His friends, his family, his students, and the mathematical community have been enriched beyond bound by his character, his wisdom, and his unfailing good cheer, and continue to be enriched by his memory.

SELECTED BIBLIOGRAPHY

1946

Concerning simple plane webs. *Trans. Am. Math. Soc.* 60:133-48.

The Kline sphere characterization problem. *Bull. Am. Math. Soc.* 52:644-53.

1948

A homogeneous indecomposable plane continuum. *Duke Math. J.* 15:729-42.

1951

Metrization of topological spaces. *Canad. J. Math.* 3:175-86.

1952

A homeomorphism between the 3-sphere and the sum of two solid horned spheres. *Ann. Math.* 56:354-62.

1953

A connected countable Hausdorff space. *Proc. Am. Math. Soc.* 4:474.

1954

Locally tame sets are tame. *Ann. Math.* 59:145-58.

1956

A simple closed curve that pierces no disk. *J. Math. Pures Appl.* 35:337-43.

1957

Upper semicontinuous decompositions of E^3. *Ann. Math.* 65:363-74.

A decomposition of E^3 into points and tame arcs such that the decomposition space is topologically different from E^3. *Ann. Math.* 65:484-500.

Approximating surfaces with polyhedral ones. *Ann. Math.* 65:456-83.

1958

Necessary and sufficient conditions that a 3-manifold be S^3. *Ann. Math.* 68:17-37. (See also correction, *Ann. Math.* 77(1963):210.)

1959

An alternative proof that 3-manifolds can be triangulated. *Ann. Math.* 69:37-65.

Conditions under which a surface in E^3 is tame. *Fund. Math.* 47:105-39.

The Cartesian product of a certain nonmanifold and a line is E^4. *Ann. Math.* 70:399-412.

1961

A wild surface each of whose arcs is tame. *Duke Math. J.* 28:1-15.

A surface is tame if its complement is 1-ULC. *Trans. Am. Math. Soc.* 101:294-305.

1962

Each disk in E^3 contains a tame arc. *Am. J. Math.* 84:583-90.

Each disk in E^3 is pierced by a tame arc. *Am. J. Math.* 84:591-99.

1963

Approximating surfaces from the side. *Ann. Math.* 77:145-92.

1964

Inequivalent families of periodic homeomorphisms of E^3. *Ann. of Math.* 80:78-93.

1965

With K. Borsuk. Some remarks concerning topologically homogeneous spaces. *Ann. Math.* 81:100-111.

1968

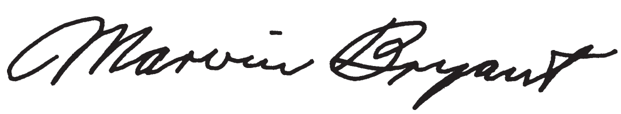
With R. D. Anderson. A complete elementary proof that Hilbert space is homeomorphic to the countable infinite product of lines. *Bull. Am. Math. Soc.* 74:771-92.

1983

The Geometric Topology of 3-Manifolds. Coll. Pub. Vol. 40. Providence, R.I: American Mathematical Society.

1988

Shrinking without lengthening. *Topology* 27(4):487-93.



MARVIN P. BRYANT

July 4, 1925–October 16, 2000

BY ARNOLD L. DEMAIN AND RALPH F. WOLFE

MARVIN P. BRYANT, EMERITUS professor of microbiology at the University of Illinois, died on October 16, 2000, at his home in Savoy. Illinois, at the age of 75. Marv was born on July 4, 1925, to Melvin Berry and Emna Louise Bucklin Bryant. He was raised on the edge of the foothills in Boise, Idaho, with summer and fall excursions to the family ranch next to the primitive area of the Middlefork of the Salmon River. The environment provided by the area, especially the associations with horses and various ruminants, the freedom and support he received from his parents, and his natural inclination toward biology directed him toward his then unknown goal of doing research in rumen microbiology.

After serving in the U.S. Air Corps during World War II he vowed in 1945 that he would never leave the mountain area, and he completed his diploma at Boise Junior College. In 1946 Marv married Margaret Amelia Betebenna. He started in forestry and switched to soils. Counseling by botany professor Donald Obee moved him into bacteriology and propelled him toward Washington State College in Pullman. According to Marv, his reticence to meet the public and his belief that research and publications alone would largely satisfy his goals helped to move him toward a career in research.

THE PULLMAN YEARS

In three short years, the general theme of his life's work was set. As a new student with junior standing and with a wife and three-month-old daughter to support, he needed to supplement his GI Bill funds with part-time labor. His first official contact was with Professor Robert E. Hungate, the father of rumen microbiology research and anaerobic microbiology. Hungate was a scientific descendent of the Delft school of microbiology (Biejerinck → Kluyver → van Niel) and was the latter's first American Ph.D. student. Marv started working in Hungate's lab as the glassware washer during the daytime and was later switched to lab work, expediting the research of Hungate and of his Ph.D. student, R. H. McBee. This work was a revelation and better than any possible formal course. The poor funding of research outside of agriculture in this early postwar period made it necessary for Hungate and McBee to make essentially all of their glass apparatus by hand from such materials as Pyrex culture tubes, Erlenmeyer flasks, Kjeldahl flasks, glass tubing, and assorted salvage. Among the things "manufactured" were a complete Warburg apparatus, micro-modification of the Newcomer-Haldane constant pressure volumetric gas analyzer, all condensers, and various units required for the determination of lactate and volatile fatty acids when chromatographic and enzymatic methods were just beginning to evolve.

Among Marv's duties were maintenance of a few stock cultures including the important thermophilic cellulolytic species, *Clostridium thermocellum*; determination of fermentation end products and fermentation balances of various anaerobic species; enumeration and isolation of anaerobic soil cellulolytic bacteria, *Ruminococcus albus*; and the first isolation of the "less actively cellulolytic rod" later named *Butyrivibrio fibrisolvens.* In association with the General Electric Research Laboratory in Schenectady, N.Y., Hungate outlined experiments in which Marv did in vitro rumen fermentations of wood treated with cathode rays. Results showed that the cellulosic fraction of wood was released from lignin and made available to anaerobic microbial digestion and volatile acid production, while the lignin remained indigestible at certain radiation dosages.

In June of 1949 he received his B.S. degree, and Hungate, having acquired funds for research from state liquor tax money, placed Marv on a half-time research assistantship at a salary of about $1,500 a year. His research involved the isolation and characterization of the small rumen spirochete of the genus *Treponema*, which could move through agar or particulate forage and compete with cellulolytic bacteria for use of the soluble sugar energy sources produced by the latter from cellulose. The report of his research was the first published work on fermentation products of a spirochete and suggested strong metabolic interactions between cellulolytic and noncellulolytic fermentative bacteria in anaerobic ecosystems, a finding that only later received extensive documentation. Electron micrographs of the aging cells taken with the aid of a physics graduate student showed the periplasmic membrane and fibrils and protoplasmic cylinder of spirochetes, but these were not recognized until much later.

Because Marv wanted to continue on to his Ph.D. at Pullman and Hungate believed that he needed more interactions with course work and research in another area of the country, Marv continued his assistantship through Washington State College for an eight-month period in 1949 at Cornell University. During this period he took course work in animal nutrition, bacterial metabolism, industrial microbiology, and bacterial cytology. He also had a large number of associations with other professors and students in both veterinary medicine and bacteriology. These included H. H. Dukes, professor of veterinary physiology; James M. Sherman, professor of bacteriology and long-time editor of the *Journal of Bacteriology;* and Meyer J. ("Mike") Wolin, then an undergraduate student. Marv's research was conducted in association with Professor Robert Dougherty on the microbiology and physiology of acute indigestion, lacticacidosis, in sheep. *Streptococcus bovis* was found to be the initiator of high rumen lactate and was often followed by members of the genus *Lactobacillus.*

During his stay in Ithaca, Professor William Pounden of Ohio State University visited and carried word to Beltsville Agricultural Research Center that Hungate had a graduate student working in rumen microbiology. A research bacteriology position was offered by the Bureau of Dairy Industry and, after a strong push from Hungate, Marv decided to accept.

THE BELTSVILLE YEARS

Having received his M.S. degree in 1950 from Washington State College, Marv was concerned about completing his Ph.D. degree and this was made possible at his own expense and time by Lane A. Moore, head of the dairy cattle nutrition group at Beltsville, and Professor Raymond Doetsch, Department of Microbiology, University of Maryland, College Park, just a short distance from Beltsville. He was allowed to take one course per semester at College Park and his thesis research was completed while still working at Beltsville. He received his Ph.D. degree from the University of Maryland in 1955.

Marv's faith in his ability to adequately advance basic knowledge on rumen microbiology was very low, and during the first few years at Beltsville he very much missed Hungate's guidance. He was given essentially complete freedom to work within the huge area of rumen microbiology by Moore, who was an outstanding nutrition expert and research administrator, but who could offer essentially no guidance in microbiology. Marv's main goals were to taxonomically describe, with emphasis on ecologically important metabolic features, the numerous species of rumen bacteria and to chemically identify "unusual" growth factors present in rumen fluid but not in most organically rich growth media. Hungate had worked mainly with pure cultures of the cellulolytic population and his development of classic anaerobic techniques and habitat-stimulating growth media had largely removed the blocks confronting further advances in isolation and description of rumen bacteria. However, Hungate was already beginning to feel that kinetic studies of major overall rumen biochemical reactions were more important to his research effort. In addition, Doetsch was formulating the idea that the "physiological" approach using washed suspensions of mixed rumen microorganisms would probably yield the most fruitful results in the future. There were thus major currents against Marv's emphasis on pure culture studies, but he continued this emphasis with apprehension.

During Marv's early research, the general field of anaerobic bacteriology remained in a chaotic state because of a general lack of knowledge about anaerobic bacteria, the failure of most workers to determine catabolic products of energy metabolism, and the inability of most microbiologists to grow and isolate the relevant species. Techniques such as determination of taxonomically important cellular constituents, percent guanine plus cytosine in the DNA, and DNA-DNA hybridization were for the most part yet to be developed. Even with the development of these methods and various others, many problems of relatedness among major microbial taxonomic groups still existed. When his work at Beltsville was initiated, the only rumen anaerobes that had been studied and named with enough detail for other workers to identify were the cellulolytic species, *Bacteroides succinogenes* by Hungate and *Ruminococcus flavefaciens* by Sijpesteijn. Hungate had published on various *Ruminococcus* species and *B. succinogenes* earlier but had not named them, and Sijpesteijn's work at Delft had been delayed for several years by the German invasion of Holland. Marv's first concern was to develop and evaluate methods for enumerating and isolating the more numerous bacterial species. The anaerobic roll-tube methods of Hungate were somewhat modified for larger scale studies. The 40 percent rumen fluid-glucose-cellulose agar roll tube (RGCA) medium with CO_2 gas phase, bicarbonate as the main buffer, and cysteine as added reducing agent was a slight modification of Hungate's selective cellulose agar medium and allowed the isolation of most of the predominant carbohydrate fermenting species. Traces of O_2 were removed from the commercial gases that were passed through a glass column containing hot copper filings. This column turned dark as the copper oxidized and could be quickly reduced by exposure to H_2. A balanced mineral anaerobic solution similar to the growth medium, but with rumen fluid and sugar energy sources removed, served as the rumen fluid diluent. Large numbers of bacterial strains were rapidly isolated by picking colonies from large-diameter (18 mm) roll tubes with platinum-iridium inoculating needles and stabbing them into deep slants containing a reduced amount of agar. The main concentration of cells in the water of syneresis and in the top part of the agar at the base of the slant allowed even small colonies of the more fastidious anaerobes to grow. It also provided an excellent menstrum for preparing wet mounts for study of cell morphology and motility with the phase-contrast microscope. Marv used various modifications for studying anaerobic bacteria as diverse as methanogens, photosynthetic bacteria, sulfate reducers, human GI tract anaerobes, and those of medical concern.

A large number of bacterial strains were first isolated and enumerated from dairy cattle fed diverse diets, such as hay, hay-concentrate, and forage-crop silage. These strains were studied for morphology and a few physiological features and were placed in tentative groups. Selected strains were then placed in a dry-ice cabinet so that live cultures could be maintained for detailed biochemical and nutritional studies. Unlike Hungate, Marv firmly believed that one of his most important functions was maintaining the culture collection of rumen anaerobes, many of which were later well documented as important in anaerobic degradation, and making them available to other researchers around the world. With the continuity of support at Beltsville and later at the University of Illinois he was able to continue this function. For about 20 years his group was the main and often the only source of many rumen anaerobes.

Among the important bacteria described in detail were many cellulolytic strains of *B. succinogenes*, which until detailed studies were done seemed morphologically quite different from Hungate's strains. Marv later showed that this species degraded highly resistant crystalline cellulose much faster than other known mesophilic anaerobic cellulolytic bacteria. Large numbers of cellulolytic strains of *Ruminococcus albus* and *R. flavefaciens* were studied and the work also emphasized the importance of these in xylan fermentation and the importance of ethanol formation in *R. albus* versus succinate formation in *R. flavefaciens*. The genus *Butyrivibrio* was named and great versatility in production of CO_2, lactate, and butyrate and in fermentation of important carbohydrates was found, as well as considerable variation between strains. Only a few strains fermented cellulose, but most fermented xylan, starch, pectin, and many other carbohydrates. Later work at Illinois in association with Jones, Cheng, and Simpson from Canada showed that some strains fermented important plant flavonoids. This work represented the first pure culture demonstration of anaerobic degradation of the aromatic heterocyclic ring structure.

Bacteroides ruminicola, one of the most numerous and versatile of rumen bacteria, was isolated and described. This succinate and acetate-producing species fermented complex carbohydrates including various pentosans, pectin, and starch, as well as many sugars. It was actively proteolytic and could convert amino acids, derived from peptides transported into the cell, into ammonia, CO_2, and various straight- and branched-chain volatile fatty acids.

Selenomonas ruminantium had been observed microscopically in rumen contents as early as 1889 because of its unique morphology and relatively large size and was obtained in pure culture but not recognized by Huhtanen and Gall in 1953. Marv isolated and identified this important rumen species, which produced various amounts of propionate, acetate, lactate, and CO_2 from many different sugars and starch and also degraded a number of amino acids. The subspecies *lactilytica* fermented important energy sources such as lactic acid and glycerol. *S. ruminantium* became one of the organisms most used by workers at Illinois and elsewhere in rumen microbiological studies. For example, Marv used it to examine various interactions between species, the effect of factors such as growth rate on the types of fermentation products, the various enzyme systems involved in ammonia assimilation, and regulation of urease production. A number of additional new species and often new genera involved in various rumen reactions were also described. These included the butyrate-forming *Eubacterium cellulosolvens*, pectin-fermenting *Lachnospira multiparus*, xylan-fermenting *Eubacterium ruminantium*, and the succinate- and acetate-forming *Succinivibrio dextrinosolvens* and *Succinimonas amylolytica*.

Rumen flora developing in young calves were studied concurrently with the detailed investigations of bacteria from mature animals. The studies of the flora of young calves gave Marv further insight into the diversity of anaerobic bacteria and the difficulty of identifying well-studied strains from previously published descriptions, which were still very poor in 1958. Most of the large number of anaerobes in calves one to three weeks old differed substantially from those in mature animals and Marv decided not to name them. However, it became possible to identify most representative strains, partly because of the efforts of W. E. C. Moore and his colleagues at the Anaerobe Laboratory of Virginia Polytechnic Institute. One of the most important strains that Marv identified in young calves was *Fusobacterium necrophorum*. Although long known as a pathogen and major cause of liver abscesses in cattle, it was not known as a major normal organism fermenting lactate, amino acids, and sugars and producing butyrate and other acids in young calves. Another important strain was *Clostridium clostridiiforme*, an organism whose spores were very hard to detect. It had been found in several pathologic processes and as a normal poultry intestinal isolate but had not been previously found in the rumen.

Marv's group, as well as workers in Scotland, discovered the long form of *Lactobacillus vitulinus* in young calves. This organism obviously differed from the short form found in older calves and adult ruminants. Both Marv and the Scottish workers also described the lactate-fermenting, amino-acid-catabolizing *Megasphaera elsdenii* that had been studied in detail by Elsden and Lewis in 1953. In addition, the lactate-fermenting *Eubacterium limosum* (*Butyribacterium rettgeri*) was detected in the rumen for the first time. This organism was of interest because of its ability to produce butyrate and longer-chain volatile fatty acids from one-carbon compounds such as methanol or H_2-CO_2.

The studies of pure cultures of functional rumen bacteria disclosed large numbers of species that produced such products as lactate and ethanol, which were not normal products or important extracellular intermediates in the rumen fermentation. Some microbiologists believed, because these "artifacts" occurred, that the pure cultures were not worth studying. However, Marv's view was that judicious studies of pure cultures and known mixtures were valuable because they would yield important facts about the environmental factors causing the abnormalities that would be impossible to find with studies on the total fermentation. These facts in turn would lead toward better knowledge about regulation of the rumen fermentation. Later work at Illinois and elsewhere strongly supported Marv's view.

After initiating the studies on numbers and kinds of rumen bacteria, Marv was joined by Nola Small, an outstanding technical assistant. As a result, he had time to do detailed studies on the nutrition of pure cultures. Hungate's studies had shown that a number of rumen cellulolytic species required unknown growth factors that were present in rumen fluid but not in rich sources of vitamins and other growth factors such as liver or yeast extract. Marv found that the factor required by *B. succinogenes* had two components. A straight-chain saturated fatty acid, *n*-valerate, or longer-chain acids satisfied one component, and a branched-chain acid such as D-2-methyl-*n*-butyrate or iso-butyrate satisfied the other one. This was the first indication that some anaerobic bacteria required acids produced by other rumen microbes from certain amino acids and, in the case of *n*-valerate, also from carbohydrates. Finding these factors allowed Marv to establish a chemically defined minimal medium for *B. succinogenes*. This was the first formulation of such a medium for an important rumen anaerobic bacterium. Another first was a discovery that had never before been made for a nonmarine bacterium: *B. succinogenes* required a large amount of sodium ion for growth. Later studies by Don Caldwell at the University of Wyoming showed that many other rumen anaerobes were moderate halophiles (i.e., they required moderate amounts of sodium ion for growth). Thus, the rumen had some features of an inland sea.

Marv's first professional colleague, Milton Allison, joined him in 1957 and was put to work on the unknown nutrient requirements of the cellulolytic genus *Ruminococcus*. They found that many ruminococci required one or more of the branched-chain fatty acids isovalerate, isobutyrate, and 2-methyl-*n*-butyrate for growth. Detailed studies of a strain of *R. flavefaciens* using position-labeled ^{14}C-isovalerate established that these acids were needed for (1) certain amino acid biosyntheses via previously unknown reductive carboxylation reactions and (2) biosynthesis of cellular lipids (long, branched-chain fatty acids and aldehydes). These studies were the first of a series from Marv's lab showing that many rumen bacteria, other heterotrophic bacteria, and most methanogenic anaerobic bacteria had a very limited ability to utilize organic nitrogen sources such as amino acids or peptides. Instead, they utilized ammonia as the essential and major nitrogen source and utilized CO_2 and various volatile fatty acids, such as acetate and those indicated above, as major sources of carbon but not of energy. The concept was advanced that the rumen environment, being quite low in soluble organic nitrogen and being high in ammonia, CO_2, and volatile fatty acids, had evolved and selected many bacterial species that utilize these materials for amino acid and lipid biosynthesis, and that these bacteria had lost or never gained the ability to utilize many preformed amino acids or to biosynthesize all the carbon skeletons of some amino acids. The work with Allison on the ability of *Ruminococcus* to convert ^{14}C volatile fatty acids into lipid was done in association with Professor Mark Keeney and Ira Katz of the University of Maryland. The results showed for the first time that rumen bacteria contain a large amount of *iso* and *anteso* long branched-chain fatty acids, as well as considerable long-chain aldehydes, which were shown to be present in the plasmalogen class of lipids of the cellular phospholipids. This was the first demonstration of plasmalogens in bacteria and led to the concept that many of the branched-chain and odd-numbered carbon fatty acids of ruminant milk and body fat were biosynthesized by bacteria in the rumen. Use of the then rapidly developing methodology for chromatographic separation of lipids and fatty acids was essential in these studies.

Further studies in association with another technical assistant, Isadore M. ("Ike") Robinson, established that most functional rumen bacteria could be grown in relatively simple chemically defined culture media. Many species used ammonia, rather than free amino acids or peptides, as the major and essential source of nitrogen, and all species were able to utilize ammonia as their main nitrogen source. However, a very significant number preferred a complex mixture of exogenous free amino acids. One major species, *B. ruminicola*, was found to require heme, which was shown to be biosynthesized by many other rumen bacteria. While

B. ruminicola strongly preferred ammonia to free amino acid nitrogen and carbon, it took up little ammonia when peptides were available as nitrogen sources. Further studies with Ken Pittman showed that this species transported and utilized oligopeptides very effectively as nitrogen and carbon sources for growth. However, it was ineffective in utilizing free amino acids or dipeptides as compared to ammonia or the preferred oligopeptides. These results emphasized the importance of peptides in the nitrogen economy of the rumen. Some strains of diverse bacterial species had proteolytic ability. Marv's work with Howard Bladen showed that among predominant bacteria from mature animals, only a few species, such as *S. ruminantium*, *M. elsdenii*, and *B. ruminicola*, could catabolize amino acids or peptides to ammonia and volatile fatty acids.

Marv's nutritional studies laid the foundation for development with D. R. Caldwell of a growth medium in which rumen fluid could be replaced by better standardized ingredients for enumeration and study of most rumen bacteria and of many bacteria from other anaerobic microbial ecosystems. With Caldwell, studies were initiated to determine the specificity of the heme requirement of *B. ruminicola*. David White of the Rockefeller Institute was an expert in using difference spectra and other techniques for analyses of cytochromes of aerobic bacteria. Taking Marv's anaerobic culture media and other culture paraphernalia to Rockefeller, Marv and David began a search for cytochromes as the possible reason for the heme requirement of *B. ruminicola*, though cytochromes were then not known to be functional in fermentative anaerobic organisms. They found that *B. ruminicola* contained a b-type cytochrome involved in electron transport for fumarate reduction to succinate by reduced pyridine nucleotide generated in glycolysis during the CO_2-dependent fermentation of carbohydrate. This was the first experimental evidence suggesting that cytochrome-linked electron transport was involved in energy transformations needed for growth of strictly anaerobic fermentative bacteria.

Because of the difficulty of isolating methane-producing bacteria, these organisms had received little attention until the 1950s, when Hungate emphasized the importance of their ability to utilize the H_2 produced by fermentative bacteria. The H_2 reduced CO_2 to form methane as the source of energy for the organisms' growth. Hungate and P. H. Smith isolated and described the major H_2-using methanogen of the rumen *Methanobrevibacter ruminantium* in 1958, and indicated that it needed unknown factors in rumen fluid for growth. At that time, they were not interested in further studies on the nutrition of this species. Thus, Ike Robinson and Marv, being interested in the nutrition of rumen organisms, isolated the methanogen using the techniques previously developed but with hydrogen gas replacing sugars as the energy sources. They confirmed the numerical importance of *M. ruminantium* and its need for unknown growth factors in rumen fluid. The growth assays used to determine nutrient requirements were very tedious, and studies were also complicated by the number of different "rumen fluid" factors required. They found three different rumen fluid factors. One was 2-methyl-*n*-butyrate. The second was acetate, subsequently shown by AI Joyner, a postdoctoral student all Illinois, to be the exogenous source of 60 to 70 percent of the cell carbon in this bacterium. This held even when the growth medium contained large amounts of preformed cell monomers such as amino acids and peptides, which heterotrophic bacteria usually prefer as carbon and nitrogen sources. This discovery, together with Marv's demonstration that ammonia was essential as the main source of nitrogen, showed that this H_2-CO_2-using chemolithotrophic organism resembled the major cellulolytic and some other rumen fermentative bacteria in certain major nutritional features. Because of his work at Illinois and later efforts of several other laboratories, it is now known that all species of methanogens so far studied require ammonia as the main nitrogen source and that acetate is often a preferred major source of cell carbon. The third rumen fluid factor required by *M. ruminantium* was shown by Robinson and Marv to be a quite strong acid that was much more polar than the two fatty acid factors. It could not be separated from rumen fluid by acid ether extraction, but could be separated from the residue of ether-extracted rumen fluid into two components by anion exchange resin chromatography. It was a highly stable organic compound with a low molecular weight and was mainly but loosely associated with rumen microbial cells rather that the fluids. They could not detect it in many other crude or defined materials they used to grow nutritionally exacting bacteria.

In 1963 Marv was invited to the Third Rudolfs Conference at Rutgers University to give a paper on "Bacteriology of the Rumen" under the theme "Principles and Applications in Aquatic Microbiology." At Beltsville he was somewhat isolated from researchers involved in major areas other than rumen microbiology, and this conference provided the setting for him to meet a large number of scientists who had distinguished careers in related areas. Marv later identified Perry McCarty, a sanitary engineer at MIT and Stanford University working on kinetics and physiological factors in sewage sludge methanogensis, and Ralph Wolfe, Department of Microbiology, University of Illinois, as two that greatly influenced the direction of his future research. Early in 1964 he was invited to give guest lectures in Wolfe's course, Microbiology 309, and in the Department of Dairy Science seminar, and negotiations began concerning a possible move to the University of Illinois. The prospect of being closely associated with good basic microbiological research such as that in the laboratories of Meyer ("Mike") J. Wolin and Wolfe, the anticipated interaction with excellent ruminant nutritionists such as Dick Brown and Carl Davis, and the interest and encouragement of Glenn Salisbury, then head of the department, M. B. Russell, director of the Experiment Station, and other department members, such as Harry Broquist, were too much for Marv to resist. In addition, Urbana was 800 miles closer to Idaho. His tenure at Beltsville had been very pleasant and he had exceedingly good relationships with many excellent ruminant nutritionists including Lane Moore, Bill Flatt, Peter van Soest, and Dale Waldo. However, the lack of interaction with more basic areas of microbiology and the inability to obtain research grants from other government agencies (due to USDA restrictions) or funds for a number of needed but expensive scientific instruments were among the reasons that Marv gave for leaving Beltsville after 13 years.

UNIVERSITY OF ILLINOIS

In 1964 Marv moved with his family to Illinois to be professor of microbiology in the Department of Dairy Science and Microbiology. He brought in the culture collections, continued work on the nutrition of methanogens, and initiated various other projects. His expertise in growing methanogens on hydrogen gas and CO_2 turned out to be crucial to many of the advances made in the Dairy Science Microbiology Division labs in collaboration with Wolin and in the laboratory of Wolfe in the Department of Microbiology.

After his move to Illinois, work on the unknown factor required by *M. ruminantium* was continued for several years with research associate Olga Nalbandov and technician Kenneth Holmer. They finally obtained enough relatively pure factor from 5 liters of rumen fluid to grow more than 20 liters of the methanogen using various extractions, absorption, and column chromatographic methods. However, the dry weight of the factor was too small and they failed to get enough material to determine chemical structure. Through the late 1960s and into the 1970s Wolfe's graduate students Barry McBride and later Craig Taylor were working on isolation and chemical characterization of a new coenzyme that was found in most methanogens and was required for methyl transfer reactions in the terminal stage of intracellular methane formation. The coenzyme seemed to be identical with the highly polar growth factor that was required by *M. ruminantium* and that Marv had isolated from rumen contents though not in large enough amounts for chemical characterization. In early 1974 McBride and Taylor characterized coenzyme M as 2-mercaptoethanesulfonic acid, chemically synthesized it, and gave Marv some to test as the growth factor required by *M. ruminantium*. The tests showed conclusively that the coenzyme was indeed the elusive growth factor. Only 3 to 5 nanograms of the coenzyme per ml of medium were required for half-maximal growth.

During the same period Marv's graduate student Sin-Fu Tseng worked out another enzymatic assay of *M. ruminantium*. His purpose was to determine the coenzyme(s) involved in electron transport during H_2 oxidation and the pyridine nucleotide reduction involved in the organism's energy metabolism and methane production. An unknown factor, apparently different from ferredoxin (often functional in anaerobes), was found to be involved. Previous workers in Wolfe's laboratory had isolated a chemically unknown compound with a relatively low molecular weight and with blue-green fluorescence in ultraviolet light and had found large amounts in other methanogens. In cell extracts of various methanogens in the presence of hydrogen the compound lost fluorescence and strong light absorption at 420 nm. The factor was named F (factor) 420 and F_{420} isolated from *Methanobacterium bryantii* was made available to Marv and Tseng. They found that F_{420} was the coenzyme necessary for transfer of electrons generated in H_2-oxidation to pyridine nucleotides in both *M. ruminantium* and *M. bryantii* and also in formate oxidation to CO_2 in the former. It thus became evident that methanogens contain a number of coenzymes different from those in other life forms.

Methanobacillus omelianskii was the methanogen discovered by H. A. Barker in the 1930s and isolated from San Francisco Bay mud in the 1940s. Its energy metabolism involved oxidation of ethanol to acetate with the electrons generated being used to reduce CO_2 to methane. Nongrowing suspensions of cells that had been grown on ethanol-CO_2 were known to use H_2 to reduce CO_2 to methane. Because of its ability to grow on the soluble substrate ethanol, *M. omelianskii* was easier than other methanogens to grow with techniques then in vogue. As a result of biochemically oriented studies in Barker's lab, and especially a collaborative effort starting in about 1960 between Wolfe and the Wolins at Illinois, more became known about the biochemistry of methane formation in *M. omelianskii* than in any other methanogen. When Marv arrived at Illinois, Wolfe had expressed some doubts about the purity of the culture because slightly differing cell shapes were sometimes seen in cultures and he felt that these might represent two species. He suggested that Marv isolate colonies from the ethanol-grown culture by growing them in H_2-CO_2 agar roll tubes using techniques previously used for *M. ruminantium.* To Marv's surprise, colonies grown in large numbers from H_2-CO_2-grown cells and liquid cultures grown in the same manner failed to grow or utilize ethanol when returned to the ethanol medium without hydrogen. The hydrogen-utilizing colonies of methanogens utilized only H_2-CO_2 as energy source. Later work in Wolfe's lab and elsewhere showed that these colonies constituted a new species of methanogen and were present in several ecosystems.

Using ethanol-CO_2 roll tubes without H_2 gas, Marv then isolated a nonmethanogenic ethanol-utilizing species, called "S-organism," from the ethanol-CO_2 culture of *M. omelianskii*. The S-organism produced only tiny colonies and little growth in pure culture and utilized only a very small amount of ethanol while producing acetate and H_2. Study of changes in free energy of the reaction indicated that in pure culture, the accumulation of a very small amount of H_2 would stop the ethanol-utilizing reaction needed for growth. The effective ethanol fermentation could be carried out by recombining the two species isolated *from M. omelianskii* or by combining the ethanol-utilizing S-organism with any H_2-using methanogen. This was the first demonstration of a syntrophic association of two microbial species involving "interspecies H_2 transfer" (a term coined by Wolin). The phenomenon is now known, mainly from the work at Illinois, to be of great importance in anaerobic degradation in the rumen. It is considered even more important in methanogenic ecosystems where more complete anaerobic degradation occurs (e.g., where products such as volatile and longer-chain fatty acids are largely converted to methane and $CO_{2)}$.

C. A. Reddy, having completed his M.S. work showing that several anaerobes of the human gastrointestinal tract and other anaerobes from the rumen contained cytochromes involved in fumarate reduction to succinate, was given the Ph.D. problem of further characterizing the S-organism and the enzymology involved in its production of acetate and H_2 from ethanol. The work showed that the organism had a normal type of ethanol dehydrogenase linked to reduction of pyridine nucleotide and that the reduced pyridine nucleotide was reoxidized by H_2 production via a ferredoxin-linked hydrogenase. The acetaldehyde formed was oxidized to acetate via ferredoxin-linked aldehyde dehydrogenase and hydrogenase. The microbial production of H_2 from low redox potential electrons generated from aldehyde or 2-ketocarboxylic acids such as pyruvate via dehydrogenases linked to ferredoxin-linked hydrogenases had been known for some time. However, the production of H_2 from higher redox potential electrons (reduced pyridine nucleotide) generated from alcohol oxidation or glycolysis was generally believed to be impossible. The work of Reddy and Marv documented that the production of H_2 via these latter reactions was in fact energetically very favorable when H_2 concentration was kept low by means of H_2-using organisms such as methanogens.

Norbert Pfennig from Göttingen, Germany, worked in Marv's lab briefly and showed that S-organisms could be grown fairly effectively on pyruvate in pure culture. Reddy showed that this fermentation involved production of acetate and ethanol, ethanol being the main electron sink product of pyruvate rather than H_2, which was produced in only small amounts. When the S-organism was combined with a methanogen, pyruvate was more rapidly degraded to acetate, CO_2, and hydrogen. The hydrogen did not accumulate because it was used by the methanogen, and little or no ethanol was produced. When co-cultured with the methanogen, the S-organism grew more efficiently, presumably because little energy becomes available for growth when pyruvate is degraded to ethanol whereas pyruvate fermentation to acetate, CO_2, and H_2 provides this energy. This work provided a probable explanation for the fact that many rumen and other bacteria produced ethanol and/or lactate in addition to acetate and H_2 in pure culture where H_2 accumulated but did not usually produce ethanol or lactate in the natural ecosystem, where they were closely associated with H_2-using methanogens or other H_2 utilizers. This idea was confirmed by Marv's work in association with Wolin and his students. In model experiments with *R. albus*, the organism produced more acetate and H_2 and no ethanol when co-cultured with an H_2 utilizer on carbohydrate energy sources.

Later work in Wolin's laboratory and elsewhere provided further evidence that reduced pyridine nucleotide produced in glycolysis by fermentative bacteria could be reoxidized via H_2 production if methanogens use the H_2 efficiently. The efficient use of H_2 allowed the fermentative bacteria to produce larger amounts of H_2 and acetate and smaller amounts of ethanol, lactate, succinate, propionate, and other reduced products of pyruvate. Also other ruminant nutritionists and microbiologists were beginning to realize that although only very small amounts of H_2 accumulated in the fluids of the microbial ecosystem, changes in the level could greatly affect the amount of acetate as compared to propionate and other reduced products of the ecosystem, and therefore influenced the ruminant animal's efficiency in producing milk or meat.

Unlike the carbohydrate-fermenting anaerobes where H_2 concentration affects only relative efficiency of growth and kinds of products produced, the S-organism from *M. omelianskii* could not grow on the natural exogenous substrate ethanol unless the H_2 concentration was maintained at a very low level. That is, the only way to dispose of electrons (reduced pyridine nucleotide) generated in oxidation of ethanol to acetate was via pyridine nucleotide-linked H_2 production. The organism was incapable of producing other electron-sink products. The term "obligate proton reducing (H_2-forming) acetogenic bacteria" was coined in association with Rolf Thauer and Wolfe for this previously unknown metabolic type of bacteria. Wolin hypothesized that other species that would grow anaerobically only in the presence of H_2 utilizers would be found.

Of chief interest to Marv were the bacteria involved in the important beta-oxidation of fatty acids containing even-number carbon atoms to acetate and of odd-number carbon fatty acids to acetate and propionate, and the presumably different species that oxidatively decarboxylate propionate to acetate and CO_2. Quite good documentation already existed that the one- and two-carbon fatty acids, formate and acetate respectively, were degraded by pure species of methanogens producing methane and CO_2. It was generally believed that single species of methanogens carried out the various oxidations of the three-carbon fatty acid, propionate, and longer-chain fatty acids, and disposed of electrons generated via CO_2 reduction to methane. Although several species carrying out these reactions had been named, none had been obtained in pure culture. Marv expected to find additional species that carried out these fatty acid oxidations in obligate syntrophy with H_2-using methanogens. He further expected that because of the change in free energy of the probable reaction involved, these species would require much lower concentrations of H_2 in the environment than even the ethanol degraders.

Studies showed that species of the genus *Desulfovibrio*, which in pure culture grew and degraded lactate or ethanol to acetate only when the electrons generated in the oxidation were used to reduce sulfate to sulfide, could be grown in the absence of the electron acceptor but in syntrophic association with H_2-using methanogens. This established a previously unknown ecological niche for sulfate-reducing bacteria. In further studies done by graduate student Mike McInerney, co-cultures of *Methanosarcina* (an organism that produces methane from both H_2-CO_2 and acetate) and *Desulfovibrio* completely dissimilated lactate or ethanol to methane and CO_2. More important, the degradation of acetate by the *Methanosarcina* was repressed until after the organism had utilized the H_2 that the *Desulfovibrio* produced while dissimilating the primary substrate to acetate. This finding was relevant to understanding the fact that although *Methanosarcina* is present in the rumen, it uses H_2-CO_2 (and probably methanol and methylamines) as energy source in preference to acetate degradation except under adverse conditions of very long rumen retention times and extremely low H_2 levels.

Marv had worked for many years without success to prove via isolation of co-cultures that propionate and longer-chain fatty acids were anaerobically degraded in nature by syntrophic associations of fatty acid oxidizers with H_2 utilizers. Success was finally achieved in 1976, while he was on sabbatical leave with Norbert Pfennig in Germany. The success was due to the use of the fatty acid oxidizers with sulfate-reducing *Desulfovibrio* as the H_2 user in place of *M. ruminantium*, the former apparently having much greater affinity for H_2 than the latter at the slow growth rate necessary for the fatty acid degrader. After the initial success the project was expedited by McInerny. The organism, which was named *Syntrophomonas wolfei*, beta-oxidizes fatty acids producing H_2 and either acetate (from fatty acids with even-numbered carbon atoms) or acetate and propionate (fatty acids with odd-numbered carbon atoms) in obligate syntrophy with H_2-using methanogens such as *M. hungatei, Methanosarcina,* or H_2-using *Desulfovibrio*. This was the first description of pure co-cultures of anaerobic bacteria that degrade fatty acids. Later, postdoctoral associate David Boone isolated a propionate-decarboxylating, acetate-producing species that he and Marv called *Syntrophobacter wolinii*. This organism required syntrophic conditions similar to those of *S. wolfei*.

Marv's graduate student Vincent Varel found that thermophilic methane production could be started up from bacteria in cattle waste in a period of about 12 days, a much shorter time than previously thought possible. They obtained a faster methanogenesis with higher loading of cattle waste into digestors than any previous group had achieved. The work was continued by research associate Rod Mackie who greatly expanded the knowledge of the kinetics of fatty acid degradation, bacterial growth, and protein synthesis in cattle-waste methanogenesis at both mesophilic and thermophilic temperatures.

Although ruminant nutritionists had long been interested in the amount of microbial cells and protein synthesized in the rumen in relationship to the amount of organic matter the microbes digested, considerable difficulty was involved in accurately determining this in vivo, and yield values from various laboratories gave variable results. In cooperation between Marv's laboratory and those of Frank Hinds and Fred Owens (Department of Animal Science), Ronald Isaacson set up model experiments with continuous cultures of mixed rumen bacteria growing on glucose to determine the efficiency of rumen bacterial growth in relationship to the rate of passage of material through the system. They found that at dilution rates covering the range expected in the rumen, the bacterial protein yield varied as much as two-fold. This variation emphasized the importance of the bacterial maintenance energy requirement in net growth of rumen bacteria. As rates of passage increased, more of the energy of the digested material available to the ruminant animal was used for growth and synthesis of microbial protein. This concept was later exploited in many laboratories to improve the efficiency of protein synthesis by rumen microbes.

Identity of the bacteria active in urea hydrolysis to ammonia and CO_2 via the production of urease in the rumen was long unknown. In the early 1980s Marv assigned Isaacson the special problem of selectively isolating major urease-forming bacteria, by use of urea as the main possible N source in a chemically defined medium. They theorized that the bacteria might not form urease in the presence of much ammonia or other rapidly used N source present in the growth medium. They successfully isolated a urease-producing bacterium that was shown by graduate student Andrew John to be a somewhat atypical variety of *Selenomonas ruminantium.* In this strain, urease was indeed strongly repressed by large amounts of urea, ammonia, or amino acids. Varel, using similar isolation techniques, showed that the human bowel organism, *Peptostreptococcus productus*, present in huge numbers in human feces, had similar urease activity. Graduate student Mary Ann Wozny then developed a rapid assay and growth medium in which most pure cultures of fermentative anaerobes grew and expressed urease activity. In screening many nonselectively isolated strains from the rumen and human species, she confirmed Varel's results with feces and found more human fecal anaerobes forming urease as well as more rumen species. Such strains were found to be predominantly from cattle maintained on high grain diets with unusually low levels of crude protein and thus low rumen ammonia levels. The strains were sent by Marv to Virginia Polytechnic Institute and identified as *S. dextrinosolvens, Treponema* spp and *Ruminococcus bromii.* Further studies with graduate student C. J. Smith and colleague R. B. Hespell, Marv studied urease regulation and enzymology of ammonia assimilation *in S. ruminantium.* The first enzyme of ammonia assimilation was found to be glutamate dehydrogenase, which required little energy for ammonia assimilation but which had poor affinity for ammonia and was much less active at low ammonia levels. An alternative route was the glutamine synthetase-glutamate synthase system, which had a very high affinity for ammonia but required some of the energy otherwise available for the growth of the bacterium. Both the urease and the glutamine synthetase were strongly repressed when the growth rate was limited by the amount of energy source in the medium rather than by the ammonia level. Marv and coworkers hypothesized that synthesis of both urease and glutamine synthetase was regulated by a common gene product.

There was considerable controversy concerning the concentration of ammonia necessary in the rumen to ensure maximum growth rate and yield of the fermentative rumen bacteria. Marv, along with graduate student Dan Schaefer and Professor Carl Davis, proved that important rumen bacterial species had a great affinity for ammonia as nitrogen source and could achieve maximum growth rates with 1 mM or less ammonia.

Marv's graduate student Bill Brulla, in association with Professor Smith, studied the improved feed efficiency in cattle fed the bacterial antibiotic monensin. Furthermore, the nutrition of gastrointestinal tract anaerobes remained of interest to Marv. Janice Herbeck and he showed that the nutrient requirements of *R. bromii,* one of the main species digesting starch in humans and in ruminants fed large amounts of grain, were very similar to those of the cellulolytic *R. albus*. Varel determined the simple nutritional requirements of *Bacteroides fragilis,* the most numerous species in humans, a major starch and hemicellulose fermenter, and an opportunistic pathogen in compromised humans. The minimal medium developed by Varel and Marv has since been used in many ecological, genetic, and pathology research laboratories.

Marv had long suspected that some important rumen bacteria had a growth requirement for a fat-soluble vitamin of the vitamin K group. Undergraduate student Colleen O'Dowd and graduate student Jane Leedle established this for *Succinivibrio* and Rogelio Gomez-Alarcon of Marv's group found 1,4-naphthaquinone to be the most active.

Marv's undergraduate student H. G. Betian and graduate student Barbara Lineham found large numbers of cellulolytic bacteria in the bowel microbiota in some young adult humans and isolated a new species of *Bacteroides.* Their finding of populations as high as 10^8 cellulolytic bacteria per g of feces had never been observed before in the bowel.

In another collaboration with Professor Davis, Barbara Genthner found that a lactate fermenter, *Eubacterium limosum*, which had been found earlier by Marv to exist only in the rumen of very young calves, was a very dominant organism in the rumen of sheep fed sugar cane molasses as their main energy source; it was also found to be a significant component in anaerobic digestors of domestic sewage. They established that the organism produced acetate and butyrate and some fatty acids with longer chains when it fermented the one-carbon compound methanol (from pectin breakdown) and H_2-CO_2. It also fermented branched-chain amino acids to branched-chain fatty acids, which were shown to be the major microbial products in the rumen of molasses-fed animals.

Marv served his scientific community well. He was the editor in chief of the *Journal of Applied and Environmental Microbiology* from 1967 to 1980 and was a member of the Board of Trustees of *Bergey's Manual of Determinative Bacteriology* from 1975 to 1986. He was a member of the American Society for Microbiology and the American Dairy

Science Association and a fellow of the American Association for the Advancement of Science and the American Academy of Microbiology. He also was a member of Phi Beta Kappa, Phi Kappa Phi, and Sigma Xi honor societies. For his contributions to science he received the Superior Service Award of the U.S. Department of Agriculture in 1959; the Borden Award of the American Dairy Science Association in 1978; the Paul A. Funk Award of the University of Illinois in 1979; the Fisher Award of the American Society for Microbiology in 1986; election to the National Academy of Sciences in 1987; the Alumni Achievement Award of Washington State University in 1991; and the Bergey's Medal for Distinguished Achievement in Bacterial Taxonomy in 1996. He also was made honorary member of the American Society for Microbiology, the highest honor awarded by that society.

In reviewing his many years of work in rumen and related anaerobic bacteriologic research, Marv concluded as follows:

> I became increasingly aware of my good fortune in having selected an area of work in which I have some innate competence and in having been at the right places at the right times to be associated with many outstanding, creative, unselfish colleagues whose main goals in life have been to advance the science of anaerobic bacteria and related areas in a holistic, unparochial, objective manner. I have also been very fortunate to have worked with administrators who put up with my somewhat juvenile personality and left me in the position that the major deterrents to achievement have been my own inadequacies. My wife, Margaret, has been the strong pillar of love and support essential to my progress.

Marv was the gentle giant of rumen microbiology. There was a special light in his eyes and a special tone to his voice when his beloved rumen bacteria were being discussed. He was a national treasure of information on anaerobes and his colleagues at Illinois and all over the world benefited from his presence.

Marv is survived by his wife, Margaret, of 54 years; sons Robert M. Bryant of Livermore, California, and Steven E. Bryant of Champaign, Illinois; daughters Margaret ("Peggy") Bryant of Pleasanton, California, Susan J. Bryant of Olympia, Washington, and Katherine B. Smith of Maple Plain, Minnesota; sister June Chambers of Boise, Idaho; and nine grandchildren.

MOST OF THE information in this article was derived from an autobiographical article written in 1980 by Marvin P. Bryant in honor of his receipt of the Paul A. Funk Award of the University of Illinois. He titled it "Marvin P. Bryant, A Rumen Microbiologist."

SELECTED BIBLIOGRAPHY

1956

The characteristics of strains of *Selenomonas* isolated from bovine rumen contents. *J. Bacteriol.* 72:162-67.

1958

With M. J. Allison and R. N. Doetsch. Volatile fatty acid growth factor for cellulolytic cocci of the bovine rumen. *Science* 128:474-75.

1959

Bacterial species of the rumen. *Bacteriol. Rev.* 23:125-53.

With I. M. Robinson and H. Chu. Observations on the nutrition of *Bacteriodes succinogenes*—a ruminal cellulolytic bacterium. *J. Dairy Sci.* 42:1831-37.

1961

With I. M. Robinson. Some nutritional requirements of the genus *Ruminococcus*. *Appl. Microbiol.* 9:91-95.

1962

With I. M. Robinson. Some nutritional characteristics of predominant culturable ruminal bacteria. *J. Bacteriol.* 84:605-14.

1963

With I. M. Robinson. Apparent incorporation of ammonia and amino acid carbon during growth of selected species of rumen bacteria. *J. Dairy Sci.* 46:150-54.

1964

With R. E. Hungate and R. A. Mah. The rumen bacteria and protozoa. *Annu. Rev. Microbiol.* 18:131-66.

1967

With E. A. Wolin, M. J. Wolin, and R. S. Wolfe. *Methanobacillus omelianskii:* A symbiotic association of two species of bacteria. *Archiv. Mikrobiol.* 59:20-31

1972

With C. A. Reddy and M. J. Wolin. Characteristics of S organism isolated from *Methanobacillus omelianskii*. *J. Bacteriol.* 109:539-45.

1973

Nutritional requirements of the predominant rumen cellulolytic bacteria. *Fed. Proc.* 32:1809-13.

1975

With S.-F. Tzeng and R. S. Wolfe. Factor 420-dependent pyridine nucleotide-linked hydrogenase system of *Methanobacterium ruminantium*. *J. Bacteriol.* 121:184-91.

1977

Microbiology of the rumen. In *Dukes' Physiology of Domestic Animals*, 9th ed., ed. M. P. Swenson, pp. 187-304. Ithaca, N.Y.: Cornell University Press.

With L. L. Campbell, C. A. Reddy, and M. R. Crabill. Growth of *Desulfovibrio* in lactate or ethanol media low in sulfate in association with H_2-utilizing methanogenic bacteria. *Appl. Environ. Microbiol.* 33:1105-12.

With C. A. Reddy. Deoxyribonucleic acid base composition and cytochromes of certain species of the genus *Bacteroides*. *Canad. J. Microbiol.* 23:1252-56.

1979

Microbial methane production—theoretical aspects. *J. Anim. Sci.* 48:193-201.

With R. B. Hespell. Efficiency of rumen microbial growth: Influence of some theoretical and experimental factors on Y_{ATP}. *J. Anim. Sci.* 49:1640-59.

1980

With D. R. Boone. Propionate-degrading bacterium, *Syntrophobacter wolinii* sp. nov., gen. nov. methanogenic ecosystems. *Appl. Environ. Microbiol.* 40:626-32.

1981

With M. J. McInerney. Anaerobic degradation of lactate by syntrophic associations of *Methanosarcina barkeri* and *Desulfovibrio* and effect of H_2 on acetate degradation. *Appl. Environ. Microbiol.* 41:346-54.

1986

The genus *Ruminococcus*. In *Bergey's Manual of Systematic Bacteriology*, vol. 2, ed. P. Sneath, pp. 1093-97. Baltimore: Williams and Wilkins.

With T. L. Miller, M. J. Wolin, and H. Zhao. Characteristics of methanogens isolated from bovine rumen. *Appl. Environ. Microbiol.* 51:201-202.

1987

With D. R. Boone. Isolation and characterization of *Methanobacterium formicicum* MR. *Int. J. Syst. Bacteriol.* 37:171.

1990

With R. I. Mackie. Efficiency of bacterial protein synthesis during anaerobic degradation of cattle waste. *Appl. Environ. Microbiol.* 56:87-92.

1993

With H. Zhao, D. Yang, and C. R. Woese. Assignment of fatty acid-β-oxidizing syntrophic bacteria to *Syntrophomonodaceae* fam. nov. on the basis of 16S rRNA sequence analyses. *Int. J. Syst. Bacteriol.* 43:278-86.

1994

With R. I. Mackie. Acetogenesis and the rumen: Syntrophic relationships. In *Acetogenesis*, ed. H. L. Drake, pp. 331-364. New York: Chapman-Hall.

Karl Folkers

KARL AUGUST FOLKERS

September 1, 1906–December 9, 1997

BY WILLIAM SHIVE

KARL FOLKERS WILL BE remembered for his numerous major contributions and his able assistance to many other investigators over more than six decades of chemical research. His work on the structure, synthesis, and medical use of naturally occurring, biologically active compounds, such as alkaloids, antibiotics, B-vitamins, hormones, and coenzymes, has had lasting impact. He played unique roles in the structural determination and synthesis of B-vitamins, and especially the isolation and determination of the chemical nature of vitamin B_{12}. These studies provided key advances toward making B-vitamins available for nutritional supplementation. His capacity for effective collaboration contributed to the structure determination and synthesis of the first hypothalamic hormone, provided evidence for the last position assignment of substituent groups in coenzyme Q_{10}, resulted in the synthesis of coenzyme Q_9, and generated the structure determination and synthesis of the isoprenoid precursor, mevalonic acid. His awards and honors encompassed almost all of those in his field of research. However, his highest valuation was placed on his long-term relationships—with his multiple collaborators and friends with whom he worked and consulted. He was especially aware and moved by the knowledge that he had contributed to the health and extended the life span of individuals through his research and collaborations.

Karl August Folkers was born on September 1, 1906, in Decatur, Illinois. His father, August William Folkers, was born on June 5, 1878, in Eckwarden, State of Oldenburg, Germany, and emigrated to the United States in 1882 with his parents. His mother, Laura Susan Black, was born in Reynolds County, Missouri, on March 4, 1878. Karl reaped the benefits of being the only child of a mother who, as the oldest in the family, had assisted in rearing her many siblings. As a child, Karl avidly read books on chemistry, and he worked with chemistry sets and set up chemical apparatuses even before taking the subject in high school. As a student at the University of Illinois his undergraduate experience included working in food service as well as the chemistry library and pursuing a senior thesis directed by Carl ("Speed") Marvel, who encouraged him to go to the University of Wisconsin for graduate work. Following his graduation from the University of Illinois, Karl followed Marvel's advice and attended Wisconsin, where he received a fellowship appointment and worked with Homer Adkins on high-pressure hydrogenation. During his graduate work he discovered copper-barium chromite as a catalyst for reduction of esters to alcohols. His interest in biochemistry, developed by detailed reading in this area, led him to postdoctoral study on the synthesis of pyrimidines at Yale University with Treat B. Johnson, who introduced him to pharmaceutical chemistry. At Yale, Karl met Selma Leona Johnson, who was born on July 5, 1910, in Philadelphia, Pennsylvania. Their marriage on July 30, 1932, initiated their lifelong caring relationship in which there was much mutual support and admiration. They had two children, Cynthia Carol and Richard Karl.

Karl's deep interest in pharmaceuticals led him to join Merck in 1934. This decision was influenced not only by his interests but also by the new "pure research" activity pursued by Merck. Indeed, Karl's very successful work on isolation and structures of *Erythrina* alkaloids was initiated by his director, Randolph Majors. Majors literally handed him a bag of *Erythrina* seed and suggested that Karl see what he could do with them, leaving the approach to the problem entirely to Karl. Karl later gave Majors credit for his foresight in promoting vitamin research at Merck; Majors's admonition to be aware of research outside the company and to visit other laboratories doing sound work was reflected in the rest of Karl's career.

In 1938 Karl was appointed assistant director of research and assigned the research group that had just isolated vitamin B_6 (pyridoxine). In a manner analogous to the efforts of the Richard Kuhn research group in Germany, the Merck group had limited the structure of pyridoxine to two possible isomers. Karl and his colleagues completed the final structure and then provided the first synthesis of vitamin B_6. For this work Folkers and Kuhn shared the 1940 Mead Johnson Company Award of the American Institute of Nutrition. Roger Williams discovered and partially synthesized pantothenic acid, and in 1939 the Folkers group in collaboration with Williams achieved total synthesis of pantothenic acid by completing the structure of the lactone moiety. Karl received the American Chemical Society Award for meritorious work in pure chemistry in 1941 based on this collection of studies.

During this period Vincent du Vigneaud's group was having difficulty in discerning between two possibilities for the structure of biotin. Folkers' group discovered that the hydrogen in Raney nickel could be used to remove the sulfur from these compounds, a step that facilitated the structural determination of biotin. This achievement resulted in a joint publication of the structure, and Karl and his group then went on to provide an elegant first synthesis of biotin. In 1943 Karl and his group confirmed by unequivocal synthesis the structures of pyridoxal and pyridoxamine initially obtained by Esmond Snell from pyridoxine (vitamin B_6). Based on these achievements Karl was made director of the Organic and Biochemical Research Department at Merck from 1945 to 1951. During this period he was involved in the isolation and structure of antibiotics, in particular the isolation and structure of streptomycin. Folkers' group was also deeply involved in structural studies of penicillin.

In 1942 Folkers's interest in anti-pernicious anemia led to a research project with his team of chemists. After a long period without success on this project and during a visit to the University of Maryland in 1947, Karl learned of Mary Shorb's *Lactobacillus lactis* Dorner test in which bacterial growth was responsive to commercial anti-pernicious anemia extracts from liver. As a consequence Karl arranged for Shorb to test a group of samples that included a clinically active liver extract preparation passed through alumina. The active factor in these extracts would turn out to be vitamin B_{12}. However, this preparation, unlike vitamin B_{12}, appeared colorless in the form of the lyophilized water crystals. Fermentation residues from antibiotic production were found to be potent sources of this factor, and the observation of the pink coloration on the alumina chromatograph rapidly led to the isolation of the red crystalline vitamin B_{12}. The work of the Merck group on this structure was outstanding. This large molecule, with its cobalt porphyrin-like ring and side chain interacting with cobalt complexed with cyanide, was a challenging structure determination. Although the final detailed structure was completed by X-ray diffraction elsewhere, the work of Karl and his group made vitamin B_{12} available commercially, and its identity with the animal growth factor was quickly established. Karl and Mary Shorb received the 1949 Mead Johnson Award for their work on vitamin B_{12}. Karl was elected to the National Academy of Sciences in 1948 based on the breadth and significance of his research in many areas.

When Merck merged with Sharpe and Dohme, the Folkers laboratory was enlarged, and Lemuel Wright and Helen Skeggs became an integral part of the research effort. This group discovered, isolated, and synthesized mevalonic acid as an acetate-replacing factor for growth of certain *Lactobacilli*. The relationship of this factor to the biosynthesis of cholesterol ultimately made possible direct biochemical approaches to the control of cholesterol biosynthesis associated with heart disease. For his achievements he received the Scientific Award of the Board of Directors of Merck in 1951.

In 1958 Karl and his Merck group confirmed the structure of coenzyme Q_{10} proposed initially by Fred Crane and his colleagues at the University of Wisconsin. They demonstrated that coenzyme Q_{10} from beef and human heart were identical and synthesized coenzyme Q_9. Coenzyme Q and its relevance to various chronic diseases became one of Karl's major research interests for the remainder of his life.

Karl moved through several changes in his responsibilities at Merck—from associate director of research and development (1951), director of organic and biological research (1953), executive director of fundamental research (1955), and vice president for exploratory research (1962). In 1963 he resigned from Merck to accept the position of president and chief executive officer at Stanford Research Institute, a post he held until 1968. During his tenure as president the institute doubled its revenues, increased its staff by over 50 percent and successfully completed a land acquisition and new building program. Despite his executive role, Karl continued his research focus on the biosynthesis of coenzyme Q and its role in genetic dystrophy in mice during his time at SRI.

In 1968 Karl was recruited to the University of Texas at Austin to spend full-time in graduate and postdoctoral teaching and research, a new phase of his professional life. He was appointed Ashbel Smith Professor in the graduate faculty of the Department of Chemistry and in the College of Pharmacy. He was also named director of a newly established Institute for Biomedical Research. In this new setting Karl developed new interests and directions for his work. For example, Andrew Shally and Cyril Bowers invited Karl to work on the structure and synthesis of the hypothalamic hormone, thyrotropin releasing hormone (TRH), which they had isolated. The structural proof and synthesis of this first hypothalamic hormone, TRH, were provided by Karl and his group in 1969. For his role in the structure and synthesis of the first hypothalamic hormone, Karl shared the Van Meter Prize of the American Thyroid Association with Shally and Bowers in 1969.

For over two decades Bowers and Folkers continued extensive research on hypothalamic hormones and their analogs. The luteinizing hormone releasing hormone (LHRH) and its analogs received major attention during this period. Studies on the activities of LHRH analogs as antagonists and agonists of hormone activity and assessment of their toxicities provided the basis for design of several variants with potential medical use. The synthesis of inhibitory analogs of substance P provided the means by which the role of this long known peptide hormone could be discerned. This work extended to encompass worldwide cooperative studies on peptide hormones.

Interest in compounds of medical interest persisted in all of Karl's studies. At the Institute for Biomedical Research Karl worked with John Ellis to explore further the observation that vitamin B_6 alleviated the carpal tunnel syndrome in patients. This work suggested that supplementation by vitamin B_6 would correct deficiencies of the coenzyme detected by erythrocyte transaminase assays. Subsequently, a patient with deficiencies of both vitamin B_6 and riboflavin detected by enzyme assays was found to respond to both vitamins. Karl attributed the need for riboflavin in this patient to its coenzyme role in metabolism of vitamin B_6. Such biochemical evidence for the cause of disease was a driving force in the research career of Karl Folkers.

Folkers' search for medical applications for coenzyme Q resulted in the observation that inadequate biosynthesis may occur in tissues of patients with various chronic disorders. He and his collaborators concluded that beneficial effects of supplementation by coenzyme Q were found in patients with a variety of diseases—muscular dystrophy, periodontal disease, hypertension, and cardiomyopathy. Folkers and his colleagues also discovered that lovastatin, a drug that inhibits the synthesis of cholesterol and lowers cholesterol levels in blood, also lowers coenzyme Q levels in blood. Indeed, they demonstrated that oral supplementation of lovastatin-treated patients with coenzyme Q prevented the fall in blood coenzyme Q. To aid in these investigations, Karl's laboratory developed an assay that can detect coenzyme Q in one drop of blood.

The Institute for Biomedical Research created by Karl Folkers involved undergraduate and graduate students, postdoctoral fellows, and many outstanding collaborators from throughout the world. Karl and Selma Folkers maintained close relationships with these colleagues from their Austin home during the academic year and from their Lake

Sunapee home in the summer. This New Hampshire site served as a gathering point over many summers for Karl, his family, and colleagues and their families. Indeed, my own daughters have fond memories of boating on the lake with Karl at the helm as an integral part of Gordon Research Conferences.

After the death of his beloved wife on August 12, 1992, Karl's health began to decline, but his research interest and activity persisted. He actively directed his Institute for Biomedical Research from his Lake Sunapee summer home over the last two years of his life with the aid of his colleague Richard Willis. He remained actively involved in research up through his final day, December 9, 1997.

Karl created the Folkers Foundation to support continued development of biochemical research on causes of human disease. His lifelong pursuit was to discover such causes and identify means to improve the life and health of those afflicted with various diseases. This work will be continued in the research supported by the Foundation—a fitting and permanent legacy of the life of Karl Folkers.

Karl, with his cadre of outstanding collaborators, published more than 700 papers in scientific journals and presented an equally large list of papers at scientific meetings and invited lectures. For his outstanding work he received honorary doctoral degrees in science from the Philadelphia College of Pharmacy and Science (1962), University of Uppsala, Sweden (1969), University of Illinois (1973), and the University of Wisconsin (1970) and an honorary degree in medicine and surgery from the University of Bologna, Italy (1989).

Other awards spanned a significant spectrum of recognition by a variety of organizations and included the Presidential Certificate of Merit (1948); Harrison Howe Award, Rochester Section (1949); Scientific Award, Board of Directors, Merck and Co., Inc. (1951); Spencer Award, Kansas City Section (1959); Perkin Medal, Society of Chemical Industry (1960); Scroll Award, National Association of Manufacturers (1965); Nichols Medal, New York Section (1967); Robert A. Welch International Award and Medal (1972); Research Award, J. D. and C. T. MacArthur Foundation (1981); Priestley Medal of the American Chemical Society (1986); President's National Medal of Science (1990); Karl Folkers Centennial Research Award (first recipient), Rutgers University (1992); and Infinity Award, American Academy of Anti-Aging Medicine (1996).

Karl was involved in organizing and served as the chair of many international research conferences. He was chair of multiple Gordon Research Conferences and also served on the Board of Trustees beginning in 1971. He served on the National Defense Research Committee (1943-46), on the Drug Development Committee of the National Cancer Institute (1974-78), on the Board of Editors for several scientific journals, in various positions in the American Chemical Society, and as a member of various advisory committees for the National Academy of Sciences and for many American and foreign universities. He was elected an honorary member of Societa Italiana de Scienze Pharmaceutiche (1969) and Phi Lambda Upsilon (1966); an honorary fellow of the American Institute of Nutrition (1982); and a foreign member of the Royal Swedish Academy of Engineering Sciences (1966).

The awards and activities accrued by Karl Folkers serve as testimony to his achievement and contribution to the biochemical study of disease. The combination of his intellect and his ability to engage in effective collaboration with a wide variety of colleagues resulted in significant advancements in our understanding of naturally occurring, biologically active compounds. His scientific devotion was driven by the knowledge that he could contribute to the well-being of individuals who suffered and was matched by the value he placed on his professional relationships—a cadre of friends developed over his entire lifespan.

MOST OF THIS narrative derives from my own memories over 60 years of knowing Karl Folkers, from his publication record, and from our relationship as colleagues at the University of Texas over almost 30 years. Many Sunday afternoon conversations about research provided insight into his aspirations and his motivations. I also appreciate information provided by Robert E. Olson (University of South Florida) in discussions and in his biographical article on Karl Folkers in the *Journal of Nutrition* (131[2001]:2227-30), as well as insight from conversations with Richard Willis.

(This memoir was edited by Kathleen Shive Matthews and Karen Shive Browning following the untimely death of William Shive on October 2, 2001.)

SELECTED BIBLIOGRAPHY

1931

With H. Adkins. The catalytic hydrogenation of esters to alcohols. *J. Am. Chem. Soc.* 53:1095-97.

1934

With T. B. Johnson. Hydrogenation of cyclic ureides under elevated temperatures and pressures I. 2-keto-1,2,3,4-tetrahydropyrimidines. *J. Am. Chem. Soc.* 56:1180-85.

1939

With S. A. Harris and E. T. Stiller. Structure of vitamin B_6. II. *J. Am. Chem. Soc.* 61:1242-44.

With S. A. Harris. Synthesis of vitamin B_6. I-II. *J. Am. Chem. Soc.* 61:1245-47, 3307-10.

1940

With E. T. Stiller, S. A. Harris, J. Finkelstein, and J. C. Keresztesy. Pantothenic acid. VIII. The total synthesis of pure pantothenic acid. *J. Am. Chem. Soc.* 62:1785-90.

1942

With V. du Vigneaud, D. B. Melville, D. E. Wolf, R. Mozingo, J. C. Keresztesy, and S. A. Harris. The structure of biotin: A study of desthiobiotin. *J. Biol. Chem.* 146:475-85.

1944

With S. A. Harris, D. E. Wolf, R. Mozingo, R. C. Anderson, G. E. Arth, N. R. Easton, D. Heyl, and A. N. Wilson. Biotin. II. Synthesis of biotin. *J. Am. Chem. Soc.* 66:1756-57.

1945

With F. A. Kuehl, Jr., R. L. Peck, and A. Walti. Streptomyces antibiotics. I. Crystalline salts of streptomycin and streptothricin. *Science* 102:34-35.

1948

With F. A. Kuehl, Jr., R. L. Peck, and C. E. Hoffhin, Jr. Streptomyces antibiotics. XVIII. Structure of streptomycin. *J. Am. Chem. Soc.* 70:2325-30.

1950

With D. E. Wolf, W. H. Jones, and J. Valiant. Vitamin B_{12}. XI. Degradation of vitamin B_{12} to D_g-1-amino-2-propanol. *J. Am. Chem. Soc.* 72:2820.

1952

With E. A. Kaczka, D. Heyl, and W. H. Jones. Vitamin B_{12}. XXI. Crystalline α-ribazole phosphate and its synthesis. *J. Am. Chem. Soc.* 74:5549-50.

1953

With E. A. Kaczka. Vitamin B_{12}. XXII. Relation of α-ribazole phosphate to vitamin B_{12}. *J. Am. Chem. Soc.* 75:6317-18.

1955

With F. A. Kuehl, Jr., C. H. Shunk, and M. Moore. Vitamin B_{12}. XXV. 3,3-Dimethyl-2,5-dioxopyrrolidine-4-propionamide: A new degradation product. *J. Am. Chem. Soc.* 77:4418-19.

1956

With L. D. Wright, E. L. Cresson, H. R. Skeggs, G. D. E. MacRae, C. H. Hoffman, and D. E. Wolf. Isolation of a new acetate-replacing factor. *J. Am. Chem. Soc.* 78:5273-75.

With D. E. Wolf, C. H. Hoffman, P. E. Aldrich, H. R. Skeggs, and L. D. Wright. β-Hydroxy-β-methyl-δ-valerolactone (divalonic acid), a new biological factor. *J. Am. Chem. Soc.* 78:4499.

1958

With D. E. Wolf, C. H. Hoffman, N. R. Trenner, B. H. Arison, C. H. Shunk, B. O. Linn, and J. F. McPherson. Coenzyme Q. I. Structure studies on the coenzyme Q group. *J. Am. Chem. Soc.* 80:4752.

1967

With P. Friis and G. D. Daves, Jr. Complete sequence of biosynthesis from p-hydroxybenzoic acid to ubiquinone. *J. Am. Chem. Soc.* 88:4754-56.

1972

With H. Sievertsson, J.-K. Chang, A. Von Klaudy, C. Bogentoft, B. Currie, and C. Bowers. Hypothalamic hormones. 35. Two syntheses of the luteinizing hormone releasing hormone of the hypothalamus. *J. Med. Chem.* 15:222-26.

1978

With J. Y. Choe and A. B. Combs. Rescue by coenzyme Q_{10} from electrocardiographic abnormalities caused by the toxicity of adriamycin in the rat. *Proc. Natl. Acad. Sci. U. S. A.* 75:5178-80.

1982

With J. M. Ellis, M. Levy, S. Shizukuishi, J. Lewandowski, S. Nishii, H. A. Schubert, and R. Ulrich. Response of vitamin B-6 deficiency and the carpal tunnel syndrome to pyridoxine. *Proc. Natl. Acad. Sci. U. S. A.* 79:7494-98.

1984

With A. Wolaniuk and S. Vadhanavikit. Enzymology of the response of the carpal tunnel syndrome to riboflavin and to combined riboflavin and pyridoxine. *Proc. Natl. Acad. Sci. U. S. A.* 81:7076-78.

1985

With J. Wolaniuk, R. Simonsen, M. Morishita, and S. Vadhanavikit. Biochemical rationale and the cardiac response of patients with muscle disease to therapy with coenzyme Q_{10}. *Proc. Natl. Acad. Sci. U. S. A.* 82:4513-16.

1988

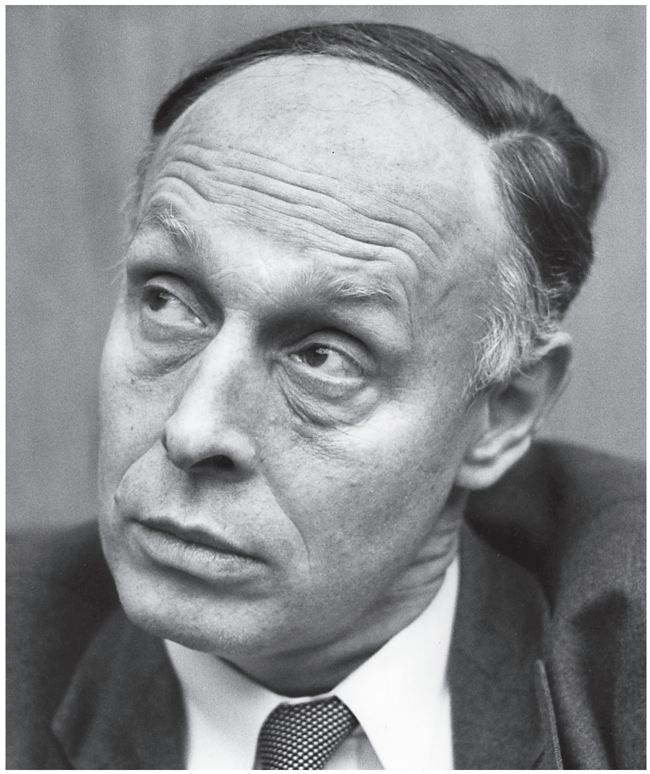
With A. Ljungqvist, D.-M. Feng, W. Hook, Z.-X. Shen, and C. Bowers. Antide and related antagonists of luteinizing hormone release with long action and oral activity. *Proc. Natl. Acad. Sci. U. S. A.* 85:8236-40.

1990

With P. Langsjoen, R. Willis, P. Richardson, L.-J. Xia, C.-Q. Ye, and H. Tamagawa. Lovastatin decreases coenzyme Q levels in humans. *Proc. Natl. Acad. Sci. U. S. A.* 87:8931-34.

1995

With R. Simonsen. Two successful double-blind trials with coenzyme Q_{10} (vitamin Q_{10}) on muscular dystrophies and neurogenic atrophies. *Biochim. Biophys. Acta* 1271:281-86.



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KLAUS HOFMANN

February 21, 1911–December 25, 1995

BY FRANCES M. FINN AND BERT W. O'MALLEY

KLAUS HOFMANN WORKED in many areas of chemistry and biochemistry over his long and productive career. His published work covers the fields of steroids, enzymes, vitamins, fatty acids, and peptides. Without question, though, he was best known for his contributions to the field of peptides. His most publicized, though not the one he considered his most fundamental contribution, was the synthesis of a fully active, shortened chain of the pituitary hormone adrenocorticotropin (ACTH). His work on ACTH led to the recognition that peptide hormones, unlike steroid hormones, could be dramatically modified without substantially altering their biological potency. In his later work on peptides he was able to delineate the types of amino acids that contributed to the strong interactions between peptide chains that were vital to the strong and specific interactions responsible for recognition and binding of the hormone by its specific receptor.

Klaus Hofmann was born in Karlsruhe, Germany. His father died when he was only a year old and his mother returned with her son to Switzerland, where he was to remain until a Rockefeller Foundation Fellowship brought him to the United States in 1938 at the age of 27. Even as a boy he was interested in science. At the boarding school he attended in Switzerland he became a close friend of his natural history teacher, Hans Noll, who profoundly influenced his subsequent education. Together they banded sea gulls on the Lake of Zürich and determined from the rings returned to them that the gulls wintered in Spain and southern France. During this period he also became interested in chemistry, soaking filter papers in the nitroglycerin he had prepared in the school lab and exploding them on an anvil with a hammer.

The family, engaged in the natural silk business, felt that young Hofmann should embark on a career in business. That is, until they were defrauded by someone who sold them on a "new" process to produce synthetic silk. By the time they realized that the so-called new process was the same process everyone else was using, they had lost considerable sums of money and the prospect of having Hofmann study chemistry before entering the business suddenly became appealing. He enrolled at the Federal Institute of Technology in Zürich as a chemical engineer, and by the time he graduated he was fascinated with the work being done on steroid hormones in the laboratories of Leopold Ruzicka and Thaddeus Reichstein. No more silk for him.

Hofmann did his thesis work on terpenes. Ruzicka was convinced that there was a structural relationship among the various terpenes based on a common building block (now known as the isoprene unit). In the hope of finding a synthetic principle for the construction of this class of compounds, Ruzicka put his students to work on determining structures of and synthesizing many of the terpenes. By the time Hofmann had completed his Ph.D. and two years of postdoctoral work with Ruzicka, he had produced 13 publications on structure determination and synthesis of a pentacyclic triterpene, oleanolic acid, a dehydroandrosterone derivative, and incidentally, the prototype for the birth control pill. The biology of reproduction was not understood at that time and therefore the potential significance of the latter compound was not appreciated.

As a young Swiss male Hofmann was required to train and serve in the militia, which he did with enthusiasm. Not only did he complete the basic requirements but he also enrolled in officer's training and specialized in heavy artillery, commanding a battery of guns at the age of 25. In his own words, "This was an exhilarating experience for a young man."

In 1938 he came to the United States to work for Max Bergman at the Rockefeller Institute on a one-year fellowship. There he worked out the lysine specificity of the enzyme trypsin. In Bergman's laboratory he met Joseph Fruton, William Stein, and Stanford Moore, and he enjoyed a lifelong friendship with all of them. During a second fellowship year, the Swiss army was mobilized in response to the beginning of World War II, and as an artillery officer Hofmann reported to the Swiss consulate and prepared to set sail. The Swiss government chose not to call military personnel from abroad and he was able to complete his second year of training at Rockefeller. As he was preparing to return to Switzerland he had a chance encounter with Vincent du Vigneaud. He told du Vigneaud of his plans to depart and said his farewell. Du Vigneaud immediately offered him another fellowship, this time working on the vitamin biotin at Cornell Medical College, and he decided to accept. He characterized this period as "a very pleasant three years." Hofmann had learned the column chromatography techniques of Martin and Synge while still a postdoctoral student in Ruzicka's laboratory, and he applied these to the isolation of biotin. In less than one month he had succeeded in isolating crystalline biotin. Together he, du Vigneaud, and Melville elucidated the structure of the vitamin.

The United States was already involved in World War II when Hofmann left Cornell to find a job. With so many academic institutions engaged in war-related work, it was impossible for a foreigner to find a university position. A close friend Ernst Oppenheimer, an endocrinologist and then vice-president for research at the Ciba Company in Summit, New Jersey, offered Hofmann a salary, a laboratory, and a technician as a scientific guest at Ciba. During this period Hofmann synthesized analogs of biotin, among them oxybiotin, in which oxygen was substituted for the ring sulfur. Oxybiotin was biologically active, proving that the sulfur was not essential for activity.

When the war was over he applied for a position at the University of Pittsburgh, which was to become his scientific home for the next 51 years. At that time the university had no strong research program, but the newly appointed dean for research, Herbert Longenecker, was given the task of remedying that situation. He hired Hofmann and several other young scientists as assistant research professors for the express purpose of building a research component in the natural sciences.

Hofmann moved to Pittsburgh, a city whose principal businesses were engaged in all aspects of steel production. The transition was an experience never to be forgotten. This was a period in the history of Pittsburgh when the air was so filled with smoke from the soft-coal-burning furnaces of the local residents that it was frequently impossible to see from one side of the street to the other even at noon. His first act was to scrub his new laboratory from top to bottom, but he soon learned that the lab benches had to be cleaned each morning to remove the previous day's soot deposits.

Still, Pittsburgh held many pleasant memories for Hofmann. He loved to play the violin and particularly enjoyed playing string quartets with his new friends from the university. His only child, Suzanne, showed a gift for music at a very early age, and he began to teach her violin. By the time she reached six she was playing at a level well beyond her years, and he decided to get formal instruction for her. He liked to tell the story of his first encounter with the man who was to become her teacher for the next 12 years, the assistant concertmaster of the Pittsburgh Symphony, Willie Frisch. Although Hofmann had told him of Suzanne's remarkable ability, Willie was used to parents overestimating the talents of their children, and he took a wait-and-see attitude, telling Hofmann that the child might be ready for a lesson once a month considering her youth. When he heard her play a Bach solo sonata, he was so impressed with her mastery of the instrument that he vigorously endorsed weekly sessions. Suzanne's musical gifts were a constant source of enjoyment for Hofmann.

Through a collaboration with Abraham Axelrod, who was conducting the biological assays for biotin analogs, Hofmann developed an interest in the fatty acids of bacteria. These compounds seemed to replace biotin in bacterial growth. As little was known in general about the fatty acids of bacteria, Axelrod and Hofmann set about isolating them from large batches of lactobacilli. A novel acid, which Hofmann named lactobacillic acid, was isolated and found to contain a three-membered ring. The precursor for this new fatty acid was not oleic acid as conventional wisdom would have dictated but *cis*-vaccenic acid.

During his first eight years at Pittsburgh, Hofmann rose from assistant research professor of chemistry to chairman of the Biochemistry Department in the School of Medicine. Concomitant with his move to the medical school, Hofmann began to develop methods for the synthesis of peptides. With the isolation and synthesis of the posterior pituitary hormones—oxytocin and vasopressin—by du Vigneaud, Hofmann became convinced that peptides would eventually become a very important part of biomedical research. At this time the Armour Company in Chicago had become very interested in the anterior pituitary hormone, ACTH, and had begun to purify it from concentrates. From early on it was clear that ACTH was rich in the amino acid arginine. There were no methods as yet for introducing arginine into peptides, so Hofmann's entry into the peptide hormone field began with development of methods to produce arginine-containing peptides.

A group at the Lederle Laboratories in Pearl River under the direction of Paul Bell managed to isolate pure ACTH and determine its structure. They also showed that the entire 39 amino acid peptide was not necessary for biological activity; a fragment containing amino acids 1 to 24 was able to stimulate the adrenal cortex just as effectively as the entire structure. By 1960, applying his newly developed methods, Hofmann and his research group were able to synthesize a peptide from the constituent amino acids corresponding to the sequence of the first 23 amino acids of natural ACTH and show that it, too, had full biological activity. At approximately the same time a group in the Yale medical school led by Aron Lerner isolated another anterior pituitary hormone and showed that it could darken the skin of frogs bleached by hypophysectomy. The material was the melanocyte-expanding hormone, MSH. There were in fact several substances with melanocyte-expanding activity and the one called α-MSH had the same structure as the first 13 amino acids of ACTH. This, too, was synthesized by Hofmann and his coworkers, and with it Lerner was able to prove that the same factor that restored color to the frog could darken a human.

Once the synthetic methods had been successfully applied to ACTH and α-MSH, Hofmann began preparing peptide hormone analogs to determine which amino acids in the sequence were important for biological activity. He hypothesized that the peptide hormone combines with some structural counterpart (receptor) from the target cell by virtue of noncovalent forces. He noted that species variation in the sequence of ACTH occurred outside the minimal sequence essential for full biological activity and designated the amino acids in these portions of the peptide "filler sequences." By synthesizing peptides in which the chain of the fully active $ACTH_{1-23}$ was systematically shortened and peptides in which specific amino acids were replaced, he hoped to distinguish two classes of amino acids, those whose replacement or elimination resulted in diminished activity and those whose replacement abolished activity. He postulated that the former were involved in binding the hormone to its receptor, while the latter might be involved directly in biological activity. The sulfur-containing amino acid, methionine, was replaced by an aliphatic amino acid, α-amino *n*-butyric acid without destroying biological activity. Thus, in ACTH as in biotin, sulfur was not essential for biological activity. From the results of the studies conducted during this period, it was also concluded that the positively charged sequence arg-arg-lys-lys made strong contributions to the binding of the hormone to its receptor. Peptides in which all of the positive charges were eliminated had exceedingly low activity. Working with ACTH was a frustrating experience, however, because the assay systems that existed involved injecting the peptide into an animal in order to measure biological activity. Too many unknowns affecting the peptide from the site of injection to its interaction with the target organ created ambiguities in the results. Hofmann searched for a simpler, more direct assay system in which to test his theories of peptide hormone action.

The S-peptide/S-protein system was discovered by Frederick Richards while working in Linderstrøm-Lang's laboratory. It presented what seemed to be the ideal model for peptide hormone action. Ribonuclease A, whose complete structure was known from the work of Hirs, Stein, and Moore, could be split with the enzyme subtilisin between amino acids 20 and 21 to yield ribonuclease S, a structure in which the peptide corresponding to the first 20 amino acids (S-peptide) remained attached to the remainder (S-protein, amino acids 21-124) by noncovalent forces. The proteolytically cleaved ribonuclease S had the full enzymatic activity of the parent protein. The two components, S-peptide and S-protein, could be separated by reversible denaturation, and the separation abolished enzymatic activity; however when the individual components were mixed together again, fully active ribonuclease S reformed. Eventually it was established that the enzyme's active site was composed of amino acids located both in S-peptide and in S-protein. Furthermore, the noncovalent forces that held the two pieces together were sufficiently strong to align the amino acids correctly to reconstitute the active site. This system provided the model Hofmann needed. He viewed S-peptide as the "hormone" and S-protein as "its receptor." At last here was a system where measuring activity of analogs could be done directly without all the vagaries introduced by injecting the peptides into whole animals.

Using the S-peptide/S-protein model, he and his colleagues synthesized dozens of analogs to test the contributions that specific amino acid side chains made to noncovalent interactions in proteins. The chain of S-peptide was shortened by preparing a peptide that contained only the first 14 amino acids of the prototype, mimicking the same process that was done with ACTH. S-peptide$_{1\text{-}14}$ proved to be fully active as well. Next, methionine was replaced just as had been done previously with ACTH. The results were parallel; sulfur played no role in activity, only in binding. One by one the importance of each of the amino acid side chains of the peptide for binding strength was investigated by replacing them. When the putative active site amino acid histidine, in position 12, was replaced by a synthetic, isosteric analog with an entirely different acid-base behavior (pK ~2.5), β-(pyrazolyl-3)-alanine, (pyr-3-ala) the reformed enzyme was devoid of activity. Moreover, it was shown that when pyr-3-ala peptides were mixed with analogous histidine-containing peptides, the inactive pyr-3-ala peptides could bind to S-protein as well as their histidine-containing counterparts. At a ratio of pyr-3-ala peptide to histidine peptide of 1:1, the resulting enzymatic activity of the reformed enzyme was reduced 50 percent.

When the X-ray structures of ribonucleases A and S became available through the work of the groups led by David Harker at Rosewell Park and by Frederick Richards at Yale, the identity of the amino acids with which the various side chains of S-peptide were interacting could be ascertained and general information on protein-protein interactions were established with these studies. This system had provided an interesting paradigm for Hofmann's view of hormone-receptor interaction, showing that indeed binding and active site amino acids could be distinguished from one another.

The opportunity to test these ideas on an authentic hormone/receptor pair presented itself when techniques became available for isolating highly purified plasma membranes. Hofmann's group prepared adrenal cortical plasma membranes, and the interaction of various ACTH analogs was measured by inhibiting the binding of synthetic radiolabeled $ACTH_{1\text{-}20}$ to the membranes. The results obtained with this system confirmed the earlier findings derived from measuring biological activity of ACTH analogs in whole animals.

Techniques for isolating hormone receptors and measuring in quantitative terms their ability to interact with their respective hormones were being developed and applied to the field. Another development that influenced the direction of work in Hofmann's laboratory was the synthesis by Gerald Mueller and his group of a derivative of biotin (N-hydroxysuccinimide ester) that activated it for attachment to other reactive sites. A biotin-containing estrogen derivative was synthesized to isolate estrogen receptors. Hofmann remembered his early work with biotin and its unusually strong affinity for the egg-white protein avidin. He decided to attach avidin to a support and use it to anchor a biotin-derivatized peptide hormone. This combination could then be used to bind the peptide hormone's receptor selectively. Using this technique on ACTH receptors was at that time out of the question. Adrenal cortical plasma membranes were difficult to prepare in large amounts, and it had not been established that soluble ACTH receptors were still capable of binding the hormone. Pedro Cuatrecasas had, however, shown that soluble insulin receptor retained affinity for insulin, and large amounts of the receptor could be prepared from human placenta. A sabbatical leave, productively spent in the laboratories of Helmut Zahn in Aachen, equipped Hofmann with the synthetic know-how to attach biotin to a specific site on the hormone insulin without altering the affinity of insulin for its receptor. With avidin the biotinyl insulin derivative and large quantities of partially purified insulin receptor in hand he and his coworkers successfully isolated insulin receptor.

Due to the high capacity of the affinity chromatographic columns provided by the method used to attach biotin to insulin, and the mild conditions that were developed in Hofmann's laboratory for recovery of the receptor from the chromatographic column, both the hormone-binding activity and the tyrosine kinase activity of the pure receptor were preserved.

The time was ripe for applying these methods to the ACTH receptor. Biotin-containing derivatives of ACTH were synthesized and evaluated and eventually one was used to construct an analogous affinity column for receptor isolation. Initial attempts produced a material with the correct ACTH analog affinities that was shown to have a molecular weight of ~43,000. Just as it seemed that his dream of obtaining ACTH and its receptor in purified form, illness struck and the business of living from day to day became the overwhelming focus of life for Klaus Hofmann.

During his tenure as chairman of biochemistry in the School of Medicine he spent many hours learning about medicine in order to make the study of biochemistry more meaningful for medical students. He considered it his mission as chairman to inspire students with the knowledge that comes from understanding the practical aspects of medicine and how biochemistry relates to it. One of us (B.W.O.) had the "pleasure" of participating as a medical student in Klaus Hofmann's notorious biochemistry course at the University of Pittsburgh School of Medicine. It was an intimidating and difficult course but one that challenged this student first to a summer lab experience, then to part-time lab employment during the school year, and finally to a career in biomedical research.

Despite Hofmann's deep commitment to his research, his presence was regularly observed at scheduled teaching activities in the clinical department of his institution. Every month he went to the surgical suite to witness the latest procedures and his surgical colleagues were pleased that a basic scientist was so deeply interested in their world. Weekly clinical pathology conferences were also part of his life during this and later years, and he read avidly on the basic biochemical principles associated with disease. His knowledge of medicine gave him a clear understanding of the course of his own illness, but despite this he remained optimistic throughout this period. He continued his pursuit of medicine, reading everything connected with his own malignancy and participated in an informed way in decisions concerning treatment. Although he went every day to the laboratory until he was hospitalized in the terminal phases, his energy and concentration were visibly drained and he could no longer function with the vigor and enthusiasm that had characterized his career in the laboratory.

The laboratory he led was often, but not always, first to report its findings or syntheses because throughout his career his motto was *"Einmal ist Keinmal."* A single result never sufficed; a single synthesis was not enough for him. His coworkers had to show that everything they did and made was reproducible. It meant more to him to be right than to be first and this principle guided him in his pursuit of truth in science.

His attitude toward his chosen career can probably best be summed up in the words used in his epitaph.

Science was his greatest joy and he practiced it with wisdom, intuition and uncompromising honesty. His life was rich with experiences and knowledge that he shared willingly, in his unique style, with those who were fortunate enough to have been his students.

MEMBERSHIP ON NATIONAL COMMITTEES

1960 Panel to evaluate National Science Foundation predoctoral fellows
1960-64 Member, Biochemistry Study Section, National Institutes of Health
1964-69 Scientific Review Committee, Health Research Branch, National Institutes of Health
1970-74 National Advisory Council on Health Research, National Institutes of Health
1975 Ad Hoc Committee on Drug Development, National Institutes of Health

MEMBERSHIP IN PROFESSIONAL AND SCIENTIFIC SOCIETIES

American Association for the Advancement of Science
American Chemical Society
American Society for Biochemistry and Molecular Biology
Endocrine Society
National Academy of Sciences
Sigma XI
Swiss Chemical Society

HONORS

1962 Pittsburgh Award
1963 Election to membership in the National Academy of Sciences
Borden Medal
Chancellors Medal, University of Pittsburgh
1972 Mellon Lecture, University of Pittsburgh
1976 Senior Scientist Award, Alexander Von Humboldt Foundation, Bonn, West Germany
1981 Third Alan E. Pierce Award by the American Peptide Chemists

1983	Japan Society for the Promotion of Sciences Fellowship Award
1987	First Huggins Memorial Award, University of Pittsburgh

NATIONAL LECTURESHIPS

1962	Squibb lecture, Rutgers University
1963	DuPont lecturer, University of Pennsylvania Medical School
	Harvey lecture, New York Academy of Medicine
1964	Reilly lecturer, University of Notre Dame
1965	Hanna lecture, Western Reserve University
1966	Venable lecture, University of North Carolina
1966	Rennebohm lecture, University of Wisconsin
1986	Distinguished lecture series, University of Pittsburgh School of Medicine (first lecture in connection with the medical school's 100th anniversary)

EDUCATION AND TRAINING

1936	Ph.D., organic chemistry, Federal Institute of Technology, Zürich, Switzerland
1936-38	Postdoctoral fellow, Department of Organic Chemistry, Federal Institute of Technology, Zürich, Switzerland. (Prof. L. Ruzicka)
1938-40	Fellow of the Rockefeller Foundation, Rockefeller Institute for Medical Research, New York City (Prof. Max Bergman)
1940-42	Research associate, Department of Biochemistry, Cornell Medical College, New York City (Prof. V. du Vigneaud).
1942-44	Scientific guest, Ciba Pharmaceutical Products, Inc., Summit, New Jersey.

APPOINTMENTS AND POSITIONS

1944	Assistant, associate, and research professor, Department of Chemistry, University of Pittsburgh
1952	Chairman, Biochemistry Department, University of Pittsburgh
1964	Professor of experimental medicine and director of the Protein Research Laboratory, University of Pittsburgh
1992	University professor emeritus, University of Pittsburgh

EDITORIAL SERVICES

1960-65	Associate member, Editorial Board, *Journal of Biological Chemistry*
1974-78	Editorial Advisory Board, *Journal of the American Chemical Society*

SELECTED BIBLIOGRAPHY

1939

With L. Ruzicka. Zur Kenntnis von 17-Athinyl- und 17-Vinyl-androstan- bezw. - androsten-Derivaten und deren Oxydationsprodukten. *Helv. Chim. Acta* 22:150-55.

With M. Bergmann. The specificity of trypsin II. *J. Biol. Chem.* 130:81-86.

1941

With V. du Vigneaud, D. B Melville, and P. Gyorgy. Isolation of biotin (vitamin H) from liver. *J. Biol. Chem.* 140:643-51.

With V. du Vigneaud, D. B. Melville, and J. Rachele. The preparation of free crystalline biotin. *J. Biol. Chem.* 140:763-66.

1942

With D. B. Melville and V. du Vigneaud. Adipic acid as an oxidation product of the diaminocarboxylic acid derived from biotin. *J. Biol. Chem.* 144:513-18.

1945

With R. H. McCoy, J. R. Felton, A. E. Axelrod, and F. J. Pilgrim. The biological activity of oxybiotin for the rat and chick. *Arch. Biochem.* 7:393-94.

1950

With R. A. Lucas. The chemical nature of a unique fatty acid. *J. Am. Chem. Soc.* 72:4328.

1952

With R. A. Lucas and S. M. Sax. The chemical nature of the fatty acids of *Lactobacillus arabinosus*. *J. Biol. Chem.* 195:473-85.

1953

With A. Rheiner and W. D. Peckham. Studies on polypeptides. V. The synthesis of arginine peptides. *J. Am. Chem. Soc.* 75:6083.

1956

With W. D. Peckham and A. Rheiner. Studies on polypeptides. VII. The synthesis of peptides containing arginine. *J. Am. Chem. Soc.* 78:238-42.

1958

With M. E. Wollner, H. Yajima, G. Spühler, T. A. Thompson, and E. T. Schwartz. Studies on polypeptides. XII. The synthesis of a physiologically active blocked tridecapeptide amide possessing the amino acid sequence of α-MSH. *J. Am. Chem. Soc.* 80:6458.

1960

With T.-Y. Liu. Lactobacillic acid biosynthesis. *Biochim. Biophys. Acta* 37:364-65.

1961

With H. Yajima, N. Yanaihara, T.-Y. Liu, and S. Lande. Studies on polypeptides. XVIII. The synthesis of a tricosapeptide possessing essentially the full biological activity of natural ACTH. *J. Am. Chem. Soc.* 83:487-89.

1962

With H. Yajima, T.-Y. Liu, and N. Yanaihara. Studies on polypeptides. XXIV. Synthesis and biological evaluation of a tricosapeptide possessing essentially the full biological activity of ACTH. *J. Am. Chem. Soc.* 84:4475-80.

With H. Yajima, T.-Y. Liu, N. Yanaihara, C. Yanaihara, and J. L. Humes. Studies on polypeptides. XXV. The adrenocorticotropic potency of an eicosapeptide amide corresponding to the N-terminal portion of the ACTH molecule; Contribution to the relation between peptide chain-length and biological activity. *J. Am. Chem. Soc.* 84:4481-86.

1963

With F. M. Finn, W. Haas, M. J. Smithers, Y. Wolman, and N. Yanaihara. Studies on polypeptides. XXVI. Partial synthesis of an enzyme possessing high rnase activity. *J. Am. Chem. Soc.* 85:833.

With R. D. Wells, H. Yajima, and J. Rosenthaler. Studies on polypeptides. XXVII. Elimination of the methionine residue as an essential functional unit for in vivo adrenocorticotropic activity. *J. Am. Chem. Soc.* 85:1546-47.

1965

With F. M. Finn. Studies on polypeptides. XXXIII. Enzymic properties of partially synthetic ribonucleases. *J. Am. Chem. Soc.* 87:645-51.

1966

With M. J. Smithers and F. M. Finn. Studies on polypeptides. XXXV. Synthesis of S-peptide$_{1\text{-}20}$ and its ability to activate S-protein. *J. Am. Chem. Soc.* 88:4107-4109.

1970

With J. P. Visser and F. M. Finn. Studies on polypeptides. XLIV. Potent synthetic S-peptide antagonists. *J. Am. Chem. Soc.* 92:2900-2909.

1977

With F. M. Finn, H.-J. Friesen, C. Diaconescu, and H. Zahn. Biotinylinsulins as potential tools for receptor studies. *Proc. Natl. Acad. Sci. U. S. A.* 74:2697-2700.

1980

With S. W. Wood, C. C. Brinton, J. A. Montibeller, and F. M. Finn. Iminobiotin affinity columns and their application to retrieval of streptavidin. *Proc. Natl. Acad. Sci. U. S. A.* 77:4666-68.

1984

With F. M. Finn, G. Titus, and D. Horstman. Avidin-biotin affinity chromatography: Application to the isolation of human placental insulin receptor. *Proc. Natl. Acad. Sci U. S. A.* 81:7328-32.

1988

With C. J. Stehle and F. M. Finn. Identification of a protein in adrenal particulates that binds ACTH specifically and with high affinity. *Endocrinology* 123:1355-63.

With K. D. Ridge and F. M. Finn. ATP sensitizes the insulin receptor to insulin. *Proc. Natl. Acad. Sci. U. S. A.* 85:9489-93.

华罗庚 Loo-Keng Hua

LOO-KENG HUA

November 12, 1910–June 12, 1985

BY HEINI HALBERSTAM

LOO-KENG HUA WAS one of the leading mathematicians of his time and one of the two most eminent Chinese mathematicians of his generation, S. S. Chern being the other. He spent most of his working life in China during some of that country's most turbulent political upheavals. If many Chinese mathematicians nowadays are making distinguished contributions at the frontiers of science and if mathematics in China enjoys high popularity in public esteem, that is due in large measure to the leadership Hua gave his country, as scholar and teacher, for 50 years.

Hua was born in 1910 in Jintan in the southern Jiangsu Province of China. Jintan is now a flourishing town, with a high school named after Hua and a memorial building celebrating his achievements; but in 1910 it was little more than a village where Hua's father managed a general store with mixed success. The family was poor throughout Hua's formative years; in addition, he was a frail child afflicted by a succession of illnesses, culminating in typhoid fever that caused paralysis of his left leg; this impeded his movement quite severely for the rest of his life. Fortunately Hua was blessed from the start with a cheerful and optimistic disposition, which stood him in good stead then and during the many trials ahead.

Hua's formal education was brief and, on the face of it, hardly a preparation for an academic career—the first degree he would receive was an honorary doctorate from the University of Nancy in France in 1980; nevertheless, it was of a quality that did help his intellectual development. The Jintan Middle School that opened in 1922 just when he had completed elementary school had a well-qualified and demanding mathematics teacher who recognized Hua's talent and nurtured it. In addition, Hua learned early on to make up for the lack of books, and later of scientific literature, by tackling problems directly from first principles, an attitude that he maintained enthusiastically throughout his life and encouraged his students in later years to adopt.

Next, Hua gained admission to the Chinese Vocational College in Shanghai, and there he distinguished himself by winning a national abacus competition; although tuition fees at the college were low, living costs proved too high for his means and Hua was forced to leave a term before graduating. After failing to find a job in Shanghai, Hua returned home in 1927 to help in his father's store. In that same year also, Hua married Xiaoguan Wu; the following year a daughter, Shun, was born and their first son, Jundong, arrived in 1931.

By the time Hua returned to Jintan he was already engaged in mathematics and his first publication, "Some Researches on the Theorem of Sturm," appeared in the December 1929 issue of the Shanghai periodical *Science*. In the following year Hua showed in a short note in the same journal that a certain 1926 paper claiming to have solved the quintic was fundamentally flawed. Hua's lucid analysis caught the eye of a discerning professor at Quing Hua University in Beijing, and in 1931 Hua was invited, despite his lack of formal qualification and not without some reservations on the part of several faculty members, to join the mathematics department there. He began as a clerk in the library, and then moved to become an assistant in mathematics; by September 1932 he was an instructor and two years later came promotion to the rank of lecturer. By that time he had published another dozen papers and in some of these one could begin to find intimations of his future interests; thanks to his natural talent and dedication, Hua was now, at the age of 24, a professional mathematician.

At this time Quing Hua University was the leading Chinese institution of higher education, and its faculty was in the forefront of the endeavor to bring the country's mathematics and science abreast of knowledge in the West, a formidable task after several hundred years of stagnation. During 1935-36 Hadamard and Norbert Wiener visited the university; Hua eagerly attended the lectures of both and created a good impression. Wiener visited England soon afterward and spoke of Hua to G. H. Hardy. In this way Hua received an invitation to come to Cambridge, England, and he arrived in 1936 to spend two fruitful years there. By now he had published widely on questions within the orbit of Waring's problem (also on other topics in diophantine analysis and function theory) and he was well prepared to take advantage of the stimulating environment of the Hardy-Littlewood school, then at the zenith of its fame. Hua lived on a $1,250 per annum scholarship awarded by the Culture and Education Foundation of China; it is interesting to recall that this foundation derived its funds from reparations paid by China to the United States following wars waged in China by the United States and several other nations in the previous century. The amount of the grant imposed on him a Spartan regime. Hardy assured Hua that he could gain a Ph.D. in two years with ease, but Hua could not afford the registration fee and declined; of course, he gave quite different reasons for his decision.

During the Cambridge period Hua became friendly with Harold Davenport and Hans Heilbronn, then two young research fellows of Trinity College—one a former student of Littlewood and the other Landau's last assistant in Göttingen—with whom he shared a deep interest in the Hardy-Littlewood approach to additive problems akin to Waring's. They helped to polish the English in several of Hua's papers, which now flowed from his pen at a remarkable rate; more than 10 of his papers date from this time, and many of these appeared in due course in the publications of the London Mathematical Society.

About the only easy thing about Waring's problem is its statement: In 1770 Waring asserted without proof (and not in these words) that for each integer $k \geq 2$ there exists an integer $s = s(k)$ depending only on k such that every positive integer N can be expressed in the form

$$N = x_1^k + x_2^k + \ldots + x_s^k \tag{1}$$

where the $x_i (i = 1,2, \ldots, s)$ are non-negative integers. In that same year Lagrange had settled the case $k = 2$ by showing that $s(2) = 4$, a best possible result; after that, progress was painfully slow, and it was not until 1909 that Hilbert solved Waring's problem in its full generality. His argument rested on the deployment of intricate algebraic identities and yielded rather poor admissible values of $s(k)$. In 1918 Hardy and Ramanujan returned to the case $k = 2$ in order to determine the number of representations of an integer as the sum of s squares by means of Fourier analysis, an approach inspired by their famous work on partitions, and they succeeded. This encouraged Hardy and Littlewood in 1920 to apply a similar method for general k, and they devised the so-called circle method to tackle the general Hilbert-Waring theorem and a host of other additive problems, Goldbach's problem among them. During the next 20 years the machinery of the circle method came to be regarded about as difficult as anything in the whole of mathematics; even today, after numerous refinements and much progress, the intricacies of the method remain formidable.[1] In outline, the circle method of Hardy-Littlewood-Ramanujan, as modified by I. M. Vinogradov, is as follows: Let

$$T(\alpha) = \sum_{x=0}^{P} e^{2\pi i \alpha x^k}, P = \lfloor N^{1/k} \rfloor,$$

and denote by $R_s^{(k)}(N)$ the number of representations of N in the form (1). Then

$$R_s^{(k)}(N) = \int_0^1 T(\alpha)^s e^{-2\pi i N\alpha} d\alpha,$$

and to prove the Hilbert-Waring theorem it is enough to show that $R_s^{(k)}(N) > 0$ for all large enough positive integers N, with s some natural number depending only on k. The least admissible value of s is denoted by $G(k)$. The generating function $T(\alpha)$ is well approximable on each of a family of disjoint intervals in [0,1] centered at rational numbers with small denominators, and the plan is to show that the main contribution to $R_s^{(k)}(N)$ comes from integration over these intervals while the integral over the complement, usually referred to as the minor arcs, is of a lesser order of magnitude. The latter task, estimation on the minor arcs, is the harder, but here Hardy and Littlewood used an estimate of a trigonometric sum more general that $T(\alpha)$ that Hermann Weyl had established in 1916 in connection with his fundamental work on criteria for the uniform distribution of a sequence. In this way they were able to show that

$$G(k) \le k2^{k-1} + 1.$$

This is the background against which Hua set to work as a young man, and it is probably fair to say that it is for his contributions in this area that Hua's name will remain best remembered: notably for his seminal work on the estimation of trigonometric sums like $T(\alpha)$, singly or on average. One such average result, now known as Hua's lemma, asserts that for any $\varepsilon > 0$ and for $1 \le j \le k$,

$$\int_0^1 \left|T(\alpha)\right|^{2^j} d\alpha = O_\varepsilon\left(P^{2^j - j + \varepsilon}\right);$$

since $\left|T(\alpha)\right| \le P$ trivially, this estimate yields a saving over the trivial of almost j, for each $j \le k$, in the exponent of P. When used on the minor arcs in conjunction with Weyl's estimate of $T(\alpha)$, Hua's Lemma led to the improved bound

$$G(k) \le 2^k + 1.$$

Nowadays better results are known,[1] but all involve major difficulties.

Hua might well have remained in England longer, but home was never far from his thoughts and the Japanese invasion of China in 1937 caused him much anxiety. He left Cambridge in 1938 to return to his old university, now as a full professor. However, Quing Hua University was no longer in Beijing; with vast portions of China under Japanese occupation, it had migrated to Kunming, the capital of the southern province of Yunan, where it combined with several other institutions to form the temporary Associated University of the South West. There Hua and his family remained through the World War II years, until 1945, in circumstances of poverty, physical privation, and intellectual isolation. Despite these hardships Hua maintained the level of intensity of his Cambridge period and even exceeded it; by the end of 1945 he had more than 70 publications to his name. During this time he studied Vinogradov's seminal method of estimating trigonometric sums and reformulated it, even in sharper form, in what is now known universally as Vinogradov's mean value theorem. This famous result is central to improved versions of the Hilbert-Waring theorem, and has important applications to the study of the Riemann zeta function. Hua wrote up this work in a booklet that was accepted for publication in Russia as early as 1940, but owing to the war, did not appear (in expanded form) until 1947 as a monograph of the Steklov Institute.

Hua spent three months in Russia in the spring of 1946 at Vinogradov's invitation. Mathematical interaction apart, he was impressed by the organization of scientific activity there, and this experience influenced him when later he reached a position of authority in the new China. In the years ahead, even though Hua's scientific activities branched out in other directions, Hua was always ready to return to Waring's problem, to number theory in general and especially to questions involving exponential sums; thus as late as 1959 he published an important monograph on "Exponential Sums and Their Aplications in Number Theory" for the *Enzyklopädie der Matematischen Wissenschaften*. His instinct for what was important and his marvelous command of technique make his papers on number theory even now virtually an index to the major activities in that subject during the first half of the twentieth century.

In the closing years of the Kunming period Hua turned his interests to algebra and to analysis, as much as anything for the benefit of his students in the first instance, and soon began to make original contributions in these subjects too. Thus Hua became interested in matrix algebra and wrote several substantial papers on the geometry of matrices. He had been invited to visit the Institute for Advanced Study in Princeton, but because C. L. Siegel was working there along somewhat similar lines, Hua declined, at first in order to develop his ideas independently. In September 1946, shortly after returning from Russia, Hua did depart for Princeton, bringing with him projects not only in matrix theory but also in functions of several complex variables and in group theory. At this time civil war was raging in China and it was not easy to travel; therefore, the Chinese authorities assigned Hua the rank of general in his passport for the "convenience of travel."

According to his biographer, Hua's "most significant and rewarding research work" during his stay in the United States was on the topic of skew fields, that is, on (non-commutative) division rings, of which the quaternions are a classic example. Thus, Hua was the first to show that every semi-automorphism of a skew field F is either an automorphism or an anti-automorphism—more explicitly, if σ is a one-to-one mapping of F onto itself such that $1^\sigma = 1$ and

$$(a+b)^\sigma = a^\sigma + b^\sigma, \ (aba)^\sigma = a^\sigma b^\sigma a^\sigma,$$

for all a, b in F, then either

$$(ab)^{\sigma} = a^{\sigma} b^{\sigma} \text{ for all } a,\ b \text{ in } F$$

or

$$(ab)^{\sigma} = b^{\sigma} a^{\sigma}.$$

He also gave a spectacular demonstration of his "direct" approach to problems with his proof that every normal subfield of a skew field is contained in its center. The argument is only one and a half pages long and rests on the following identity: if $ab \neq ba$, then

$$a = \left(b^{-1} - (a-1)^{-1} b^{-1} (a-1)\right)\left(a^{-1} b^{-1} a - (a-1)^{-1} b^{-1} (a-1)\right).$$

This result is now known in the literature as the Cartan-Brauer-Hua theorem; originally H. Cartan's proof had used much deeper tools.

There was much else, of course, to distinguish this last major creative period of his life. Hua wrote several papers with H. S. Vandiver on the solution of equations in finite fields and with I. Reiner on automorphisms of classical groups. Much of his algebraic work later provided the basis for the monograph "Classical Groups" by Wan Zhe Xian and Hua (published by the Shanghai Scientific Press in Chinese in 1963).

On the personal side, in the spring of 1947 Hua underwent an operation at the Johns Hopkins University on his lame leg that much improved his gait thereafter, to his and his family's delight. Also in 1947 their daughter Su was born; two more sons had arrived earlier, Ling and Guang, the latter in 1945 and one more daughter, Mi, was born a little later. In the spring of 1948 Hua accepted appointment as a full professor at the University of Illinois in Urbana-Champaign. There he directed the thesis of R. Ayoub, later a professor at Pennsylvania State University; continued his work with I. Reiner; and influenced the thinking of several young research workers, L. Schoenfeld and J. Mitchell among them. His stay in Illinois was all too brief; exciting developments were taking place in China, and Hua watched them eagerly, wanting to be part of the new epoch. Although he had brought his wife and three younger children to Urbana and they had settled in quite well, the urge to return was too great; on March 16, 1950, he was back in Beijing at his alma mater, Quing Hua University, ready to add his contribution to the brave new world. He was then at the peak of his mathematical powers and, as he wrote to me many years later, the 1940s had been to him in retrospect the golden years of his life. Despite the trials that he would face, he did not at any subsequent time regret his decision to return.

Back in China, Hua threw himself into educational reform and the organization of mathematical activity at the graduate level,[2] in the schools, and among workers in the burgeoning industry. In July 1952 the Mathematical Institute of the Academia Sinica came into being, with Hua as its first director. The following year he was one of a 26-member delegation from the Academia Sinica to visit the Soviet Union in order to establish links with Russian science. At this time Hua entertained doubts whether the Communist Party at home trusted him, and it came as an agreeable surprise to him to learn in Moscow that the Chinese government had agreed to a proposal by the Soviet government to award Hua a Stalin Prize. Following Stalin's death the prize was discontinued, and Hua missed out; in view of later developments, he told me, he had a double reason to be satisfied!

Despite his many teaching and administrative duties, Hua remained active in research and continued to write, not only on topics that had engaged him before but also in areas that were new to him or had been only lightly touched on before. In 1956 his voluminous text, *Introduction to Number Theory,* appeared. (The preface to the 1975 Chinese edition was excised by government order because Hua was out of favor during much of the Cultural Revolution); later this was published by Springer in English translation and is still in print. *Harmonic Analysis of Functions of Several Complex Variables in the Classical Domains* came out in 1958 and was translated into Russian in the same year, followed by an English translation by the American Mathematical Society in 1963. Most of the results of this important monograph are due to Hua, with some overlap with the work of Siegel. The results have applications to representation theory, the theory of homogeneous spaces, and to the theory of automorphic forms. The monograph also includes joint work with K. H. Look on the Poisson and Bergman kernels. This work was useful in later investigations by E. Stein on boundary behavior of holomorphic functions. Another aspect of this work reveals that by 1959 Hua appreciated the importance of extending Hodge theory to open Hermitian manifolds; J. J. Kohn did this successfully in 1962. The monograph on exponential sums mentioned earlier, which was published in 1959, has also since been translated into English. Hua was a fluent and prolific writer, there being many books and articles by him in Chinese for schools and for undergraduate use to make modern mathematics accessible to students. He also wrote poetry all his life, for his own amusement and for the pleasure of his friends.

In 1958 he suffered a rude awakening from utopian dreams with the so-called Great Leap Forward, when a Mao-inspired, savage assault on intellectuals swept the country, implemented with enthusiasm by a compliant bureaucracy inspired by Orwellian slogans like "the lowliest are the smartest, the highest the most stupid." Despite his eminence and some protection in high places, Hua had to suffer harassment, public abuse, and constant surveillance. Nevertheless, during this troubled period Hua developed, with Wang Yuan, a broad interest in linear programming, operations research, and multidimensional numerical integration. In connection with the last of these, the study of the Monte Carlo method and the role of uniform distribution led them to invent an alternative deterministic method based on ideas from algebraic number theory. Their theory was set out in *Applications of Number Theory to Numerical Analysis*, which was published much later, in 1978, and by Springer in English translation in 1981. The newfound interest in applicable mathematics took him in the 1960s, accompanied by a team of assistants, all over China to show workers of all kinds how to apply their reasoning faculty to the solution of shop-floor and everyday problems. Whether in ad hoc problem-solving sessions in factories or open-air teachings, he touched his audiences with the spirit of mathematics to such an extent that he became a national hero and even earned an unsolicited letter of commendation from Mao, this last a valuable protection in uncertain times. Hua had a commanding presence, a genial personality, and a wonderful way of putting things simply, and the impact of his travels spread his fame and the popularity of mathematics across the land.[3] When much later he traveled abroad, wherever he stayed Chinese communities of all political persuasions flocked to meet him and do him honor; in 1984 when he organized a conference on functions of several complex variables in Hangzhou, colleagues from the West were astonished by the scale of the publicity accorded it by the Chinese media.

But all that was in the future. In 1966 Mao set in motion the next national calamity, which came to be known as the Cultural Revolution and would last 10 years. A pronouncement of Mao dated as early as June 26, 1965, sent a dire signal of things to come to the intellectuals: "The more you read, the more stupid you become." Hua spent many of these years under virtual house arrest. He attributed his survival to the personal protection of Chou En-lai. Even so, he was exposed to harassing interrogations, some of his manuscripts (on mathematical economics) were confiscated and are now irretrievably lost, and attempts were made to extract from his associates and former students damaging allegations against him. (In 1978 the Chinese ambassador to the United Kingdom described one such occasion to me; Chen Jing-run, then probably the best known Chinese mathematician of the next generation, was made to stand in a public place for several hours, surrounded by a mob, and exhorted to bear witness against Hua. Chen, present at this conversation, chimed in to say that, actually, he had quite enjoyed the occasion, since no student could trouble him with silly questions and he had had time, uninterrupted, to think about mathematics!) It is surely no accident that the flow of Hua's publications came to an untimely end in 1965. He continued to work, of course. There are several joint papers on numerical analysis (with Wang Yuan) and on optimization (with Ke Xue Tong Bao) in the 1970s, but these are probably based on work done earlier; there are also expository articles and texts derived from the vast teaching and consulting experience he accumulated over the years. As he would reminisce sadly in a 1991 article, "Upon entering [my] sixtieth year . . . almost all energy and spirit were taken from me."

With the end of the Cultural Revolution in 1976 Hua entered upon the last period of his life. Honor was restored to him at home, and he became a vice-president of Academia Sinica, a member of the People's Congress and science advisor to his government. In addition, Chinese Television (CCTV) produced a mini-series telling the story of Hua's life, which has been shown at least twice since then. In 1980 he became a cultural ambassador of his country charged with reestablishing links with Western academics, and during the next five years he traveled extensively in Europe, the United States, and Japan. In 1979 he was a visiting research fellow of the then Science Research Council of the United Kingdom at the University of Birmingham and during 1983-84 he was Sherman Fairchild Distinguished Scholar at the California Institute of Technology. For much of this time he was tired and in poor health, but a characteristic zest for life and a quenchless curiosity never deserted him; to a packed audience in a seminar in Urbana in the spring of 1984 he spoke about mathematical economics. One felt that he was driven to make up for all those lost years. In his last letter to me, dated May 21, 1985, he reported that unfortunately most of his time now was devoted to "non-mathematical activities, which are necessary for my country and my people." He died of a heart attack at the end of a lecture he gave in Tokyo on June 12, 1985.

Hua received honorary doctorates from the University of Nancy (1980), the Chinese University of Hong-Kong (1983), and the University of Illinois (1984). He was elected a foreign associate of the National Academy of Sciences (1982) and a member of the Deutsche Akademie der Naturforscher Leopoldina (1983), Academy of the Third World (1983), and the Bavarian Academy of Sciences (1985).

Professor Wang Yuan has written a fine biography of Hua,[4] and I am indebted to it for some of the information I have used. I have also drawn on the obituary notice I wrote for *Acta Arithmetica* (LI(1988):99-117).

NOTES

1. R. C. Vaughan. *The Hardy-Littlewood Method,* 2nd ed. Cambridge: Cambridge University Press, 1997.

2. Among his students were Chen Jing-run, Pan Chen-dong, and Wang Yuan in number theory; Wan Zhi Xian in algebra; and Kung Sheng and Lu Qi Keng in analysis.

3. For a selection of the problems dealt with, see *Popularizing Mathematical Methods in the People's Republic of China*, by L.-K. Hua and Y. Wang. Boston: Birkhäuser, 1989.

4. Hua Loo-keng. Translated by Peter Shiu. Singapore: Springer, 1999.

SELECTED BIBLIOGRAPHY

1936

With S. S. Shu. On Fourier transforms in L^p in the complex domains. *J. Math. Phys.* 15:249-63.

1938

On Waring's problem. *Q. J. Math.* 9:199-202.

On the representation of numbers as the sums of the powers of primes. *Math. Z.* 44:335-46.

1940

On an exponential sum. *J. Chin. Math. Soc.* 2:301-12.

With H. F. Tuan. Some "Anzahl" theorems for groups of prime-power orders. *J. Chin. Math. Soc.* 2:313-19.

1942

On the least primitive root of a prime. *Bull. Am. Math. Soc.* 48:726-30.

The lattice-points in a circle. *Q. J. Math.* 13:18-29.

1944

On the theory of automorphic functions of a matrix variable. I. Geometrical basis. II. The classification of hypercircles under the symplectic group. *Am. J. Math.* 66:470-88, 531-63.

1945

Geometries of matrices. I. Generalizations of von Staudt's theorem. II. Arithmetical construction. *Trans. Am. Math. Soc.* 57:441-81, 482-90.

1946

Orthogonal classification of Hermitian matrices. *Trans. Am. Math. Soc.* 59:508-23.

1947

Geometries of matrices. III. Fundamental Theorems in the geometries of symmetric matrices. *Trans. Am. Math. Soc.* 61:229-55.

With S. H. Min. On a double exponential sum. *Sci. Rep. Tsing Hua Univ.* A4:484-518.

1948

On the automorphisms of the symplectic group over any field. *Ann. Math.* 49:379-759.

1949

On the automorphisms of a sfield. *Proc. Natl. Acad. Sci. U. S. A.* 35:386-89.

Some properties of a sfield. *Proc. Natl. Acad. Sci. U. S. A.* 35:533-37.

An improvement of Vinogradov's mean-value theorem and several applications. *Q. J. Math.* 20:48-61.

1951

Supplement to the paper of Dieudonné on the automorphisms of classical groups. *Mem. Am. Math. Soc.* 2:96-122.

With I. Reiner. Automorphisms of the unimodular group. *Trans. Am. Math. Soc.* 71:331-48.

1957

On exponential sums. *Sci. Rec. (N. S.)* 1(1):1-4.

On the major arcs of Waring problem. *Sci. Rec. (N. S.)* 1(3):17-18.

On the Riemannian curvature in the space of several complex variables. *Schr. Forschungsinst. Math.* 1:245-63.

1959

Abschätzungen von Exponentialsummen und ihre Anwendung in der Zahlentheorie. Leipzig: Teubner. (Chinese translation: Peking: Academic Press, 1963; Russian translation: Moskva: Mir, 1964.)

1963

Harmonic Analysis of Functions of Several Complex Variables in the Classical Domains (English translation). Providence, R.I.: American Mathematical Society. (In Chinese: Peking: Academic Press, 1958, rev. ed., 1965. Russian translation: Moskva: Izd. Inostran. Lit., 1959.)

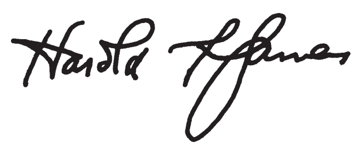
1965

Additive theory of prime numbers (English translation). Providence, R.I.: American Mathematical Society. (In Russian: *Trudy Inst. Math. Steklov* 22(1947):1-179; Chinese translation [revised]: Peking: Academic Press, 1957; Hungarian translation: Budapest: Académiai Kiadó, 1959; German translation: Leipzig: Teubner, 1959.)

1981

With W. Yuan. *Application of Number Theory to Numerical Analysis* (English translation). New York: Springer. (In Chinese: Peking: Academic Press, 1978.)

U.S. Geological Survey.



HAROLD LLOYD JAMES

June 11, 1912–April 2, 2000

BY PAUL BARTON

HAROLD LLOYD JAMES IS widely recognized for his trailblazing interpretations of the field relationships and petrology of the metamorphosed and structurally complex iron-rich sedimentary rocks known as "iron-formation." Although James focused his research primarily in northern Michigan, the fundamental interpretations he made there have proven applicable worldwide, and northern Michigan has served as the archetype of sedimentary iron deposits that constitute the bulk of the world's iron ore resources. He is broadly acknowledged to have been a world leader in this scientifically and economically important subject.

Prior to James's work, the unusual chemical and mineralogical character of iron-formation was attributed to metamorphism and hydrothermal alteration of iron-rich carbonate sedimentary rocks. James peered through the veil of metamorphism and subsequent local oxidation, unraveling the spatial relations among rock types, deciphering their primary igneous and sedimentary patterns, understanding their structural and petrogenic affiliations, and showing that the iron-rich assemblages of rocks exhibit a systematic and oft repeated sequence of intergradational facies that reflect the integrated sedimentary environments in ancient marine basins. These deposits include (1) a carbon-rich and sulfide-rich series of lithologies indicative of a highly reduced, deep water, euxinic part of a basin; (2) a carbonate-rich facies reflecting non-euxinic but still poorly oxygenated water; (3) a silicate facies deposited in waters having an intermediate oxidation state; and (4) a shallow-water, variably well-oxygenated facies having two subfacies distinguished by the oxidation state of the iron, the less oxidized represented by magnetite + chert and more strongly oxidized by hematite + chert. The magnetite or hematite + chert type constitutes the banded iron-formation of major resource interest. James showed that all these rock types may have been locally, and with varying intensities, metamorphosed and/or hydrothermally altered to yield different textures and mineral assemblages, yet for the most part, retaining distinctive features that enable their protoliths to be identified, thereby making possible the conceptual reconstruction of the parent sedimentary basins. The effective use of that reconstruction is a powerful tool to locate the economically important oxide facies rocks that represent the principal economic targets. James's model for the genesis of iron-formation became widely acclaimed, and the Michigan deposits became a Mecca for geologists worldwide who wished to learn about iron resources.

The Michigan work spawned another significant contribution having global application. Descriptions of diverse terranes of ancient, almost entirely unfossiliferous Precambrian rocks (that represent more than 85 percent of the total age of Earth) had resulted in an array of names for rock units that were only locally applicable. This disjointed situation impeded correlations and interpretations between different areas. James (1978, 1981) was the leader in an international community of geologists that organized the evidence based on geochronologic correlation and under his guidance introduced the now widely accepted "W-X-Y-Z" terminology for Precambrian rocks that facilitates communication.

James's constructive influence extended far beyond his own scientific work: as friend, advisor, mentor, role model, and colleague to many associates, as an active member of the geologic community, and culminating in service (1965-71) as chief geologist of the U.S. Geological Survey. He taught advanced courses at Northwestern University and the University of Minnesota. He was active in the professional community as a leader in several societies and an active participant in various study groups.

Harold Lloyd James (known to his many friends and colleagues as Hal) was born on June 11, 1912, in Nanaimo, British Columbia, the eldest of five children (two sons and three daughters) of Evan and Blodwen James, who had emigrated from Wales in 1911. Hal's father was a coal miner in Wales, in British Columbia, and finally in Washington state, and he loved music, playing the organ and the piano, and choral singing. His mother (nee Davies) had been the head mistress of an elementary school in Wales and taught briefly in Canada. The family moved to Bellingham, Washington, in 1923 and Hal became eligible to declare himself a U.S. citizen when his father became naturalized in 1929; but through no fault of his own, the paperwork for his naturalization was not completed until 1940.

Hal attended public schools in Nanaimo and Bellingham and graduated from the latter's Whatcom High School in 1933 at the age of 20, having spent six years of full-time work to supplement his family's finances, beginning at age 14 as a lumber mill worker and shifting at 18 to a contract coal miner (often teamed with his father, he was evidently quite proficient at it). He began college at Bellingham Normal School (now Western Washington University) in the summer of 1934 and transferred to Washington State College (now University) for the fall term, intending to major in mining geology. In a 1995 letter to his sons he relates that although he initially lacked specific academic goals and certainly did not visualize a career as a scientist, he did feel that he needed to become a professional of some sort, and in view of his experience, mining geology came closest. Hal repeatedly interrupted his formal education to recoup his finances by working as a coal miner, but he returned to earn a bachelor of science degree in geology as a member of Phi Beta Kappa and with highest honors in 1938; he was the first of his family to graduate from college. He had spent only five semesters on campus, but met graduation requirements by transfer credits from Bellingham Normal School and correspondence courses, plus some helpful boosts from Washington State faculty who recognized Hal's exceptional potential and went out of their way to help him.

His is an excellent example of an immensely productive career whose direction and accomplishments hinged several times on good fortune, generous responses from supervisors and educators, and support from family and associates, combined with his own persistent quest for long-range betterment rather than immediate gratification. Perhaps his best good fortune came on February 13, 1936, when he married the former Ruth Graybeal, daughter of close family friends in Bellingham and younger sister of his youthful best friend, Herb. Ruth provided steady support and encouragement for more than 53 years; they raised four sons: David E., Robert C., Hugh L., and Herbert T.

Just prior to James's graduation in 1938 the departmental chair, Harold Culver, recommended him to be a summer field assistant to Charles Park, then with the U.S. Geological Survey (USGS) and later dean of earth sciences at Stanford, who was mapping the supposedly extensive manganese deposits of the Olympic Peninsula, Washington. This association began James's career-long affiliation with the USGS. As it turned out, Park and coworkers (James among them) demonstrated that the manganese deposits were indeed widespread but of marginal quality and trivial quantity. (We will return to the consequences of this study later.) James had intended to return to Washington State for graduate work, but two of his coworkers, Ralph Roberts and Bob Yates, were graduate students at the University of Washington, and they persuaded him to undertake graduate work there where a compact but vigorous department was headed by petrologist George Goodspeed and included geomorphologist J. Hoover Mackin. James spent 1938-40 as a graduate student in geology at the University of Washington and assisted in Goodspeed's petrology laboratory. A long field season in 1939 was split between the ongoing Olympic manganese study and a study of chromite deposits in Oregon and California as an assistant to Francis Wells. James spent the early summer of 1940 with Preston Hotz on chromite studies in southwestern Oregon and then a final month completing work with Park on the Olympic manganese showings. In 1940, before James completed a degree, several of the Washington faculty advised him to transfer to the University of Minnesota, which had a very strong hardrock-dominated Department of Geology. However, Minnesota lacked an appropriate opening that year, and Princeton provided an attractive fallback choice with a graduate assistantship with Harry Hess. This proved to be a very fortuitous turn of events, and Princeton provided an ideal intellectual and social environment. In 1942 Hess, who held a reserve commission in the Navy, was called to active service, and James took over as instructor in mineralogy.

Let us digress for a moment to provide some context for external events influencing James's early career. In the late 1930s and early 1940s competition for mineral resources among nations contributed substantially to international instability that precipitated actions such as Japan's expansion into Manchuria and other parts of China, Korea, and eventually most of southeast Asia; Italy's struggle in Ethiopia; and Germany's aggression in central Europe, Scandinavia, and Russia. The United States, although relatively well endowed with mineral raw materials and fuels, did not possess extensive proven deposits of most ferrous metals (manganese, chromium, vanadium, tungsten, nickel, cobalt), aluminum, and a few other minerals essential for defense purposes. Evaluation of domestic resources became a major national concern and resulted in many high-priority, quick response studies by the USGS and the U. S. Bureau of Mines. Resource geologists were more valuable than soldiers and were deferred from the draft; and James, with his almost accidental experience with manganese and chromium, was among them.

One example of resource evaluation was the previously mentioned study of Park and others of the Olympic manganese deposits that, based on a 1918 reconnaissance report, had been widely touted to contain valuable resources; moreover, metallurgists at Washington State had already developed a process to extract manganese from refractory manganese silicate minerals typical of the Olympic deposits. Pressure for development mounted. In October of 1941 a "manganese convention" was held at Aberdeen, Washington, to review progress, and USGS Director Walter Mendenhall was invited to present the agency's findings. Mendenhall deferred the presentation of what he knew were unfavorable prospects to Charles Park. Park, not wishing to journey all the way from Washington, D.C., to Aberdeen just to present highly negative findings, sent some slides and notes to James, who was then in Oregon evaluating a chromite prospect in the Twin Sisters Mountains. With no little trepidation, Harold James, a newly minted junior geologist (grade P-1) presented the USGS results to an audience many members of which were both disappointed and hostile. The well-documented facts that James presented, however, burst the Olympic manganese bubble and saved the nation fiscal resources for more productive pursuits. He was subsequently commended by several persons (representing railroads, utilities, and other infrastructure parties) who had been under pressure to make major expenditures, without credible assurances, based on the proposition that the amount of ore theretofore advertised actually existed.

James had intended to study some interesting hornblende gabbros of southwestern Oregon for his doctoral dissertation, but because of wartime concerns, he abandoned that project. He completed his Ph.D. qualifying exam in May of 1942 and began full-time USGS employment in June as part of the Strategic Minerals program. Until mid-1943 he worked mostly on chromite deposits near Red Lodge, Montana, and used the results of that study as his Princeton Ph.D. dissertation. He completed the dissertation in 1945 under Arthur F. Buddington as his principal mentor, and it was published in 1946 as USGS Bulletin 945-F, "Chromite Deposits near Red Lodge, Montana." Although these deposits ultimately proved to be marginal in both size and metallurgical grade, they were within a few miles of the Stillwater mafic complex, which contained the principal known chromium resources within the United States, and thus their evaluation was of major interest for the war effort.

During those early war years James also made rapid-response evaluations of occurrences of materials of interest to the war effort: talc, optical calcite, graphite, sapphire (a critical mineral for bearings in instruments), abrasive corundum, asbestos, and copper in southwest Montana, chromite in Oregon, and nickel in Washington. It was an intense existence, with steep learning curves. In August 1943 he joined John Albers, Paul Sims, and several others in a more sustained study of the lead-zinc ores of the Metaline district, Washington; they were supervised by Edward Sampson, then on wartime leave from Princeton. In contrast to the targets of his many brief prior studies of strategic and critical minerals, supplies of neither lead nor zinc were deficient for national defense; and James felt that his efforts were inappropriately applied. Therefore, in early 1944, after receiving no response to a request to the USGS for a more meaningful assignment, he sought a commission in the Navy. This action did awaken his supervisors, and they successfully urged James to reconsider and to join the USGS Military Geology Unit based in Washington, D.C. The Military Geology Unit had been established by Wilmot Bradley and Charles Hunt earlier in the war to perform terrain analysis to aid military operations, such as selecting beaches for landings, sites for forward airfields, and availability of water supplies, and identifying problems and opportunities that various terrains offered for operations. The unit had large, highly qualified scientific and library staffs that provided timely strategic technical information presented in a non-technical mode. It was a busy and satisfying task, and it even had some humor. For example, although his security clearance was at the secret level, some reports he prepared were immediately stamped “Top Secret,” so that he was forbidden to view some of his own work.

In early 1945 James was invited to join a special Engineering Terrain Intelligence Team attached to the 30th Engineer Battalion in Hawaii under Philip S. Shenon. Their status was peculiar, being uniformed civilians in a military organization. James’s simulated rank was that of major. They puzzled about saluting rules and whether they should be addressed "sir" or "mister" before finally settling on "doctor" regardless of whether it was academically correct. The team worked intensively with aerial photographs in a secluded underground facility near Schofield Barracks, providing tactical support by producing detailed maps on very short notice for operations in the Pacific theater. In the spring of 1945 the team began examining southern Kyushu preparatory for the invasion of the Japanese home islands, noting with considerable concern the many sheltered potential gun positions offered by caves along the proposed beachheads. James's part of the team was scheduled to follow on the third day of the initial landings to provide close advisory support for the combat engineers of the 6th Army. Fortunately the atomic bombing of Hiroshima and Nagasaki terminated that plan, and James returned to his family in Bellingham in September 1945.

In November 1945 his old supervisor, Charles Park, assigned James to a joint USGS-state of Michigan study of the iron deposits in the 300-square-mile Iron River-Crystal Falls district, a task that he accepted unenthusiastically because the intellectual challenges were ill defined at the time. The family moved to Iron River, Michigan, and remained there until 1954; it was an excellent environment in which to raise children and offered an opportunity for Hal to hone his skills in hunting, with the bow as well as rifle. James worked with a group initially under Carl E. Dutton and including full-timers Larry Smith and Dwight Lemmon, supplemented by summer mapping by Francis J. Pettijohn and Carl Lamey. Dutton soon was transferred to Madison, leaving James in charge. His slot had been previously occupied by geophysicist James Balsley, who was reassigned to follow up his innovative geologic use of airborne magnetometry initially developed as an antisubmarine tool by the

Navy. Thus James found himself the project magnetics expert, an important role because magnetics was an essential tool to extend direct geologic observations into the subsurface, especially pertinent for magnetic iron-formation. This task passed on to Ken Wier in late 1946.

In 1945 what at first seemed a mundane assignment soon evolved into an opportunity to unravel geologic intricacies about iron-resource occurrences that had theretofore been undecipherable and to clarify the geologic history of the oldest part of northern Michigan. A large group of geologists was associated with the project, each member contributing significant pieces; but it was James who led the assembly of the regional picture, inserted the iron deposits into their genetic context, and prepared three classic papers. The first, in 1954, definitively described the stratigraphic relations among the facies of iron-formation and was preceded by abstracts of two papers presented in 1949 and 1951 at the Geological Society of America annual meetings. The second, in 1955, defined the nodal pattern of metamorphism in northern Michigan and established the relation between the metamorphic grade and the character of the iron ore. The third, in 1958, assembled and clarified the stratigraphic relations among the diverse older Precambrian rocks throughout northern Michigan. These three seminal studies defined the core of James's personal scientific work and formed the principal basis for his election to the National Academy of Sciences in 1962.

In 1953 and again in 1954 James interrupted his studies in Michigan to become visiting lecturer for the spring terms at Northwestern University. There he taught graduate courses in mineral deposits and shared a graduate course in petrology with Arthur Howland. In 1954 the project headquarters was transferred to the newly opened USGS center in Menlo Park, California. This center included many exceptional earth scientists such as Richard Doell, Arthur Lachenbruch, Allan Cox, Vincent McKelvey (who subsequently became director of the USGS), and Donald White, and it provided a mutually stimulating scientific environment that continues to this day. He joined with McKelvey and White to review the design for an expansion of the Menlo Park center and, to the temporary chagrin of USGS Director Tom Nolan, to redesign Building 2 so that, to paraphrase James's own words, the design fitted the needs of its earth-scientist occupants rather than the artistic concepts of the architects. The essential elements of that design proved exceptionally workable and were incorporated 15 years later into the design of the John Wesley Powell headquarters building for the USGS in Reston, Virginia.

James served a two-year tour as assistant chief of the large Mineral Deposits Branch in Washington under Charles Anderson. He returned to Menlo Park in 1958 and began a field study of the bedded iron deposits in the Early Proterozoic rocks of southwestern Montana. In 1961 he interrupted these studies to accept an appointment as professor of mineral deposits at the University of Minnesota, where he taught graduate courses concerning the origins and methods of study of mineral deposits. His work on the Michigan iron deposits continued and included a path-blazing study with Robert Clayton in 1962 on the fractionation of oxygen isotopes between magnetite, hematite, and quartz. At Minnesota, James established a laboratory for oxygen isotope analysis in collaboration with Eugene Perry. He remained affiliated with the USGS on a when-actually-employed basis, a common practice at the time that was used to ensure optimal interaction with academia.

In 1965 James was called on to serve a four-year term as chief geologist for the USGS in Washington, where he managed more than 2,000 scientists and support personnel working on topics such as oil and gas, uranium, astrogeology, paleontology, regional geology, geophysics, and of course, mineral deposits. He initiated a program of environmental geology in the USGS. This service was extended until 1971, when following the USGS's traditional practice of recycling scientists into and out of administrative assignments, he returned to Menlo Park to pick up the trail of those ancient rocks in southwestern Montana. In 1974 he retired but retained an official affiliation as research geologist until 1996, continuing work in Montana and remaining involved in national and international professional affairs. He and Ruth moved to Port Townsend, Washington. After Ruth died in 1989 he moved to Bellingham and continued to contribute to the earth-science literature until the mid-1990s.

Harold James was active in scientific and professional organizations, serving as national program chair (1961-62), councilor (1962-65), and president (1970-71) of the Society of Economic Geologists, which honored him with its Penrose Medal in 1976; councilor of the Mineralogical Society of America (1964-66); councilor of the Geological Society of America (1959-62) and associate editor of its *Bulletin* (1964-66); member (1967-84) and chair (1976-84) of the Subcommission on Precambrian Stratigraphy of the International Union of Geological Sciences; and associate editor of *Precambrian Research* (1973-92). He chaired the Governor's Advisory Committee on the Minnesota Geological Survey (1961-63). He served as chair of the Section of Geology in the National Academy of Sciences (1969-72) and on the Report Review Committee (1984-91), National Committee on Geology (1969-71), Commission on Natural Resources (1973-78), Board on Mineral and Energy Resources (1977-79), and Board on Radioactive Waste Management (1978-82). The Department of the Interior awarded him its Distinguished Service Award in 1966. He was a member of Phi

Beta Kappa, Sigma Xi, Phi Kappa Phi, and Sigma Gamma Epsilon.

We remember Hal for his penetrating questions, contagious smile, and ready humorous quips; and although most of us were accustomed to seeing his uneven gait, a consequence of combining youthful exuberance with a toboggan and a precipitous hill, it scarcely slowed him in getting around in the field or elsewhere.

Hal died by his own hand on April 2, 2000, at Ruth's gravesite in Bellingham.

I HAVE BEEN aided by thoughtful reviews and commentaries from David James, Cliff Nelson, Philip Bethke, Paul Sims, and Wallace Pratt. The most prolific contributor to this memorial, however, has been Hal James himself, with a pair of long letters addressed to his four sons written in 1991 and 1995 and kindly made available by his son David.

SELECTED BIBLIOGRAPHY

1946

Chromite deposits near Red Lodge, Montana. U.S. Geological Survey Bulletin 945-F, pp. 151-89.

1954

Sedimentary facies of iron-formation. *Econ. Geol.* 48:235-93.

1955

Zones of regional metamorphism in the Precambrian of northern Michigan. *Geol. Soc. Am. Bull.* 66:1455-88.

1958

Stratigraphy of pre-Keewenawan rocks in parts of northern Michigan. U.S. Geological Survey Professional Paper 314-C, pp. 27-44.

1960

Problems of stratigraphy and correlation of Precambrian rocks with particular reference to the Lake Superior region. *Am. J. Sci.* 258A:104-14.

1961

With L. D. Clark, C. A. Lamey, and F. J. Pettijohn. Geology of central Dickinson County, Michigan. U.S. Geological Survey Professional Paper 310. 172 pp.

1962

With R. C. Clayton. Oxygen isotope fractionation in metamorphosed iron-formations of the Lake Superior region. In *Petrologic Studies, a volume in honor of A. F. Buddington,* eds. A. E. J. Engle, H. L. James, and B. F. Leonard, pp. 217-40. Geological Society of America.

1965

With L. T. Aldrich and G. L. Davis. Ages of minerals from metamorphic and igneous rocks near Iron Mountain, Michigan. *J. Petrol.* 6:445-72.

1966

Chemistry of the iron-rich sedimentary rocks. In *Data of Geochemistry*, U.S. Geological Survey Professional Paper 440-W. 60 pp.

1968

Mineral resource potential of the deep oceans. In *Mineral Resources of the Deep Oceans - Symposium*, Newport, R.I., 1968, Occasional Paper, pp. 39-44. Kingston: University of Rhode Island Graduate School of Oceanography.

With C. E. Dutton, F. J. Pettijohn, and K. L. Weir. Geology and ore deposits of the Iron River-Crystal Falls District, Iron County, Michigan. U.S. Geological Survey Professional Paper 570. 134 pp.

1969

Comparison between Red Sea deposits and older ironstone and iron-formation. In *Hot Brines and Recent Heavy Metal Deposits in the Red Sea: A Geochemical and Geophysical Account,* eds. E. T. Degens and D. A. Ross, pp. 525-32. New York: Springer-Verlag.

With K. L. Weir. Geology and magnetic data for the southeastern Iron River area, Michigan. Michigan Geological Survey Report 6. 33 pp.

1970

With F. J. Pettijohn and L. D. Clark. Geology and magnetic data between Iron River and Crystal Falls, Michigan. Michigan Geological Survey Report 7. 17 pp.

1973

With R. W. Bayley. Precambrian iron-formations of the United States. *Econ. Geol.* 68:934-59.

1978

Subdivisions of the Precambrian: A brief review and a report on recent decisions by the Subcommission on Precambrian Stratigraphy. *Precambrian Res.* 7:193-304.

1980

Resource potential of bedded iron deposits in the Tobacco Root Mountains, Montana. U.S. Geological Survey Professional Paper 1175. 7 pp.

1981

Reflections on problems of time subdivisions and correlation. *Precambrian Res.* 15:191-98.

Bedded Precambrian iron deposits of the Tobacco Root Mountains, southwestern Montana. U.S. Geological Survey Professional Paper 1187. 16 pp.

1982

With A. F. Trendall. Banded iron-formation: Distribution in time and paleoenvironmental significance. In *Mineral Deposits and the Evolution of the Biosphere: Report on the Dahlem Workshop on Biospheric Evolution and Precambrian Metallogeny,* eds. H. D. Holland and M. Schidlowski, pp. 199-217. Berlin: Springer-Verlag.

With H. Klemic and G. D. Eberline. Iron. In *United States Mineral Resources,* eds. D. A. Brobst and W. P. Pratt. U.S. Geological Survey Professional Paper 820, pp. 291-306.

1983

Distribution of banded iron-formation in time and space. In *Iron-formation: Facts and Problems,* eds. A. F. Trendall and R. C. Morris, pp. 471-90. Amsterdam: Elsevier.

1984

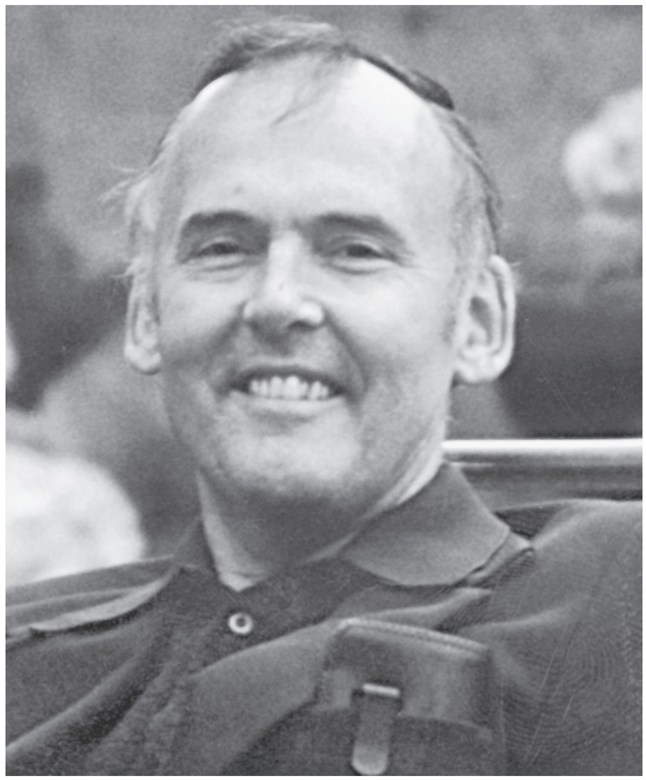
With P. K. Sims. Banded iron-formations of late Proterozoic age in the central Eastern Desert, Egypt: Geology and tectonic setting. *Econ. Geol.* 79:1777-84.

1990

Precambrian geology and bedded iron deposits of the southwestern Ruby Range, Montana. U.S. Geological Survey Professional Paper 1459. 39 pp.

1992

Precambrian iron-formations: Nature, origin, and mineralogic evolution from sedimentation to metamorphism. In *Developments in Sedimentology,* vol. 47, eds. K. H. Wolf and G. V. Chilingarian, pp. 543-89. Amsterdam: Elsevier.



WILLIAM M. KAULA

May 19, 1926–April 1, 2000

BY DONALD L. TURCOTTE

Bill Kaula was the father of space-based geodesy. As an academic scientist for some 37 years at the University of California, Los Angeles, Bill was unique: He graduated from West Point and did not have a Ph.D. His initial move into geodesy was to improve missile trajectories. He soon learned that tracking satellites could provide revolutionary information on how Earth works. He lived to see the determination of absolute positions on Earth to a millimeter accuracy using the military Global Positioning System array of satellites. Bill was also one of the fathers of comparative planetology: Understand the planets and you improve the understanding of Earth.

Bill Kaula was born in Sydney, Australia, on May 19, 1926, to Edna Mason, an Australian of British descent, and Edgar (Ed) Kaula, an American of Czech descent. Ed was a Texaco executive in the days when the United States exported petroleum products. Moves to New Zealand and Holland followed, but in 1935 Ed lost both his job and his wife due to alcoholism. Edna stayed in New York with their younger son David, while Ed and Bill returned to the Kaula home in Somerville, Massachusetts.

Bill found schoolwork easy, so he spent his adolescence in ways consistent with his introspective nature—chess, playing the piano, and reading novels, philosophy, and so forth: a true nerd. As graduation from high school approached, Ed suggested that Bill apply to West Point, which Bill did, for lack of an articulated alternative. In his own words, "Turning 18 in the middle of a world war made West Point relatively attractive. Otherwise, I probably would have eventually become an English professor, like my brother."

As a plebe, Bill continued in his indolent introspection, which garnered a lot of demerits and a modest academic standing. At the start of yearling year, he had the good luck to be assigned Graham Kent as a roommate. Graham had trouble with his studies, so to help him Bill started studying the night before class for the first time in his life. Suddenly Bill's grades shot up. Bill kept studying even after Graham went off in 1947, and remained a starman for his last three years, despite being near the bottom of the class in athletics and military aptitude.

Bill considered going into the Air Force, but after nearly killing his instructor and himself goofing his first recovery from a tailspin, Bill decided he lacked the coordination, patience, and attention to detail to survive as a pilot. Hence he went into the Corps of Engineers. Meanwhile, he became engaged to a pretty French girl, Denise Bouche, which led after EOBC to an assignment in Hanau, Germany (the bachelor engineers gallantly volunteered to take the assignments in the Far East, where there was a shortage of family housing).

Two years in the Hanau Engineer Depot were rather desultory, but a year in the Fourth Combat Engineers was quite stimulating. Meanwhile, Bill was offered a year in graduate school. He decided that civil engineering was dull and that his record was not good enough to qualify for nuclear engineering, and so he chose a new option: geodesy. In his own words, "In 1951, as a regular officer in the Army

Corps of Engineers, I was offered a year of graduate school, with the program option of nuclear engineering, civil engineering, and geodesy. I elected the geodesy because it was vaguely a mixture of something easy—mathematics—and something that got you out-of-doors—surveying. Later I tried to renege but was compelled to go because no one else had asked for it. The resulting year at Ohio State was stimulating because I was the only student in the program; I did not have to attend lectures in my subject; I wrote my own syllabus; and I got to do a thesis leading to a published paper."

Bill often referred to the geodesy assignment as the biggest piece of dumb luck in his life. On arriving in Columbus in June 1952 Bill found that he was the first student in a new program with one faculty, an aged Finn, Weiko Heiskaneu, who said, "I thought you weren't coming until September. I'm going to Finland for the summer. Here, study this book." Hence the West-Point-taught self-reliance paid off. Bill studied the book (and other geodetic texts) diligently and signed up for summer courses. In the fall no other students showed up, and the Finn said he would not give lectures to only one student—so Bill wrote his own syllabus for weekly discussions, thus getting a more comprehensive view of the subject. He also cooked up a thesis topic that led to his seeing a lot of Ohio countryside.

The geodetic label resulted in his assignment as project officer for the topographic survey of the island of New Britain, just northeast of New Guinea. This proved to be his most satisfying military posting: a tri-racial, quadri-national command, 2,500 miles from his boss in Tokyo, lasting one year. Bill was very proud of the Pidgin English he learned during this assignment. This spell of independence spoiled him, because two years later when the word from OCE was "your next turn is with the Third Engineer Combat Battalion at

Fort Benning," he decided to seek other employment for which his talents were more satisfying to himself as well as useful to the nation, in those days of the "missile gap."

Bill quickly found his choices were limited to the Department of Defense: three offers, two Air Force, one Army. He chose the one with the most stimulating boss: John O'Keefe, head of geodetic research at the Army Map Service. In November 1957 Bill resigned from the military to support five dependents on a GS-12 salary ($7,520 a year, but an adequate house in nearby Bethesda, Maryland, cost only $17,000 then). On arrival at the map service he was surprised to be asked the question "What do you want to do?" To which his immediate response was "research on properties of Earth's gravity field" (then thought to affect inertial guidance significantly). He was further surprised to get the freedom to do it, with support.

A year later O'Keefe moved to the National Aeronautics and Space Administration (NASA), leaving the map service research supervision to Bill. In 1960 Bill moved to NASA to be project scientist for a geodetic satellite. The project, however, kept being postponed because of security objections, which left him free to do his own research. After mastering satellite orbit dynamics Bill turned his interests in two directions: implications of the gravity field for Earth's interior and applications of the dynamical techniques to the evolution of natural orbits. The void of talent in satellite geodesy made it easy for Bill to get papers published, and he regularly presented his results in the *Journal of Geophysical Research* and similar outlets—an average of about six papers per year for 40 years.

Bill's work interested a visiting consultant at NASA, Gordon MacDonald of the University of California, Los

Angeles. This led to a tenured faculty appointment at UCLA, an unusual event for someone without a Ph.D. In partial compensation for never having gotten a Ph.D. Bill wrote two books, *Theory of Satellite Geodesy* (1966) and *An Introduction to Planetary Physics* (1968).

In addition to teaching, Bill served UCLA twice as a department chair and twice as a member of the Council of Academic Personnel, a committee that advises on appointments and key promotions for the entire campus (about 600 cases per year). He frequently served NASA as a project participant (e.g., team leader for the altimeter on Apollos 15, 16, and 17) and proposal reviewer. He was twice a member of the National Research Council Space Science Board. His other principal association outside UCLA was with the American Geophysical Union, as section officer, journal editor, and advisory committee member.

During the mid-1970s Bill's scientific productivity was invigorated by a move into comparative planetology. He made many important contributions concerning the origin and evolution of the solar system. Another very important event in his life took place at about this time, the marriage to his second wife, Gene. They remained inseparable until Bill's untimely death. I remember one wonderful trip with the Kaulas in the late 1970s. We were attending a conference in Newcastle and for a lunch we drove across England to the Lake District. We had an unforgettable lunch at the Shallow Bay Hotel. We reminisced about the decadent sticky toffee pudding right up until a few weeks before Bill's death.

Bill had a very wry sense of humor and a rare ability to transmit scientific ideas. An example was his poem "The Seven Ages of a Planet" published in the journal *Icarus* (1975).

Our system is a stage,
And both the Sun and planets merely players.
They had their birth and'll have their fiery end.
A planet in its time plays many parts,
Its acts being seven ages. The first of these
Is condensation: dust grains drifting to
The nebula plane in chondrite clods. And then
The planetismals: breaking sometimes, but
Most growing, though the Sun's hot breath blows gas
Away. And then formation: sweeping up
The bodies in its way, in fierce infalls
To bring then full convective vigor, too hot
For crust to form, though iron may sink and seas
Outgas, by radioactive energy driven.
And then comes plate tectonics: cooling leads
To lithosphere, with many marginal breaks.
Convective thrusts a crust create in belts
Complex. But heating slows; the sixth age shifts
Into the final volcanism: no
More lithospheric spreading, only vents
For magma, Nix Olympica or mare
To surface, ending fractionation. Last scene
That ends this history is quiescence: time
Sans melt, sans plates, sans almost everything.

In the mid-1980s Bill took leave from UCLA to serve three years as head of the National Geodetic Survey in the National Oceanic and Atmospheric Administration. While on this tour he was diagnosed with hairy cell leukemia, but within five years was fortunate to be one of the first beneficiaries of the now standard cure. After 1991 his principal health problem was squamous cell cancer in the scalp.

The onset of leukemia was followed closely by three honors: the Whitten Medal of the American Geophysical Union; the Brouwer Medal of the American Astronomical Society; and in 1987 membership in the National Academy of Sciences.

A moving testimony to Bill's unique abilities and contributions was given by Stan Peale, chair of the Division of Dynamical Astronomy of the American Astronomical Society, at the division's thirty-second annual meeting on April 9, 2000.

As most of you know, our friend and colleague, Bill Kaula, died peacefully a week ago last night after a decade-long battle with cancer that was anything but peaceful. Bill was a member of the original organizing committee for the DDA in 1969, served as a DDA Committeeman from 1971 to 1973, as DDA Vice Chairman from 1974 to 1975 and as Chairman from 1975 to 1976. In recognition of his outstanding contributions to dynamical astronomy, Bill received the Brouwer Award in 1989. As one of the founders of the DDA, after a remarkably productive scientific career in dynamical astronomy, in the dynamics of planetary interiors, and broad aspects of solar system science, and after a lifetime of unselfish service to government agencies, to professional societies, to his university, and most of all to his innumerable friends, it is most appropriate that we dedicate this meeting to remembering Bill.

Bill developed some of the earliest expansions of the Earth's gravitational field using satellite geodesy, and he published a book describing the state of the art of geodesy at that time. After he moved to UCLA in the early sixties, he rapidly expanded his knowledge of planetary science, and he published papers on an incredibly broad range of subjects during his career. These include applications of his geodesy expertise to other terrestrial bodies, and interpreting the gravitational fields of these bodies in terms of interior properties. He also published on tidal evolution, chaotic dynamics, history and stability of planetismal distributions, the formation of terrestrial planets through accretion, the formation of the solar system, origin of the Moon, comparative planetology including compositional implications, thermal history of terrestrial bodies—especially Venus—and the quest for fast and accurate numerical integration schemes to follow solar system history and evolution. He must have devoured most of the literature in dynamical planetary science and in the physics of the solid solar system bodies, for one could ask him questions on almost any subject and he would understand the material in detail and know who had published what when. We celebrate his career.

Bill's fight with cancer would have driven most of us to all consuming self-pity and anger. Yet he remained always cheerful and optimistic. He wore a hat to hide the wounds that would not heal, and proceeded with his life as if nothing were wrong. He remained scientifically active until the very end, having coauthored at least 6 papers last year, and he is a coauthor of a paper at this conference. Ever optimistic, only a month ago, while in the hospital for the last time, he was still intending to come to this meeting. His service to the University also continued until the very end as he was a member of the extremely demanding UCLA Committee on Academic Personnel when he died—fretting a few days before the end that he was not doing his share. We shall miss his energy, enthusiasm, and council. Let's make this a memorable meeting in memory of Bill Kaula—always interested and always our friend.

MY THANKS TO JOHN Wood and Gene Kaula who reviewed and contributed to my efforts in writing this memoir.

SELECTED BIBLIOGRAPHY

1959

Statistical and harmonic analysis of gravity. *J. Geophys. Res.* 64:2401-21.

1963

Tesseral harmonics of the gravitational field and geodetic datum shifts derived from camera observations of satellites. *J. Geophys. Res.* 68:473-84.

1964

Tidal dissipation by solid friction and the resulting orbital evolution. *Rev. Geophys.* 2:661-85.

1966

Theory of Satellite Geodesy. Waltham, Mass.: Blaisdell.

1968

An Introduction to Planetary Physics. New York: John Wiley.

1972

Global gravity and mantle convection. *Tectonophysics* 13:341-59.

1975

With A. W. Harris. Dynamics of lunar origin and orbital evolutions. *Rev. Geophys.* 13:363-71.

The seven ages of a planet. *Icarus* 26:1-15.

1979

Thermal evolution of Earth and moon growing by planetismal impacts. *J. Geophys. Res.* 84:999-1008.

1980

Material properties for mantle convection consistent with observed surface fields. *J. Geophys. Res.* 85:7031-44.

1983

Inference of variations in the gravity field from satellite-to-satellite range-rate. *J. Geophys. Res.* 88:8345-50.

1986

With A. E. Beachey. Mechanical models of close approaches and collisions of large protoplanets. In *The Origin of the Moon,* eds. W. K. Hartmann, R. J. Phillips, and G. J. Taylor, pp. 567-76. Houston, Tex.: Lunar and Planetary Institute.

1990

Venus: A contrast in evolution to Earth. *Science* 247:1191-96.

1993

With A. Lenardic. A numerical treatment of geodynamic viscous flow problems involving the advection of material interfaces. *J. Geophys. Res.* 98:8243-60.

1994

The tectonics of Venus. *Phil Trans. R. Soc. Lond. A* 349:345-55.

1995

Formation of the terrestrial planets. *Earth Moon Plan.* 67:1-11.

With R. S. Nerem and C. Jekeli. Gravity field determination and characteristics: Retrospective and prospective. *J. Geophys. Res.* 100:15053-74.

With A. Lenardic. More thoughts on convergent crustal plateau formation and mantle dynamics with regard to Tibet. *J. Geophys. Res.* 100:15193-203.

With A. Lenardic and D. L. Bindschadler. Some effects of a dry crustal flow law on numerical simulations of coupled crustal deformations and mantle convection on Venus. *J. Geophys. Res.* 100:16949-57.

Venus reconsidered. *Science* 270:1460-64.

With A. Lenardic. Mantle dynamics and the heat flow into the Earth's continents. *Nature* 378:709-11.

1996

Regional gravity fields on Venus from tracking of Magellan cycles 5 and 6. *J. Geophys. Res.* 101:4683-90.

With A. Lenardic. Near surface thermal/chemical boundary layer convection at infinite Prandtl number: Two-dimensional numerical experiments. *Geophys. J. Int.* 126:689-711.

1997

With A. Lenardic, D. L. Bindschadler, and J. Arkani-Hamid. Ishtar Terra. In *Venus II*, eds. S. W. Bougher, D. M. Hunten, and R. J. Phillips, pp. 879-900. Tucson: University of Arizona Press.

1999

Constraints on Venus evolution from radiogenic argon. *Icarus* 139:32-39.

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Wolfgang Köhler

WOLFGANG KÖHLER

January 21, 1887–June 11, 1967

BY ULRIC NEISSER

WOLFGANG KÖHLER, distinguished psychologist and co-founder of Gestalt psychology, made many important contributions to science. Although he is probably best known for his empirical studies of chimpanzee problem solving (*The Mentality of Apes* [1925]), Köhler's deepest commitments were theoretical and philosophical. Perhaps his most fundamental commitment was to the principle of psychophysical isomorphism: Because brain and mind are identical, the structure of conscious experience during perception or memory or problem solving necessarily mirrors the physical structure of activity in the brain. "Experienced order in space," for example, "is always structurally identical with a functional order in the distribution of underlying brain processes" (1947, p. 61). In Köhler's view those underlying processes were trans-neuronal electrical currents flowing in well-defined regions of the brain. Isomorphism in this sense was one of the founding assumptions of Gestalt psychology, one that Köhler did more than anyone else to explore both empirically and theoretically.

In psychology the first half of the twentieth century was a time of competing schools: Titchener's structuralism, Freud's psychoanalysis, the behaviorism of Watson and Skinner, the functionalism of many American experimentalists, and—out of nowhere, it seemed, just after the First World War—the remarkable Gestalt psychology of Max Wertheimer, Kurt Koffka, and Wolfgang Köhler. Of course it did not really come out of nowhere. Its three founders were German, with intellectual roots in Husserl's phenomenology and in Kant. They saw themselves as fighters against positivism, as humanistic scientists engaged in a life-and-death struggle against vitalism on one side and against a series of dreary mechanistic psychologies on the other. Their chief opponents were behaviorism, associationism, and classical introspective psychology; much of Köhler's research was designed to refute the assumptions of those schools.

Wolfgang Köhler was born of German parents in Reval, Estonia, where his father was a schoolmaster; his family returned to Germany when he was six years old. He studied at several universities, receiving his Ph.D. from Carl Stumpf in 1909 with a thesis in psychoacoustics. After taking his degree at Berlin Köhler moved to Frankfort, where Kurt Koffka was also in residence and Max Wertheimer was just beginning his famous studies of apparent motion. Together they planned the future of what would soon become Gestalt psychology.

That future took a surprising turn in 1913, when Köhler was appointed the director of the Prussian Primate Research Center on Tenerife in the Canary Islands. Although he had no experience with animal research, the appointment was urgent. The Center was being directed by a graduate student, Eugen Teuber, whose term was about to expire (M. L. Teuber, 1994). Köhler and his family arrived at the Center in December 1913, expecting to stay for a single year. Eight months later, the First World War began.

Köhler tried to go home to do his military service, but this turned out to be impossible. No neutral ship would carry German nationals through waters controlled by the

British fleet. In the upshot he remained on Tenerife and continued to direct the primate station until it closed in 1920. Ronald Ley (1990) has made the interesting suggestion that Köhler—a German patriot isolated on a Spanish island—may have engaged in espionage during the war years. While some such espionage probably did take place (the Canary Islands lay close to major shipping lanes where British warships and German submarines were active), there is no convincing evidence that Köhler took part in it.

The station at Tenerife was the first primate laboratory ever devoted to behavioral research, and Köhler's experiments there are justifiably famous. From the beginning his chief aim was to show that the apes acted with *insight,* that their behavior was not governed by blind trial and error, their problem solving not due to chance. In this he was entirely successful. In experiment after experiment the apes took detours, pulled on strings, built climbing towers, broke up boxes to make sticks, and then fitted the sticks together to make longer implements. No one who reads Köhler's account of these achievements can seriously doubt the intelligence of chimpanzees; subsequent primate research has been built on the foundation that he established.

Although Köhler spent half a decade in Tenerife, almost all his important experiments were completed in the first six months. (An early version of *The Mentality of Apes* appeared as a technical report in 1917.) The rest of his time was occupied with a very different book, one that he hoped would establish the scientific basis of Gestalt psychology beyond any doubt. Its title—a mouthful even in German—was *Die Physischen Gestalten in Ruhe und im Stationaren Zustand* (1920), which goes into English as *The Physical Gestalten at Rest and in Steady State.*

Die Physischen Gestalten has one introduction "for philosophers and biologists" and another "for physicists." There is none for psychologists; perhaps Köhler thought it would be too difficult for them. Although the book does occasionally resort to differential equations and other mathematical devices, its purpose is easy to understand. Köhler wanted to show that *Gestalten* could occur in purely physical settings, and specifically in the electrochemical systems that he assumed must exist in the brain. What are *Gestalten*? "Since von Ehrenfels, the term 'Gestalten' has been used to denote those mental phenomena and processes whose typical properties and effects cannot be derived from the similar properties and effects of their so-called parts" (p. ix). A Gestalt is a whole that is more than the sum of its parts.

There are indeed many organized wholistic systems in the world: Why should there not be? On this point the triumph of Gestalt psychology has been so complete that it is hard to understand how this was ever disputed or why Köhler had to demonstrate it. Interestingly, his demonstration anticipated many of the dynamic concepts that are now the "bread and butter" of cognitive science. Self-organizing systems, parallel distributed networks, and attractor states (for example) are all physical Gestalten. It is unfortunate that the scientists who developed those concepts in the 1980s and 1990s were largely unfamiliar with this aspect of Köhler's work. (One exception is Stephen Palmer, who cites *Die Physischen Gestalten* in his book *Vision Science* (1999, p. 220): "Marr and Poggio's . . . stereo algorithm is . . . an interesting example of dynamic neural networks as physical gestalten."

The last chapter of *Die Physischen Gestalten* introduces a new concept, one that came to have particular significance for Köhler and Gestalt psychology. When a dynamic process reaches a steady state, that steady state must differ somehow from the "unsteady" states that preceded it. But in what way? Physical processes tend toward energy minima, but what do psychological processes tend toward? Are their end states especially simple? Regular? Symmetric? Köhler thought that all these candidate principles were inadequately defined, but he could find nothing better himself. He did manage to give the problem a name: "We will provisionally refer to this incompletely specified parameter as a 'tendency to establish simpler Gestalt structure,' or just [a tendency] 'to Pragnanz of the Gestalt'" (1924, p. 259).

Köhler was well aware of and embarrassed by the circularity of the "law of Pragnanz." Although his interests soon turned elsewhere, he never stopped hoping that a better definition would be found. When I took "the Köhler seminar" at Swarthmore in 1952, decades after *Die Physischen Gestalten*, one of the first tasks he put before us was to suggest definitions for "Pragnanz." I don't recall that we had anything useful to say.

Whatever doubts Köhler may have had about Pragnanz, he had none about isomorphism. On any particular occasion the phenomenal field has a given structure (i.e., the world looks as it does) because the electrical currents flowing in the visual cortex have that structure too. In his William James Lectures of 1934 (later published as *The Place of Value in the World of Facts* [1938]), Köhler developed the implications of this idea for such issues as evolution, the mind-body problem, and the distinction between fact and value. This was primarily a philosophical enterprise, and a very ambitious one at that. By the end of the 1930s, however, Köhler had returned to empirical research. He did so in a new setting, on a new campus, in a new country.

The 1920s and early 1930s had been a very successful time for Wolfgang Köhler. On his return from Tenerife he was briefly appointed professor at Göttingen, but soon (1922) moved to Berlin as professor of psychology and director of the psychological institute. (He succeeded his old teacher

Carl Stumpf, who had held the chair since 1894.) In the Berlin institute Köhler attacked a wide range of problems from the Gestalt point of view; these included psychophysics, apparent movement, and especially memory. With his student Hedwig von Restorff he studied the role of uniqueness in memory, establishing a phenomenon that is still called "the von Restorff effect." He also wrote a new book, *Gestalt Psychology,* which was first published in English (1929). By this time Köhler was an international figure, and Gestalt psychology was flourishing under his leadership.

In Germany at large, however, the 1920s and early 1930s were anything but successful. It was a time of chaos, of inflation and depression, of fascism and communism, of the ill-fated Weimar Republic and the stridently anti-Semitic National Socialists. By early 1933 conditions were ripe for Adolf Hitler, and his Nazis came to power. Hitler quickly turned his attention to the universities, issuing a decree that all Jewish professors and academics—from Nobel Prize winners down to laboratory research assistants—were to be dismissed at once. There was surprisingly (and disturbingly) little open resistance to this decree. Wolfgang Köhler was one of the few non-Jews who spoke out against it, publishing an eloquent protest that Henle calls "the last anti-Nazi article to be published openly in Germany under the Nazi regime" (1978, p. 940). In the same year the Nazis ruled that all professors must begin their lectures with the Hitler salute, a decree that Köhler openly mocked. For some months longer he tried to retain his professorship while maintaining his academic autonomy, but it was a losing battle. Eventually he resigned. In 1935 Wolfgang Köhler took up a professorship at Swarthmore College in Pennsylvania. He became a naturalized American citizen in 1946.

Hans Wallach, who had been Köhler's assistant at Berlin, also moved to Swarthmore. There they conducted their famous studies of "figural after-effects," which Köhler presented as new support for the hypothesis of psychophysical isomorphism. These experiments, which Köhler described briefly in his book *Dynamics in Psychology* (1940), showed that prolonged inspection of visual patterns can change the apparent shapes and positions of other figures that are shown subsequently. (For a more complete account see Köhler and Wallach [1944].) He had expected such effects because an electric current flowing in a medium may produce localized changes that alter the conductivity of that medium itself, and hence alter the distribution of any new current that uses the same conductor at a later time. If this happens in the visual cortex of the brain, it may have noticeable consequences for the structure of the visual field. Somewhat surprisingly, it turned out that such after-effects appear not only in frontal displays but also in the third dimension of visual space and even in other sensory modalities. Although figural after-effects were a real discovery, it is by no means clear today that they are best explained by Köhler's isomorphism hypothesis.

In his later years at Swarthmore Köhler tried to test that hypothesis more directly. Did visual patterns really give rise to figure currents in the brain? With Richard Held he succeeded in recording direct currents from the brains of waking human observers, using scalp electrodes placed over the occipital region (1949). Their experiments were initially successful: With eye movements controlled, the direction of current flow changed in synchrony with the back-and-forth movement of a visible object. Similar flows were observed in the human auditory cortex during stimulation of the ear and also more directly in the cortex of the cat. Köhler was encouraged by these findings, but he was never able to prove that such currents play the key role in perception that is assigned to them by the isomorphism hypothesis.

Many honors came to Wolfgang Köhler in later life. Elected to the National Academy of Sciences in 1947, he became an international figure again. One of the few Americans to be named an honorary citizen by the Free University of Berlin, Köhler was awarded both the Warren Medal (by the Society of Experimental Psychologists) and the Wundt Medal (by the German Society for Psychology). He was elected president of the American Psychological Association for 1959 and was made honorary president of the analogous German association on the occasion of his eightieth birthday.

The international scientific community honored Wolfgang Köhler in these ways not only for his wide-ranging theoretical and empirical contributions but also for his courage and his character. As the holder of one of Germany's most distinguished professorial chairs in the 1930s he could easily have collaborated with Hitler as so many others did. Publicly rejecting that course, he spoke out against the brutal Nazis for as long as it was possible to do so. Then, here in the United States, Köhler resumed his productive research career and continued to make new contributions to science in his adopted country. A genuinely creative thinker as well as a person of great dignity and honor, a physicist and philosopher as well as a psychologist, a cultured citizen of a war-torn world, Wolfgang Köhler showed us by his own personal example what it can mean to be a scientist.

REFERENCES

Henle, M. 1978. One man against the Nazis—Wolfgang Köhler. *Am. Psychol.* 33:939-44.

Ley, R. 1990. *A Whisper of Espionage.* Garden City N.Y.: Avery.

Palmer, S. E. 1999. *Vision Science.* Cambridge Mass.: MIT Press.

Teuber, M. L. 1994. The founding of the primate station, Tenerife, Canary Islands. *Am. J. Psychol.* 107:551-81.

SELECTED BIBLIOGRAPHY

A more complete bibliography of Köhler's writings appears in M. Henle, ed. *The Selected Papers of Wolfgang Köhler*. New York: Liveright, 1971.

1909

Akustische Untersuchungen. I. *Z. Psychol.* 54:241-89. (Doctoral dissertation also published separately as *Akustische Untersuchungen. I.* Leipzig: Johann Ambrosius Barth, 1909.)

1910

Akustische Untersuchungen. II. *Z. Psychol.* 58:59-140

1917

Die Farbe der Sehdinge beim Schimpansen und beim haushuhn. *Z. Psychol.* 77:248-55.

Intelligenzprüfungen an Anthropoiden. I. *Abh. K. Preuss. Akad. Wiss.* No. 1.

1920

Die physischen Gestalten in Ruhe und im stationären Zustand; Eine naturphilosophische Untersuchung. Braunschweig: Friedr. Vieweg and Sohn.

1921

Intelligenzprüfungen an Menschenaffen. Zweite durchgesehene Auflage. Berlin: Julius Springer.

1923

Zur Theorie des Sukzessivvergleichs und der Zeitfehler. *Psychol. Forsch.* 4:115-75.

1925

The Mentality of Apes. (Translated from the 2nd revised edition by Ella Winter.) New York: Harcourt, Brace.

1929

Gestalt Psychology. New York: Liveright.

1935

With H. von Restorff. Analyse von Vorgängen im Spurenfeld. II. Zur Theorie der Reproduktion. *Psychol. Forsch.* 21:56-112.

1938

The Place of Value in a World of Facts. New York: Liveright.

1940

Dynamics in Psychology. New York: Liveright.

1942

With H. Wallach and D. Cartwright. Two theories of visual speed. *J. Gen. Psychol.* 27:93-109.

1943

A perspective on American psychology. *Psychol. Rev.* 50:77-79.

1944

Max Wertheimer: 1880-1943. *Psychol. Rev.* 51:143-46.

With H. Wallach. Figural after-effects: An investigation of visual processes. *Proc. Am. Philos. Soc.* 88:269-357.

1947

Gestalt Psychology: An Introduction to New Concepts in Modern Psychology. New York: Liveright.

With D. Dinnerstein. Figural after-effects in kinesthesis. In *Miscellanea Psychologica Albert Michotte,* pp. 196-220. Louvain: Éditions de l'Institute Supérieur de Philosophie.

With D. A. Emery. Figural after-effects in the third dimension of visual space. *Am. J. Psychol.* 60:159-201.

1949

With R. Held. The cortical correlate of pattern vision. *Science* 110:414-19.

1951

Relational determination in perception. In *Cerebral Mechanisms in Behavior: The Hixon Symposium,* ed. L. A. Jeffress, pp. 200-243. New York: John Wiley.

1952

With R. Held and D. N. O'Connell. An investigation of cortical currents. *Proc. Am. Philos. Soc.* 96:290-330.

1955

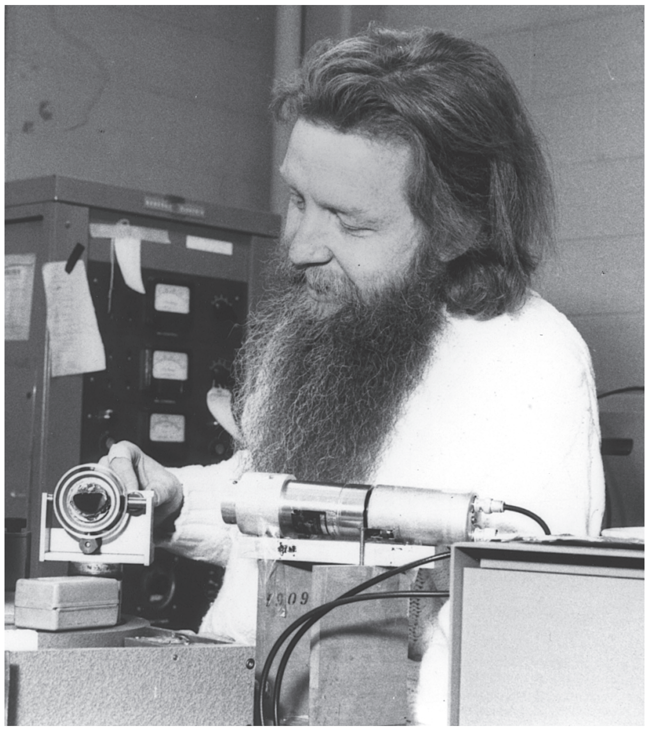
With J. Wegener. Currents of the human auditory cortex. *J. Cell. Comp. Physiol.* 45(Suppl. I):25-54.

1959

Gestalt psychology today. *Am. Psychol.* 14:727-34.

1969

The Task of Gestalt Psychology. Princeton, N.J.: Princeton University Press.



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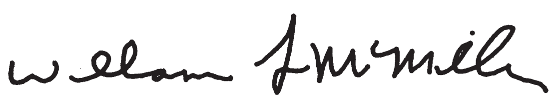


WILLIAM L. McMILLAN

January 13, 1936–August 30, 1984

BY P. W. ANDERSON

THE TRAGIC ACCIDENT THAT killed Bill McMillan in August 1984 at the age of 48 deprived the world of the ablest condensed matter physicist of his generation. The best student of John Bardeen at least since J. R. Schrieffer, the most successful of several outstanding products of the postdoctoral program at AT&T Bell Labs during its greatest period, he went on to a full professorship at Illinois in 1972 at the age of 36, where he continued to be outstanding both as a research scientist and as a teacher until he was struck by a confused teenage driver while cycling along a deserted country road. He has been appropriately commemorated by a prestigious prize lectureship for young condensed matter physicists.

A group including Bill's father's progenitors left the Isle of Skye in Scotland in 1820 and founded the small community of Union Springs, Alabama. Over a century later Bill's father, Laughlin, was the first McMillan to leave Union Springs permanently, when he went off to college at Auburn, where he played football and earned a degree in civil engineering. He then moved to Little Rock, Arkansas, where he worked for a foundry company. He married Edna Shergold Mashburn, the daughter of a judge and a member of an old southern family—her grandfather had owned the Georgia

Southern Railroad. She had some social pretensions and may have felt she had married "beneath herself"; later on, Bill told his wife, Joyce, that he had no interest in becoming rich, which she attributed to his reaction to family tensions. He also disliked team sports, in a mild rebellion from his father's preoccupations.

Bill was born on January 13, 1936, and was named after his grandfather, William Laughlin McMillan. His namesake was something of a patriarch and demanded that he be brought to the family farm as a very young infant for inspection. Bill was the elder of two brothers, and there were also younger cousins in Little Rock. Bill was the leader of the group and was known among them as "gentle Will" for, among other things, his habit of taking the blame for any mischief. He was an outstanding student in high school and also led a jazz group that won a national contest. Later, in college, he led several bands, playing almost any instrument, and earning spare cash thereby, as well as disc-jockeying at a local radio station, despite his stutter. He took a degree in electrical engineering, spending summers at RCA (where he first conceived the ambition to build his own computer using Bell Labs transistors) and at IBM in Poughkeepsie.

In January 1958, in the middle of his senior year, he married Joyce Ann Stairs whom he had met the previous year and had proposed to by phone during the summer. Joyce is also from a small-town background: She came from Heber Springs, Arkansas. The two of them always shared equally in the demands of the household and of the four children who resulted from the marriage: (Kenneth Laughlin, 1962, at Illinois; Lawrence Edward, 1965, and Julie Anber, 1966, in Summit, N.J.; and William Albert, 1967, in Cambridge, England). Joyce was urged by Bill to finish her Ph.D. degree in spite of Kenny's arrival, and she did so in 1963. Bill had stayed on at Arkansas for a master's degree in order to let Joyce graduate. Fortunately for the world of physics, the department of physics at Arkansas was quicker and more flexible in processing his application for graduate school, so he switched to physics. At some time during this year he conceived the ambition of working with John Bardeen, so he submitted a single application for a Ph.D. program, to Illinois—if it failed, apparently he would have gone to work as an engineer. After passing the qualifying exam at the top of his class, he did indeed start work with John in 1960. Later, he would apply for only one postdoctoral job, at Bell. It seems relevant to note that his stutter and quiet manner did not connote a lack of self-confidence.

At Illinois, Bardeen proposed several topics to Bill, but in fact it was Bill himself who selected the topic and chose the method of attack he used in his thesis. Neither was very characteristic of Bardeen's style—Bill was simply being Bill. This thesis is a classic, and is to my mind the most conclusive demonstration in existence of the nature of superfluidity in liquid helium. It starts out from a brief remark of Onsager's, that a Jastrow-type product wave function for helium is exactly equivalent in its density-density correlations to a classical Boltzmann gas with an artificial two-particle potential energy. The Jastrow function of interatomic distance is at one's disposal, but its asymptotic limits can be accurately estimated: the long range part, from the two-particle correlation implied by the known phonon spectrum, and the short-range limit, by solving the zero-energy Schrödinger equation for the fairly well-known interatomic potential. Then the intermediate portion is adjusted variationally to minimize the total energy. The density correlation can be evaluated by molecular dynamics using the Monte Carlo algorithm, and the energy and many other properties (including superfluidity) of the system evaluated. (R. B. Laughlin, much later, brilliantly exploited the same kinds of identities for the fractional quantum Hall effect.) The method gave good agreement for the lambda point, the liquid-solid phase transition, and a value for the condensate fraction in agreement with present estimates from neutron scattering and other sources. Work over a decade later using the same methods, by Lupe Velez, improved the accuracy only fractionally. The outstanding excellence of this thesis is that very sophisticated theoretical concepts were blended with precise numerical work to the very great benefit of both. Other attempts at microscopic theories of *He* have to this date not led to any much more satisfactory description.

This thesis marked Bill as the first, and possibly the best, of a new breed of theorist. He was as comfortable as the previous generation of formalistic theorists with the mathematical methods and concepts of many-body theory, but he had the additional dimension afforded by the sophisticated use of the electronic computer, not by the brute force method of direct simulations at the atomic level but in tandem with the best formalisms available at the time. In these days computer skills are taken for granted, and software is available for almost any task; but I sense that Bill's achievements even now may still be close to the edge of the possible.

John Bardeen, who was already a Nobelist, continued the single-track progression of Bill's career by virtually directing us at Bell to employ him as a postdoc, which was all right with us. He arrived in 1964, just after the pair of *Physical Review Letters* by Rowell, Thomas, and Anderson, and by Schrieffer, Wilkins, and Scalapino had established superconducting tunneling spectroscopy as a semi-quantitative method of correlating electron and phonon data on real metals with superconductivity. The "tunnel conductance" dI/dV between two normal metals was shown by Schrieffer to be featureless, so that the striking structure in dI/dV

displayed when the metals become superconducting is a precise measure of the renormalization of the quasi particles by the electron interactions. Given plausible simplifying hypotheses about the phonon spectrum and coupling constants, a set of complex integral equations due to Eliashberg could predict the tunneling characteristic with some accuracy, as the above authors showed. But it seemed to us inconceivable to do the problem the other way round: given the experimental tunneling characteristic, to try to deduce the phonon coupling constant and the entire phonon spectrum. Nonetheless, given the merest hint, this was what Bill proceeded to do: calculate the phonon spectrum, and the order-parameter as a function of energy, given accurate tunneling data. This tour de force of computational skill led to a series of magnificent papers with John Rowell who simultaneously developed tunneling as an exact spectroscopic tool.

The period of the middle 1950s had seen a remarkable development of the theory of metals in which Migdal's theorem, that the effects of lattice phonons could be handled in lowest-order perturbation theory in the mass ratio m_e/m_{ions}, played an important role. It was Eliashberg and Schrieffer's insight that the same theorem was valid for superconductors, and Morel-Anderson's approximation that the interactions were effectively local, that led to the integral equations, complicated but involving only the frequency variable, which McMillan was able to invert. This was, as I remarked in a historical lecture 25 years later, the defining moment when one could say that the "fat lady had sung" to mark the final success of the theory of metals and of superconductivity based on BCS and phonon interactions. It is fair to say that, as of then, it was the most precise calculation ever made of any thermodynamic phase transition from first principles. It was also a remarkable vindication of the basic ideas of many-body perturbation theory in fermion systems. For this work he and John Rowell jointly received the only major award of his career, the London Prize of the international low-temperature physics community (jointly with Gunther Ahlers of Bell Labs).

In the meantime, far from requiring mentoring, Bill was himself acting as mentor for a young English postdoc, David Taylor, and between them they were discovering one version of the "coherent potential" or "effective medium" approximation, which has been remarkably successful in explaining the energy band spectra of disordered alloys. It is noteworthy and typical that he let David author this work alone.

By this time Bill had become a full member of staff at Bell Labs and was working with a wide variety of people: Bob Dynes, as well as Rowell and his postdoc Lawrence Shen, on superconductivity; with me, teaching me to program (but not to make serious errors) in a project on the spectra of disordered inner-shell resonances; and with many others. His most well-known result was the "McMillan equation," a semi-empirical distillation of the physical implications of his work with Rowell that estimated T_c on the basis of fundamental physical parameters of the metal. The BCS theory itself appears to give such a formula, the BCS equation for T_c

$$kT_c = \hbar\omega_D e^{\frac{-1}{N(0)V}}$$

but the parameters ω_D and V are those of a schematic model, only vaguely related to the real physics of the electrons in the metal. This BCS formula often led to great confusion if taken literally. What McMillan did was to combine insights into the real physics of electron screening, phonon restoring forces, and the "dynamic screening" of the repulsive electron-electron interaction, with semi-empirical knowledge gained from his actual work with Rowell's experiments, to produce a meaningful estimate of T_c valid for all conventional metals, and that showed which material properties of the metal were important. This in turn was the basis on which Cohen and I estimated possible upper limits for T_c from the BCS phonon mechanism, violated by the new cuprate superconductors. I cannot help deeply regretting Bill's absence from the post-1986 discussions on high T_c superconductivity as a voice invariably to be found on the side of rationality. I expect that he would have mocked out of existence the school of theorists who drag his equation and his programs far out of context and attempt to apply them to the high-T_c cuprates. Bill was at all times aware of the limitations of the assumptions he relied upon and every paper contained an accurate and honest estimate of possible errors.

His work in superconductivity was of real importance entirely aside from the tunneling method and the McMillan equation. We began a collaboration that continued in Cambridge on the "Tomasch effect" and electron-hole interference in proximity junctions, and he collaborated with Dick Werthamer on strong-coupling theory. The "Tomasch effect" work, which exploited the ideas of interference between hole-like and electron-like components of the quasi particles, and of what is now called "Andreev" reflection, led him to produce a working mathematical model for metal-metal junctions that was well ahead of its time and has been recently revived by a French group.

He was one of the early visitors to our Theory of Condensed Matter group in Cambridge, spending a sabbatical year and bringing Joyce and the children. Kenny quickly began to speak in Cambridge cockney, and it was occasionally necessary to rescue Joyce or Bill when the "old banger" they had bought broke down. It was a household of small children, and Joyce was pregnant with Billy. To the casual observer it would have seemed that Bill's devotion to sharing the domestic demands would have left him little time at the Cavendish, but his productivity did not seem to abate; and at the end of this Cambridge visit, he spent a couple of months at the Orsay Laboratories near Paris, learning about liquid crystals from P.-G. de Gennes. This was the beginning of a friendship and collaboration that was strong enough that de Gennes alluded to it in his Nobel address in 1991. Bill was sufficiently intrigued by liquid crystals to try his own hand at experimental work at Bell with castoff apparatus and a legendarily messy laboratory. But the work he produced was fruitful; he submitted three papers on this subject before leaving Bell in 1972 for the University of Illinois. One of these was his first basic contribution to the field, a Ginsburg-Landau theory for the smectic A phase, and the other two were focused on verification of the fluctuations to be expected from this theory. He continued to publish significant results on liquid crystals for a number of years, culminating in two significant review articles on phase transitions and on molecular theories of the various phases. He returned to Orsay, spending another sabbatical year in de Gennes's group in 1978-79.

The move to the University of Illinois was, I regret to say, an excellent one for Bill and for Joyce. She had been working at Princeton with no formal position, learning protein crystallography, but was able to take a permanent job at Illinois; Bill himself blossomed as one of the most popular and dynamic teachers on the staff: In fact, he won a teaching award. He was able to attract able students and collaborators at will.

Again and again, he would see the relevance of what he was doing to some new field and enter this field with a break-through paper. From complex order parameters in liquid crystals to charge-density waves in dichalcogenides was to him an obvious step, but here he brought in a new and valuable idea, the discommensuration. The discommensuration concept was an immediate success and came into its own with the later discovery of "sliding" charge-density waves, when the sliding motion could be visualized as motion of the discommensurations (which in this case are charged). The concept of the discommensuration foreshadowed the important work of Su, Schrieffer, and Heegev on anomalous quantum defects in one-dimensional charge-density waves. From this to the puzzling A15 martensitic transitions is also a small step. The effort here was, as in the liquid crystals, to develop a heuristic (Ginsburg-Landau) description of these phases. This was carried out with Ravin Bhatt, his student, now at Princeton.

It is not so logical how he came to his next subject. This was the result of being called in to help understand results by Jack Mochel on disordered Ge-Au alloys, where he used both his experimental expertise as a tunneler and his theoretical insight to construct and verify a general theory of the metal-insulator transition, including interactions as well as localization. Here, in one paper, he leapfrogged over work of Abrahams et al. and Altshuler and Aronov and took the next step. This subject remains very difficult and controversial and may not to this day have reached a full solution; but Bill's brilliant paper applying Thouless's scaling ideas to the problem of interactions was an important and promising start.

In his final two years he was preoccupied with the random Ising model (the spin glass), for which he built a special purpose computer in his basement using special high-speed chips and all of his programming wiles. I am not sure results exist in the literature that are more reliable yet than the several papers he published in those years. In particular, he demonstrated conclusively that the two-dimensional spin glass did not have a phase transition.

I have had to pass over quite a number of isolated works—on such things, for instance, as He_3-He_4 mixtures, He_4 thin films, and so on. At the time of his death 12 papers were in preparation or submitted, of which apparently at least 5 were posthumously printed. Bill may have been one of the last examples of what one might call the complete physicist. He was equally at home with abstract field theory and complicated mathematics, he was one of the first to integrate computational techniques and simulation into his papers, and he was at home doing his own experimental work and electronics. This gave him a great advantage in collaborations with experimentalists, since he understood their problems as well as his own.

Bill was a striking, even charismatic character, towards whom almost everyone felt an instant attraction. His very pronounced stutter was an affliction that never left him, but as is usual and particularly difficult for Bill, it was strongest before large audiences and when he was directly questioned. I always felt that his stutter was part of the reason why his written papers—and his work—were always concise but very complete and crystal clear. They were never overstated and he never explained an idea twice, but every idea was clearly stated: Nothing was missing.

He immensely enjoyed sight gags, of which the most continuous was his own appearance. He had a rather luxuriant red beard, which changed length and style from month to month—this month he would appear with a van Dyke and flowing mustache, another a bushy full Stracheyan beard, the next clean-shaven with long red hair. He started right out at Bell Labs in the iconoclastic vein. When he allowed his beard to grow, a guard noticed that the clean-shaven graduate student on his pass was not the bushy-bearded individual who was wearing it. Bill's response was to allow himself to be re-photographed, and as soon as the new pass was issued he shaved off the beard.

An early exponent of the graphic T-shirt, he could be counted on to grace any occasion with some inappropriate piece of clothing: stocking cap, baggy corduroys, or whatever. For our formal celebration of the award of the London Prize he gave his talk in a T-shirt reading, "Where in Hell is Urbana Illinois," the rest of us being in ties and jackets. He was capable of making the best of an opportunity: I well remember the glee with which he reversed the order of my transparencies when I dropped them during a talk at John Bardeen's retirement conference.

He was also an early member of the new generation in his attitude to family life: He was always ready to take on his full share of the duties of parenthood and made it clear that he was an equal partner in raising the family. Everyone who knew them well could easily sense the strong affection between Bill and Joyce.

Bill's sense of humor was acute and very much in evidence. On occasion he could come up with very witty remarks, which were no respecters either of occasions or of persons. Nonetheless he was good-natured and self-deprecating enough that it was hard to take offense. Perhaps his best sight gag was when he was awarded an honorary D.Sc. at the University of Arkansas. The person who was to embellish him with a hood was bewildered by the beard, until Bill simply pulled it up over his head. He reserved his strongest barbs for pretense or pomposity; I think he always hoped that others would live up to his own high scientific and ethical standards and was capable of inserting a needle when he felt they were violated.

All those who knew him consider themselves extremely fortunate to have known Bill during the few productive years he was to be given. I feel that his loss was not only a personal tragedy but a tragedy for the progress and the intellectual health of our field of condensed matter physics.

SELECTED BIBLIOGRAPHY

1965

Ground state of liquid He^4. *Phys. Rev. A* 138:442-51.

With J. M. Rowell. Lead phonon spectrum calculated from superconducting density of states. *Phys. Rev. Lett.* 14:108-12.

1966

With P. W. Anderson. Theory of geometrical resonances in the tunneling characteristics of thick films of superconductors. *Phys. Rev. Lett.* 16:85-87.

1968

Transition temperature of strong-coupled superconductors. *Phys. Rev.* 167:331-44.

Tunneling model of the superconducting proximity effect. *Phys. Rev.* 175:537-42.

Theory of superconductor-normal-metal interfaces. *Phys. Rev.* 175:559-68.

1969

With J. M. Rowell. Tunneling and strong coupling superconductivity. In *Superconductivity*, ed. R. D. Parks, pp. 561-613. New York: Dekker.

1971

Simple molecular model for the smectic A phase of liquid crystals. *Phys. Rev. A* 4:1238-46.

With J. M. Rowell and W. L. Feldmann. Superconductivity and lattice dynamics of white tin. *Phys. Rev. B* 3:4065-73.

1973

Measurement of smectic-phase order-parameter fluctuations near a second-order smectic-A-nematic-phase transition. *Phys. Rev. A* 7:1419-22.

1974

With R. J. Mayer. Simple molecular theory of the smectic C, B, and H phases. *Phys. Rev. A* 9:899-906.

Molecular order and molecular theories of liquid crystals. In *Liquid Crystals and Ordered Fluids,* vol. 2, eds. J. F. Johnson and R. S. Porder, p. 141. New York: Plenum.

With R. N. Bhatt. Theory of anomalous dispersion in liquid He^4. *Phys. Rev. A* 10:1591-97.

1975

Landau theory of charge density waves in transition metal dichalcogenides. *Phys. Rev. B* 12:1187-96.

With R. N. Bhatt. Theory of phonon dynamics near a charge density wave instability. *Phys. Rev. B* 12:2042-44.

1976

With R. N. Bhatt. Landau theory of the martensitic transition in A-15 compounds. *Phys. Rev. B* 14:1007-27.

Theory of discommensurations and the commensurate incommensurate charge density wave phase transition. *Phys. Rev. B* 14:1496-1502.

1977

With K. C. Chu. Unified Landau theory for the nematic, smectic A and smectic C phases of liquid crystals. *Phys. Rev. A* 15:1181-87.

1978

With J. E. Rutledge, J. M. Mochel, and T. E. Washburn. Third sound, 2-D hydrodynamics and elementary excitations in very thin helium films. *Phys. Rev. B* 18:2155-68.

1981

Scaling theory of the metal-insulator transition in amorphous materials. *Phys. Rev. B* 24:2739-43.

With B. W. Dodson, J. M. Mochel, and R. C. Dynes. The metal-insulator transition in disordered germanium-gold alloys. *Phys. Rev. Lett.* 46:46-49.

1983

Monte Carlo simulation of the two-dimensional random ($\pm J$) Ising model. *Phys. Rev. B* 28:5216-20.

1984

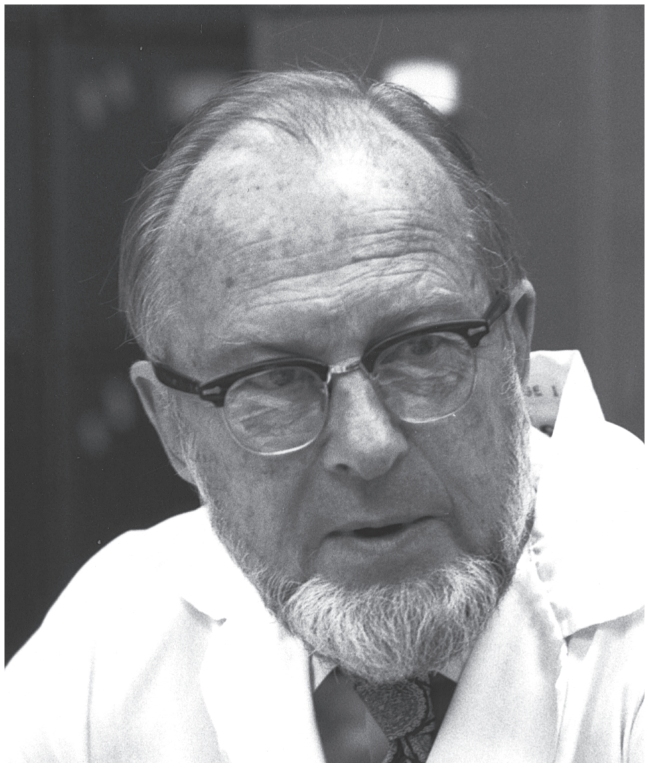
Domain-wall renormalization group study of the two-dimensional random Ising model. *Phys. Rev. B* 29:4026-29.

Scaling theory of Ising spin-glasses. *J. Phys. C: Solid State Phys.* 17:3179-87.

Domain wall renormalization-group study of the three-dimensional random Ising model. *Phys. Rev. B* 30:476-77.

1985

Fermi liquid theory for very dirty metals. *Phys. Rev. B* 31:2750-52.



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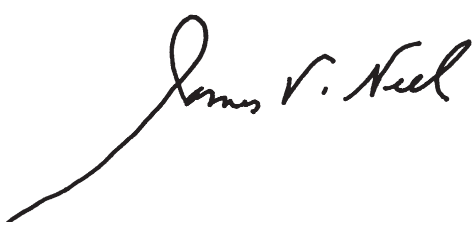


JAMES VAN GUNDIA NEEL

March 22, 1915–February 1, 2000

BY WILLIAM J. SCHULL

Arguably, genetics—particularly human genetics—was the most dynamic of the biological sciences in the second half of the twentieth century. It is widely acknowledged that one of the world's leading contributors to the latter discipline was James V. Neel. Some have called him the father of modern human genetics. Jim, as his colleagues knew him, was born in Hamilton, Ohio, on March 22, 1915, to parents comfortably placed, if not economically well off. An assured middle-class upbringing came to an end, however, with the death of his father when he was 10. His mother and her three children then moved from Detroit, where the family had been residing, to Wooster, Ohio, and it was here that he came of age. The times were parlous, and as a result of the Great Depression and the death of his father, a college education was no longer assured. Fortunately, the community his mother selected was the home of the College of Wooster, a small but outstanding liberal arts college to which he won a scholarship. Jim's career directions were not fixed when he entered college. Once enrolled, however, he came under the influence of Warren Spencer, an inspiring teacher and highly regarded *Drosophila* population geneticist and soon saw genetics as the direction he would pursue. After graduation from Wooster he enrolled in the University of Rochester, where he was the first American graduate student of Curt Stern.

Soon after receiving his Ph.D. in 1939, he accepted a position as instructor in zoology at Dartmouth College, but before his teaching duties began he set out for Edinburgh to attend the VIIth International Congress of Genetics. The latter would be interrupted by the onset of World War II. When this occurred, the Americans present sought to return to the United States as quickly as possible. Not all were lucky. Some, like his colleague Charles Cotterman, booked passage on the British passenger ship *Athenia*, which was torpedoed on September 3, and it sunk with the loss of more than 100 lives. Jim was on the American freighter *City of Flint*, one of the vessels that came to the aid of the *Athenia*. Cotterman was among the passengers the *City of Flint* saved. Even before this near debacle occurred, however, Jim's interest had begun to shift to human genetics for which he had reasoned a medical degree would be important and had set his sights on such at the University of Rochester's Medical School. His progress toward this goal would be hastened by the acceleration of medical education during the war and would be eased financially by support from the Cramer Fund at Dartmouth, the Carnegie Foundation, and enlistment in the Army's Specialized Training Program (ASTP). He was awarded an M.D. in 1944, and in the following two years completed his internship and residency at Strong Memorial Hospital.

Upon completion of his medical training in 1946 he was called to active service in the U.S. Army Medical Corps. Soon thereafter, when President Harry Truman directed the National Academy of Sciences to undertake long-term studies of the health effects on the survivors of exposure to the atomic bombing of Hiroshima and Nagasaki, he was one of five individuals (the others being Austin Brues, Paul Henshaw, Melvin Block, and Frederick Ulrich) the Academy sent to Japan to assess the needs and feasibility of the studies Truman had directed. Neel's involvement would not end with this assessment. He would serve as the first director of the agency charged with the studies, the Atomic Bomb Casualty Commission, and would design and initiate a survey to assess the genetic damage. He hinged this survey on a special provision in Japan's postwar rationing system. This provision made it possible for women, upon registering their pregnancies with the local government, to obtain rationed food to sustain themselves and their unborn offspring through gestation, and clothing for the infant once the child was born. When these mothers-to-be enrolled their pregnancies with the municipal authorities, they were also registered in the survey Neel had designed.

Implementation of this strategy was formidable. The economic circumstances in Japan were severe. Housing was scarce; food and clothing were rationed; and transportation, public or private, was limited. Personnel—American and Japanese—had to be recruited, including not only physicians to perform the examinations but also clerks to interview the prospective parents and to manage the records. Moreover, these individuals had to be motivated and impressed with the importance of each individual task, no matter how menial it might seem. These difficulties notwithstanding and through perseverance and percipience, Jim would prevail, and a program would ensue. He would guide this undertaking—the largest, most comprehensive effort to assess the mutagenic effect of ionizing radiation on human beings that has yet occurred—for over a half century.

Jim's commitments at the time were greater than merely an involvement in the Japanese studies. Before his recall to service in 1946, he had accepted a position in the University of Michigan's Heredity Clinic, where one of his colleagues was the aforementioned Charles Cotterman. Jim's first task there was to develop a research program in human genetics. Initially, he chose to focus this research on the estimation of the rate of spontaneous mutation of genes associated with a series of dominantly inherited diseases and on the mode of inheritance of several blood dyscrasias, an interest that had begun while he was still at Rochester. It was then that he deduced the genetic relationship between sickle cell anemia and the sickling trait and postulated the mode of inheritance now universally accepted. When Linus Pauling and his colleagues (1949) showed that sickle cell anemia was a molecular disease, Jim initiated a series of electrophoretic studies of families resident in Michigan; to further the understanding of the frequency of abnormal hemoglobins in Africa, he developed a working relationship with the Liberian Institute of Tropical Medicine.

In 1956, upon the retirement of Dr. Dice, who had been the director of the Institute of Human Biology of which the Heredity Clinic was a part, the university established a Department of Human Genetics. Jim was its founding chairman, and through his efforts it would become one of the stellar such departments, nationally and internationally. From its beginning, he wanted his department to have the breadth of knowledge and skills to approach genetic issues on the broadest possible front—from the biochemical, to the cytogenetic, to the immunological, to the epidemiological. He recruited to this end and steadfastly sought to establish and maintain a research milieu that fostered individual creativity, one in which his colleagues could reach their full potential. His success in this respect is attested by the scientific prominence his colleagues, past and present, have achieved and the students and postdoctoral fellows the department has trained.

The year 1956 was a noteworthy one in Neel's career in other respects as well. The results of the radiation studies in Japan were presented at international conferences in Japan and Europe, a monograph on neurofibromatosis was published, and the first of a series of studies of the life experiences of the children of consanguineous marriages that would extend over a decade commenced in Japan. When these studies began, little was certain about the effects of consanguineous marriages. It was known that the children of related parents were more likely to be homozygous for a rare gene than were children whose parents were not related to one another. If the gene's effects were harmful when homozygous, the children of related parents would be expected to exhibit these deleterious consequences more often than the children of unrelated parents. This knowledge rested largely on studies of children selected because they were known to have a rare inherited disease. It was not known, however, how common these deleterious effects would be among children of related parents who had not been chosen with a view toward some specific health outcome.

The earlier study of the effect of ionizing radiation on a pregnancy outcome in Hiroshima and Nagasaki had identified several thousand children whose parents were related. Analyses of the data collected at or shortly after the birth of these children revealed that congenital defects were more common when the parents were related, and more of the children died in the first year of life than would be expected normally. The new studies were aimed at extending these observations over a longer period of time. Again, the preliminaries and logistics were challenging, but Jim proved to be an adept, patient advocate and organizer. He recruited the faculties of several Japanese universities and initiated a series of meetings with the local municipal and educational authorities, parent-teacher associations, and the medical community to seek approval of the study and understanding of its objectives. However, other logistic problems existed. There was a need to train contactors to solicit the participation of the study cases, and a means found to transport the child (and parents, if they wished to accompany the child) to the clinic. All this planning sought to serve parental and social needs and to enhance the value of the examination to the children as well as their families.

Out of this effort came the most complete body of data available on the biological consequences of being the child of consanguineously related parents and a better appreciation of the relative magnitude of the health risks involved. Intriguing as these studies were in their own right, they were not tangential to the search for radiation-induced mutations. The aim of the latter search was not merely to count newly arisen mutations but also to estimate their long-term health impact. Because mutations can lurk in a population for generations before manifesting themselves, it had to be determined how genetic variability was maintained through this period before manifestation. Several competing theories existed but few human data to provide guidance as to which of these was correct. Finally, Newton Morton, James Crow, and Hermann Muller (1956) indicated how studies of the children of consanguineous marriages might contribute to the estimation of this "load" and to an assessment of the relative importance of these competing hypotheses.

This need to know how genetic variability is maintained stimulated a great deal of theoretical, experimental, and epidemiological research, but the populations that were being studied were generally more culturally advanced than those thought to characterize much of human evolution. Jim sought to observe humans in a more ancestrally "natural" state. Thus began his quest for less technologically acculturated populations in South America. He recognized that these populations were not unacculturated in terms of the day-to-day circumstances of their lives, but they did dwell under conditions much more like human aboriginal ones than those generally prevailing. He reasoned that a study of their lives might provide insight into the general nature of human ancestral selective pressures, with consequences for human health (1958). As a consequence, much of Jim's work in the Amazon concerned biomedically relevant phenotypes. His intent was to compare the health profiles of hunting and gathering communities with those of the industrialized world. He was intrigued by the thought that a genotype might be beneficial in one environment but not in another. Indeed, it was this notion that gave rise to his much imitated argument that diabetes today was a "thrifty" genotype made disadvantageous by environmental changes (1962, 1982).

Jim was also interested in the evolution of responses to infectious organisms. It was known that infectious diseases such as smallpox and measles devastated aboriginal New World populations. But why? Were they inherently more susceptible or did the answer lie elsewhere? An obvious way to address the first of the alternatives was to study the susceptibility of populations suddenly exposed to what is typically a rather benign disease in populations with centuries of exposure to the same agent. Measles is such a case and epidemics of this viral disease have occurred with high rates of lethal complications in Amerindians. An ethically defensible way to examine the question of susceptibility would be to vaccinate isolated previously unexposed populations to gauge their reactions to the vaccine that, in the process, would also protect them from the actual disease. Jim was planning to do this when an epidemic arose near, and even in, the villages they were about to study. Their plan gave way to an effort to limit the epidemic and minimize its health costs.

The Amazonian studies centered on all the factors contributing to population structure, including the determination of patterns of mate selection, mortality and fertility, and the estimation of effective population size and selection coefficients, as well as other parameters, such as admixture. They were surprisingly elegant, given the technology of the time, the complex logistics, and the need to coordinate substantial numbers of collaborators and government officials. While it was not possible then to document DNA variation very directly or exhaustively, limited genotyping was possible by blood typing and protein electrophoresis. Nonetheless, the global nature of many polymorphisms was demonstrated, but locally unique or "private" variants were also discovered. The overall level of variation was considerably higher than had been expected, raising questions about how that variation was maintained. Eventually these studies would embrace about 35 Yanomama villages and at least 20 other tribes in South and Central America. The result was a formidable set of data that along with the thousands of samples collected elsewhere around the world since then, has been influential in shaping our perception of human genetic diversity. The continued existence of 15,000 or so samples collected 30 or more years ago ensures that this scientific legacy will be profitably mined for many years to come.

As these studies were unfolding, Jim's interest again turned to the estimation of the frequency of radiation-induced mutation. Oliver Smithies's (1955) demonstration of the value of starch gel electrophoresis in characterizing inherited protein variability opened a new investigative door, and the growing number of electrophoretically recognizable protein differences among individuals offered an opportunity Jim was quick to seize. Most of these proteins can easily be studied in blood specimens, but if this approach was to succeed, tens of thousands of tests would be needed, and the feasibility of a study of this scale was not clear. Demonstration of feasibility meant the identification of a suitable study group and the acceptability of the study to the survivors of the atomic bombings and their children. These concerns could only be resolved through a pilot study and in 1972 one was begun. When this study was terminated in 1975, it was clear that a full-scale investigation was technically feasible and acceptable to the population of interest. When the latter began in Hiroshima and Nagasaki in 1976, the aim was to examine each participating child for rare electrophoretic variants of 28 proteins of the blood plasma and red cells, and a subset of these children for deficiency variants of 10 of the red-cell enzymes.

When either such variant was encountered and before it could be attributed to mutation, the possibility of a technical error had to be excluded and then blood samples from both parents had to be examined for the presence of a similar variant. If the variant is not found in one or the other parent and if an error in assigning parentage is improbable, it presumably represents a new mutation. To establish parentage (since a priori the probability that the putative parents might not be the real parents is several orders of magnitude larger than the probability of a new mutation) some 11 different red-cell antigenic systems and the major histocompatibility phenotypes (the HLA system) were used to search for evidence that the putative parents were not the actual parents of the child. Although such testing does not prove parentage (it can only exclude falsely identified parents), the battery used was sufficiently large that the a priori probability of failing to detect a falsely identified parent was approximately the same as the a priori probability of a new mutation.

When this study terminated in the 1980s, three probable structural mutations had been seen in 667,404 locus tests on 13,052 children born to parents whose average combined gonadal dose was about 0.47 Sv, and three in 466,881 locus tests on 10,609 children whose parents received less than 10 mSv. The mutation rates in the two groups of children were almost identical; the values are 0.60×10^{-5} mutations per generation in those who were the offspring of parents receiving more than 10 mSv of gonadal exposure, and 0.64×10^{-5} in those whose parents received less than 10 mSv. The confidence intervals for these two estimates, that is, the probable range in which the "true" value lies, were 0.2-1.5 and $0.1\text{-}1.9 \times 10^{-5}$, respectively. In addition, one probable "deficiency" mutant was seen in 60,529 locus tests on children whose parents, one or both, received more than 10 mSv of radiation, but none among the 61,741 tests on the children of distally exposed parents. Thus, when the results of the studies of structural and activity variants were combined after more than 1,256,000 biochemical tests, four mutants were seen among the children of parents receiving more than 10 mSv, and three among those whose parents received less than 10 mSv.

Despite the inconclusive results this was a landmark study integrating evolutionary, population, and molecular genetics and a clever study designed to address a question of importance to contemporary public health and to give a perspective on evolutionary biology. Moreover, in the measurement of mutation rates it shifted the focus from crude phenotypes (the product of a complex web of gene-environment interactions) to the immediate product of gene action. Nonetheless, the study had two significant limitations. First, despite the enormous amount of work involved, a sample of a million and a quarter locus tests was marginally adequate to detect the level of mutational damage thought to be most likely. Second, while the number of functional human genes was uncertain, it appeared to be no larger than 50,000 and if only 28 or so of these were studied how likely is it that they would be representative of the totality? Neither of these issues seemed likely to be resolved with the technology then available.

Two new techniques of promise had appeared on the horizon, however: gene sequencing and two-dimensional electrophoresis. In the late 1970s both of these approaches had their strengths and their limitations, and it was unclear which to pursue, if only one could be pursued. Jim chose to champion two-dimensional electrophoresis. He and his colleagues immediately turned to the standardization of the purely biochemical aspects of the technique, and the proof that the technique would work. However, the two-dimensional separation of DNA results in 500 or more recognizably discrete products. Analysis of the difference between two samples in the distribution of these products defies easy visual examination. This fact led to a substantial investment in automated methods of pattern recognition (see, e.g., Skolnick and Neel, 1986). As was his wont, Jim immersed himself in this technology until he could persuade himself that he could contribute to its furtherance. Scarcely eight weeks before his death, he was still so engaged. He and a colleague, Junichi Asakawa, were summarizing their joint study of the utility of two-dimensional electrophoresis in the estimation of radiation-induced mutation rates.

Research was not the sole function of the Department of Human Genetics; teaching was no less important. When in the late 1950s the National Institute of General Medical Sciences instituted a pre- and postdoctoral training program in genetics, Jim was asked to serve as the chairman of the Genetics Training Grant Committee, a position he would hold from 1958 through 1963. In this position he and his committee did much to codify the standards that would guide this program for several decades. Ironically, students, generally unaware of his role in the establishment of the program that supported many, were often wary of Jim. His accomplishments, prestige, and no-nonsense demeanor were intimidating. They feared he would be unreasonably demanding and insensitive. But as they soon realized, this was not the case. He was demanding but sympathetic. He sought to encourage all students to be thoughtful and critical, not only of their own work but that of others, including their mentors as well. Through subtle probing he invariably managed to bring out the best in a student.

Neel's contributions to human genetics are legion and it is difficult to discern a single thread that connects all aspects of his research career. If a thread exists, however, it is the phenomenon of mutation. His interest began at Dartmouth College, was whetted by his association with Philip Ives and Ernst Hadorn, and continued throughout his long connection with the studies in Japan. In the pursuit of this fundamental biological process he demonstrated an admirable capacity to incorporate new technologies and new ideas as these became available. His interest focused not merely on the frequency of mutation, whether spontaneously occurring or induced, but also upon the biochemistry of the process, the manifestation of mutations when present in a single dose, and the factors that govern the persistence or loss of new mutations at the population level.

Neel was elected to membership in the National Academy of Sciences (1963), American Philosophical Society (1965), American Academy of Arts and Sciences (1971), Institute of Medicine (1972), and the Royal Society of Medicine (1992), as well as other honorary societies. He received numerous awards, among these being the Lasker Award of the American Public Health Association (1960), Allen Award of the American Society of Human Genetics (1965), National Medal of Science (1975), Medal of the Smithsonian Institution (1981), and the Silvio Conte Award (1991). Among the many named lectureships he gave were the Galton Lecture (University College, London), the Cutter Lecture (Harvard), Harvey Lecture (Harvey Society), the Russel Lecture (University of Michigan), the Jacobson Lecture (University of Newcastle-upon-Tyne), the Baker Lecture (Pennsylvania State University), and the Joshua Lederberg Distinguished Lecture (Rockefeller University). His colleagues recognized his many contributions to human genetics through electing him to numerous presidencies, among them those of the American Society of Human Genetics (1953-54), International Society of Genetic Epidemiology (1991-93), and the Sixth International Congress of Human Genetics (1981). He served on many editorial boards and in a consultative capacity for countless national and international agencies. Among these editorial boards were those of *Blood, Perspectives in Biology and Medicine, Proceedings of the National Academy of Sciences, Behavioral Genetics, Mutation Research, Journal of Molecular Evolution, Clinical Genetics, and Genetic Epidemiology,* to mention only a few. The agencies he aided included the National Institutes of Health, Department of Energy, Environmental Protection Agency, National Council on Radiation Protection and Measurements, Veterans Administration, Pan American Health Organization, and the World Health Organization. He received honorary degrees from his alma maters, the College of Wooster (1959) and Rochester University (1974), as well as the Medical College of Ohio (1981).

This recitation of his scientific vision and professional achievements is a limited measure of the man. He was much more. His curiosity and interests constantly amazed his colleagues and fellow academics. He was not only an exceptionally able clinician who, despite his administrative responsibilities, periodically took on the management of a clinical ward but also a great human biologist in the premodern sense of that calling. He was also an avid orchidist and a collector of butterflies. More important, he was a person of enormous personal integrity, sensitivity, and compassion. He was deeply concerned with the lot of his fellow kind as his autobiographical book *Physician to the Gene Pool* (1994) compellingly testifies. He was truly a "man for all seasons." Above all, however, he was devoted to his family: his wife, Priscilla Baxter, and his three children, Frances, James, Jr., and Alexander. His concern for them was always foremost.

Jim was not without his foibles. For example, although his career spanned an era extending from the mechanical desktop calculator (the Monroe, Marchant, or Frieden) to the electronic marvel that now exists, he was never comfortable with these devices. He reluctantly used the calculator but never adapted to its electronic counterpart. When he needed the services these could provide, such as e-mail or word processing, he turned to his children or to his secretaries. He preferred to continue to write his manuscripts in longhand and saw no hardship in this. Some of his resistance to gadgets may reflect an anecdote he told on himself. As a doctoral student, to save money so that he might attend the international congress in Edinburgh he decided to type his doctoral dissertation himself. This proved a more traumatic experience than he had anticipated and he swore off such machines. Be this as it may, when Jim relinquished the chairmanship of the department in 1981, unlike many of his age peers who settled quickly and comfortably into the role of a senior scientist, he remained totally involved, and kept abreast of new developments in genetics with a fervor his younger colleagues envied. Although his was a full life by any accounting, his death leaves contemporary human genetics and modern clinical medicine much the poorer, and his friends and associates deprived of a concerned and willing source of counsel.

Several months after James Neel's death his family, colleagues, and friends found themselves involved in a controversy. Allegations were made that his involvement in the studies of the Xavante and Yanomama of Brazil and Venezuela stemmed largely, if not solely, from his interest in eugenics, and that he had consciously and unethically imported a measles epidemic into the Venezuelan outback to further his interest in the biology of immune response to exogenous infectious pathogens (Tierney, 2000). It was alleged that this epidemic led to the deaths of hundreds, if not thousands, of individuals who were ill prepared immunologically to cope with the new virus. Callously the individuals responsible for these allegations ignored the fact that the epidemic began before Neel and his colleagues were in the field. Informed of the raging epidemic before his departure from the United States, Neel brought gamma globulin and measles vaccine from pharmaceutical companies in the United States to combat the spread of the disease. However, even this effort was diminished. He was accused of bringing a virus less suitable to the situation than was then available. The salutary aspect of this sordid affair was the promptness with which all of those scientists who knew Jim or were aware of his work rose to his defense. Clinicians, geneticists, virologists, all spoke on his behalf. A reasonable society could reach only one conclusion. The charges are baseless, wholly unwarranted, and mendaciously cruel. The reasons that prompted these allegations may never be fully known, but whatever their bases they do no credit to the individuals who availed themselves of this opportunity to pursue their own agendas.

REFERENCES

Morton, N. E., J. F. Crow, and H. J. Muller. 1956. An estimate of the mutational damage in man from data on consanguineous marriages. *Proc. Natl. Acad. Sci. U. S. A.* 42:855-63.

Pauling, L., H. A. Itano, S. J. Singer, and I. C. Wells. 1949. Sickle cell anemia: A molecular disease. *Science* 110:543-48.

Skolnick, M. M., and J. V. Neel. 1986. An algorithm for comparing two-dimensional electrophoretic gels, with particular reference to the study of mutation. In *Advances in Human Genetics*, vol. 15, eds. H. Harris and K. Hirschhorn, pp. 55-160. New York: Plenum Press.

Smithies, O. 1955. Grouped variations in the occurrence of new protein components in normal human serum. *Nature* 175:307-308.

Tierney, P. 2000. *Darkness in El Dorado: How Scientists and Journalists Devastated the Amazon.* New York: W. W. Norton.

SELECTED BIBLIOGRAPHY

James Neel was the author of more than 600 scientific articles and the author, coauthor or editor of no less than 12 books or monographs. It is a challenging task to select from his extensive publications those that all would construe as seminal. Any selection must reflect, and perhaps unduly, one's personal preferences. Geneticists would undoubtedly select one set, human biologists another, and clinicians still a third. But these differences merely reflect the breadth of his interest and competence.

1944

With W. N. Valentine. Hematologic and genetic study of the transmission of thalassemia (Cooley's anemia, Mediterranean anemia). *Arch. Int. Med.* 74:185-96.

1947

The clinical detection of the genetic carriers of inherited disease. *Medicine* 26:115-53.

1949

The inheritance of sickle cell anemia. *Science* 110:64-69.

1951

With H. F. Falls. The rate of mutation of the gene responsible for retinoblastoma in man. *Science* 114:419-22.

1952

The study of human mutation rates. *Am. Nat.* 86:129-44.

1954

With W. J. Schull. *Human Heredity*. Chicago: University of Chicago Press.

1955

On some pitfalls in developing an adequate genetic hypothesis. *Am. J. Hum. Genet.* 7:1-14.

1958

The study of natural selection in primitive and civilized populations. *Hum. Biol.* 3:43-72.

1962

Diabetes mellitus: A "thrifty" genotype rendered detrimental by "progress"? *Am. J. Hum. Genet.* 14:353-62.

1964

With F. M. Salzano, P. C. Junqueira, F. Keiter, and D. Maybury-Lewis. Studies on the Xavante Indians of the Brazilian Mato Grosso. *Am. J. Hum. Genet.* 16:52-140.

1970

Lessons from a "primitive" people. *Science* 170:815-22.

1973

"Private" genetic variants and the frequency of mutation among South American Indians. *Proc. Natl. Acad. Sci. U. S. A.* 70:3311-15.

1978

The population structure of an Amerindian tribe, the Yanomama. *Ann. Rev. Genet.* 12:365-413.

1982

The thrifty genotype revisited. In *The Genetics of Diabetes Mellitus,* eds. J. Köbberling and R. Tattersall, pp. 137-47. New York: Academic Press.

1986

With A. A. Awa. Cytogenetic "rogue" cells: What is their frequency, origin, and evolutionary significance? *Proc. Natl. Acad. Sci. U. S. A.* 83:1021-25.

1990

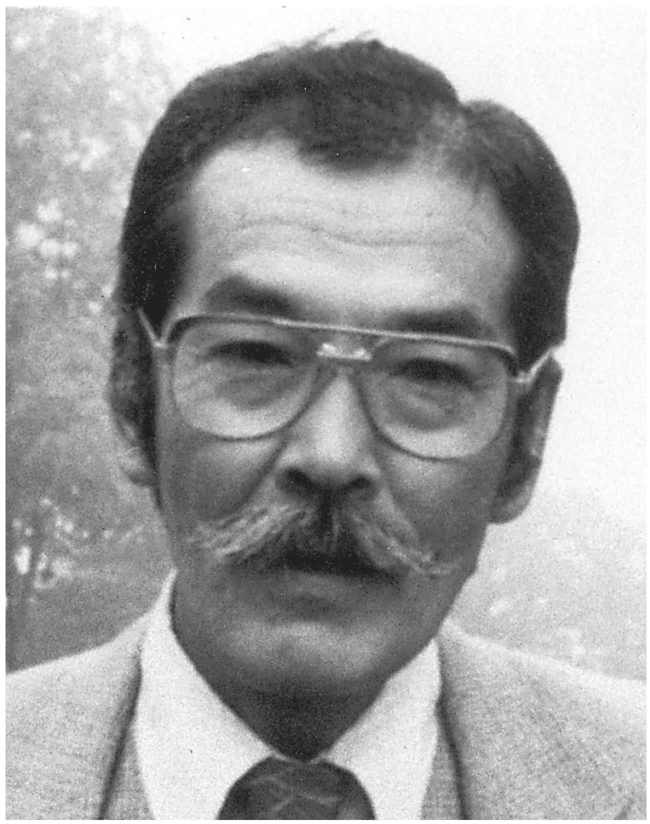
With S. E. Lewis. The comparative radiation genetics of humans and mice. *Ann. Rev. Genet.* 24:327-62.

1991

With W. J. Schull. *The Children of Atomic Bomb Survivors: A Genetic Study*. Washington, D. C.: National Academy Press.

1994

Physician to the Gene Pool. New York: John Wiley.



Susumu Ohno

SUSUMU OHNO

February 1, 1928–January 13, 2000

BY ERNEST BEUTLER

SUSUMU OHNO WAS BORN of Japanese parents in Seoul, Korea, on February 1, 1928. The second of five children, he was the son of the minister of education of the Japanese Viceroyship of Korea. He was born at a time when Japan was in many ways isolated from Western thought with its chief scientific links firmly established with Germany, and he was schooled in the years when a bitter war was fought between Japan and the United States and its Western allies. Yet, he was to emerge as one of America's greatest scientists, exerting an enormous influence on our ideas about biology and evolution.

Ohno's family was aristocratic and well educated. His maternal grandfather had been a justice of the Supreme Court of Korea and his paternal grandfather had been a scholar of Chinese language and history. As a high government official his father had traveled extensively, and Susumu lived in Korea and Japan during his childhood. His father nurtured ideas that were unusually liberal for someone in his position. He believed, for example, that people of all races were equal, an idea that impressed Susumu and one that he carried with him for his whole life. Susumu's liberal views influenced the educational opportunities that were afforded him. He was denied entry into the government public school because, he said, of his liberal propensities. Instead, he was sent by his family to one of the best private schools. In addition, he was taught by tutors to learn Chinese language and Chinese history. Of his siblings Susumu was the only one to leave Japan; all of his brothers and his sister lived their entire lives on the Japanese islands.

His love of animals, particularly of horses, proved to be one of the most pervasive influences in his life. His father was entitled to maintain both an automobile and a horse on his property, and he normally traveled to his office on horseback. That's how Susumu began riding—while waiting for his father. His interest in genetics began, Ohno said, when he realized that "when a horse is no good, there is not much you can do." His interest in horses also strongly influenced his career choice. He wanted to attend veterinary school. At first his father was opposed to this choice, suggesting a career in medicine instead. Nevertheless, veterinary school it was, and Ohno received a D.V.M. degree from the Tokyo University of Agriculture and Technology in 1949. It was also a common interest in horses that brought Susumu together with the charming Midori, who was to be his life's mate for nearly 50 years. Indeed, it was owning and training horses that were to be a lifetime avocation for both Susumu and Midori.

Ohno selected the Hokkaido University Faculty of Sciences for his graduate studies, because a professor there, Sajiro Makino, was well known for his study of chromosomes, a topic that had begun to interest Ohno. His doctoral dissertation concerned the role of plasma cells in the production of antibody, and in 1953 Ohno was awarded his Ph.D. degree.

His graduate work in the area of immunology brought him in contact with Keiji Aoyama, and it was through this acquaintanceship that he met Aoyama's daughter Midori. Although their romance flourished in a society in which, at the time, arranged marriages were common, they did not marry in Japan. Ohno saw that the future of science lay in the United States, and before they could be married, he had obtained an appointment at the University of California, Los Angeles, in the department of Charles Carpenter.

At UCLA Ohno began to work with a well-known professor, Riojun Kinosita. Although he was of Japanese origin, Kinosita had traveled extensively abroad and had worked in Germany and England. There he had discovered that butter yellow was a carcinogen, and largely because of this discovery he had become internationally known. Soon after Ohno arrived at UCLA, Kinosita was asked to initiate a research program at the City of Hope National Medical Center in Duarte, some 50 miles northeast of UCLA. He asked young Ohno to join him in establishing this new research program. Apparently it was an exciting challenge for both of them, and Ohno moved to the institution where he was to spend his entire highly productive career.

It was very difficult for a Japanese woman to obtain a visa to enter the United States in the early 1950s, so Midori stayed behind in Japan and married Susumu by proxy while she was in Japan and he in the United States. In 1953 she was able to join him. Their marriage produced three children. The oldest, a son named Azusa, was born in 1955 and is now a film director in southern California. The second child was a daughter, Yukali, who studied philosophy and now lives with her husband in Hawaii. The youngest son lives in Las Vegas, where he works as a croupier.

CONTRIBUTIONS TO SCIENCE

Ohno's productive career may be divided into several overlapping phases. When beginning his work at the City of

Hope Medical Center he skillfully devised cinematographic techniques for the study of living bone marrow. While these studies hardly foretold the profound insights that Ohno would have into biologic mechanisms, they established him as a highly skilled experimentalist.

With these skills he moved into the second phase of his career as a scientist, the study of chromosomes. Here his abilities as an experimentalist complemented his deep biologic insights and led him to a discovery that was to influence our understanding of genetic mechanisms. He recognized that the chromatin body that was found in female cells was not, as had been previously thought, the two X chromosomes lying in apposition but rather that one X chromosome was heterochromatic. This discovery, which Ohno later singled out as being possibly the most important of his career, served to focus his attention upon chromosomal function, particularly with respect to sex determination, and it was in this area that he made additional highly original contributions. Since it was known that in insects heterochromatin was genetically inactive, this suggested independently to a number of scientists that one of the two mammalian female chromosomes might be genetically inactive. In studying the phylogenetic derivation of the X chromosomes, he recognized that they must have developed from a pair of autosomes, one of which underwent specialized development. In mammals this ultimately led to the nearly functionless Y chromosome. For a time he became fascinated with the H-Y antigen but began to realize that the antisera that were available were of such poor quality that the results were not reliable. He later acknowledged that he had been, for a short time, misled by the results obtained.

In studying the chromosomes of mammals he noted that while there was great diversity in the number of chromosomes in different species, even species that were closely related, the total amount of chromosomal material appeared to be the same. At a time that many were doing much less profound work, using highly sophisticated techniques, Ohno carefully made chromosome spreads, photographed them, and cut the chromosomes from photographic paper. He then weighed the cutout chromosomes showing in this way that whether there were 17 pairs of chromosomes as in the creeping vole, *Microtus oregoni,* or 84 pairs as in the black rhinoceros, the amount of chromosomal material was the same. But he found that this was not the case in organisms lower on the phylogenetic tree. Here it seemed to him that there had been successive doublings of the amount of chromosomal material. He somewhat whimsically designated the extra DNA as "junk DNA," presciently recognizing that most of the DNA in higher organisms does not consist of coding sequences.

Ohno undertook to write three monographs in which he developed his innovative ideas about chromosomes and sex determination. These were *Sex Chromosomes and Sex-Linked Genes* published in 1967, *Evolution by Gene Duplication* published in 1970, and *Major Sex-Determining Genes* published in 1979. Although his ample bibliography is replete with multiauthored papers in leading scholarly journals, it is in these monographs that he was able to most fully explore his innovative ideas about biology. The preface of the first of these books reads as follows:

> On the premise that each field of natural science has become too complex to be comprehended by a single man, it is more fashionable today to organize a committee of specialized scientists to write one book. While a book, written by a committee tends to present an objective appraisal of current knowledges, it suffers from disunity of thoughts. It is my sincere desire that this book will manifest more merits than shortcomings in having been written by one author.

This monograph dealt with the evolution of the X and the Y chromosomes in mammals and the Z and W chromosomes in avian and ophidian species. It discussed in detail the X-inactivation hypothesis to which Ohno contributed so much and considered various mechanisms of dosage compensation.

The second monograph on gene duplication was far ahead of its time. In the preface he wrote:

> Had evolution been entirely dependent upon natural selection, from a bacterium only numerous forms of bacteria would have emerged. The creation of metazoans, vertebrates, and finally mammals from unicellular organisms would have been quite impossible, for such big leaps in evolution required the creation of new gene loci with previously nonexistent function. Only the cistron that became redundant was able to escape from the relentless pressure of natural selection. By escaping, it accumulated formerly forbidden mutations to emerge as a new gene locus.

Thus, he recognized that this DNA could serve as a powerful means by which new genes or new functions of old genes could be created. This concept had been expressed earlier by Haldane, but the explosion in modern biology and molecular genetics made it possible to assess for the first time the important role that gene duplication played in evolution.

The third volume dealt in greater detail with sex determination. Ohno was fascinated by the testicular feminization syndrome, in which XY persons do not only develop into phenotypic females but into females who are particularly beautiful. A mutation on the X chromosome that causes resistance to the effect of male hormones is responsible for this disorder.

In the middle 1980s Ohno became interested in the evolution of DNA sequences. He realized that the decamers that might be formed in the primordial soup through known chemical reactions would not be sufficient to contain the information required for even the most primitive life forms. Accordingly, he proposed that the primordial oligonucleotides were repeating pentamers that hybridized with one another, forming templates for elongation. The result would be a repeating sequence, but because the repeating unit was five nucleotides long, there would be a frameshift in a triplet code, resulting in the formation of longer amino acid sequences, which however, would also be repeating in nature. Such sequences he proposed could well give rise to the α helices and β sheets so common in protein structure.

In searching the rapidly increasing number of sequences that were becoming available, Ohno saw many recurring motifs and thought it would be interesting to assign notes to nucleotides, converting the sequences into musical passages. This made it possible to appreciate the repeating nature of motifs in the DNA sequence in a much more pleasant fashion than scanning the monotonous repeating letters of the sequences. This approach had a great deal of popular appeal and Susumu and Midori, who was musically proficient as a singer, were often called upon to perform some of their transcriptions of sequences into music.

Ohno's enormous contributions to science did not go unnoticed during his lifetime. He was elected to the American Academy of Arts and Sciences in 1974 and to the National Academy of Sciences in 1981. He was elected as a foreign member of the Royal Danish Academy of Sciences and Letters in 1992. In 1968 he received the Peter Volid special tribute award; the silver medal of the Bell Museum of Pathology at the University of Minnesota in 1972; the Japanese human genetics society prize in 1981; the Francis Amory Prize for Reproductive Biology of the American Academy of Arts and Sciences in 1981; the Kihara Prize of the Japanese Society of Genetics in 1983; and the Inaugural Queen Margarethe Prize from the Royal Danish Academy of Arts and Sciences in 1998. On the latter occasion Lennart Olsen stated,

> He has thought at least half of the thoughts that form the basis of the work being carried out all over the world in respect to genetic analysis. In particular, the notion that every new gene arises from an already existing gene has revolutionized research.

Honorary degrees were conferred upon him by the University of Pennsylvania in 1984 and by the Tokyo University of Agriculture and Technology in 1997. In the last year of his life he made a final journey to Japan with Midori. On that occasion Ohno was accorded the rare privilege of a personal meeting with the emperor of Japan, and upon his passing the emperor and empress sent their personal condolences to Mrs. Ohno.

THE ORAL HISTORY interview conducted by Steven J. Novak, director of professional education and scientific reports at the City of Hope National Medical Center, was a great aid in writing this biographical memoir, and the author appreciates this valuable resource being made available.

SELECTED BIBLIOGRAPHY

1958

With W. D. Kaplan and R. Kinosita. A photographic representation of mitosis and meiosis in the male of *Rattus norvegicus*. *Cytologia* 23:422-28.

1959

With W. D. Kaplan and R. Kinosita. On the end-to-end association of the X and Y chromosomes of *Mus musculus*. *Exp. Cell Res.* 18:282-90.

With W. D Kaplan and R. Kinosita. The centromeric and nucleolus-associated heterochromatin of *Rattus norvegicus*. *Exp. Cell Res.* 16:348-57.

With W. D. Kaplan and R. Kinosita. Formation of the sex chromatin by a single X-chromosome in liver cells of *Rattus norvegicus*. *Exp. Cell Res.* 18:415-18.

1960

With T. S. Hauscka. Allocycly of the X-chromosome in tumors and normal tissues. *Cancer Res.* 20:541-45.

With W. D. Kaplan and R. Kinosita. On isopycnotic behavior of the XX-bivalent in oocytes of *Rattus norvegicus*. *Exp. Cell Res.* 19:637-39.

1961

With S. Makino. The single-X nature of sex chromatin in man. *Lancet* 1:78-79.

With J. Trujillo, V. F. Fairbanks, and E. Beutler,. Chromosomal constitution in glucose-6-phosphate-dehydrogenase deficiency. *Lancet* 2:1454-55.

With W. D. Kaplan and R. Kinosita. X-chromosome behavior in germ and somatic cells of *Rattus norvegicus*. *Exp. Cell Res.* 22:535-44.

1964

With W. Beçak and M. L. Beçak. X-autosome ratio and the behavior pattern of individual X-chromosomes in placental mammals. *Chromosoma* 15:14-30.

1965

With C. Mathai, J. Trujillo, and E. Beutler. Sex-linkage of G-6-PD in the horse and donkey. *Fed. Proc.* 24:440.

With J. Poole and I. Gustavsson. Sex-linkage of erythrocyte glucose-6-phosphate dehydrogenase in two species of wild hares. *Science* 150:1737-38.

1966

With C. K. Mathai and E. Beutler. Sex-linkage of the glucose-6-phosphate dehydrogenase gene in *Equidae*. *Nature* 210:115-16.

With H. W. Payne, M. Morrison, and E. Beutler. Hexose-6-phosphate dehydrogenase found in human liver. *Science* 153:1015-16.

1967

Sex Chromosomes and Sex-Linked Genes. Heidelberg: Springer-Verlag.

1970

Evolution by Gene Duplication. Berlin: Springer Verlag.

1973

With L. Christian, B. J. Attardi, and J. Kan. Modification of expression of the testicular feminization (tfm) gene of the mouse by a "controlling element" gene. *Nature* (*New Biol.*) 245:92-93.

1974

With U. Drews, S. R. Blecher, and D. A. Owen. Genetically directed preferential X-activation seen in mice. *Cell* 1:3-8.

1978

With B. Beutler, Y. Nagai, G. Klein, and I. Shapiro. The HLA-dependent expression of testis-organizing H-Y antigen by human male cells. *Cell* 13:509-13.

1979

Major Sex Determining Genes. Berlin: Springer-Verlag.

1985

The notion of primordial building blocks in construction of genes and transcriptional and processing errors due to random occurrence of oligonucleotide signal sequences. *Adv. Exp. Med. Biol.* 190:627-36.

1986

With M. Ohno. The all pervasive principle of repetitious recurrence governs not only coding sequence construction but also human endeavor in musical composition. *Immunogenetics* 24:71-78.

1987

Evolution from primordial oligomeric repeats to modern coding sequences. *J. Mol. Evol.* 25:325-29.

1996

The notion of the Cambrian pananimalia genome. *Proc. Natl. Acad. Sci. U. S. A.* 93:8475-78.

1998

The notion of the Cambrian pananimalia genome and a genomic difference that separated vertebrates from invertebrates. *Prog. Mol. Subcell. Biol.* 21:97-117.

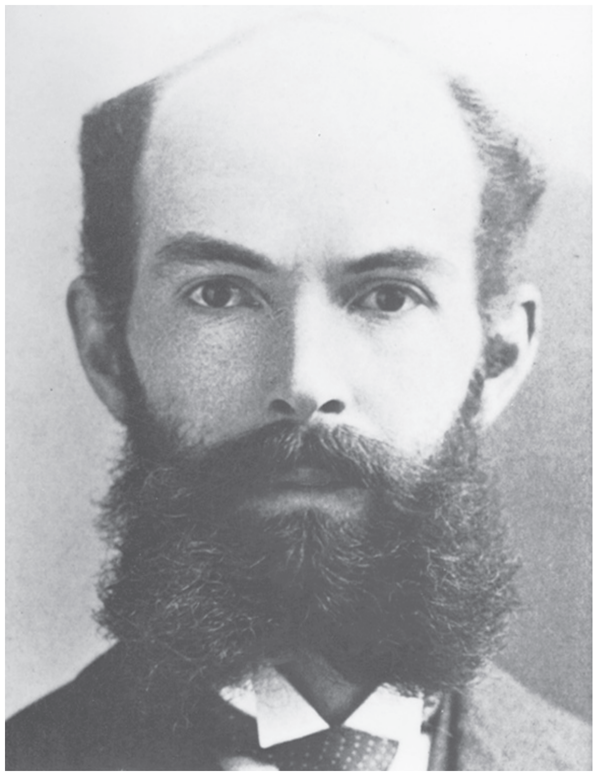


Photo courtesy of the American Mathematical Society.

William F. Osgood

WILLIAM FOGG OSGOOD

March 10, 1864–July 22, 1943

BY JOSEPH L. WALSH

WILLIAM FOGG OSGOOD WAS born in Boston, Massachusetts, the son of William and Mary Rogers (Gannett) Osgood. He prepared for college at the Boston Latin School, entered Harvard in 1882, and was graduated with the A.B. degree in 1886, second in his class of 286 members. He remained at Harvard for one year of graduate work in mathematics, received the degree of A.M. in 1887, and then went to Germany to continue his mathematical studies. During Osgood's study at Harvard, the great Benjamin Peirce (1809-1880), who had towered like a giant over the entire United States, was no longer there. James Mills Peirce (1834-1906), son of Benjamin, was in the Mathematics Department, and served also later (1890-1895) as Dean of the Graduate School and (1895-1898) as Dean of the Faculty of Arts and Sciences. William Elwood Byerly was also a member of the Department (1876-1913) and is remembered for his excellent teaching and his texts on the Calculus and on Fourier's Series and Spherical Harmonics. Benjamin Osgood Peirce (1854-1914) was a mathematical physicist, noted for

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his table of integrals and his book on Newtonian Potential Theory. Osgood was influenced by all three of those named—they were later his colleagues in the department—and also by Frank Nelson Cole. Cole graduated from Harvard with the Class of 1882, studied in Leipzig from 1882 to 1885, where he attended lectures on the theory of functions by Felix Klein, and then returned to Harvard for two years, where he too lectured on the theory of functions, following Klein's exposition.

Felix Klein left Leipzig for Göttingen in 1886, and Osgood went to Göttingen in 1887 to study with him. Klein (Ph.D., Göttingen, 1871) had become famous at an early age, especially because of his Erlanger Program, in which he proposed to study and classify geometries (Euclidean, hyperbolic, projective, descriptive, etc.) according to the groups of transformations under which they invariant; thus Euclidean geometry is invariant under the group of rigid motions. The group idea was a central unifying concept that dominated research in geometry for many decades. Klein was also interested in the theory of functions, following the great Göttingen tradition, especially in automorphic functions. Later he took a leading part in organizing the *Enzyklopädie der Mathematischen Wissenschaften*, the object of which was to summarize in one collection all mathematical research up to 1900. Klein also had an abiding interest in elementary mathematics, on the teaching of which he exerted great influence both in Germany and elsewhere.

The mathematical atmosphere in Europe in 1887 was one of great activity. It included a clash of ideals, the use of intuition and arguments borrowed from physical sciences, as represented by Bernhard Riemann (1826-1865) and his school, versus the ideal of strict rigorous proof as represented by Karl Weierstrass (1815-1897), then active in Berlin. Osgood throughout his mathematical career chose the best from the two schools, using intuition in its proper place to suggest results and their proofs, but relying ultimately on rigorous logical demonstrations. The influence of Klein on "the arithmetizing of mathematics" remained with Osgood during the whole of his later life.

Osgood did not receive his Ph.D. from Göttingen. He went to Erlangen for the year 1889-1890, where he wrote a thesis, "Zur Theorie der zum algebraischen Gebilde $y^m = R(x)$ gehörigen Ableschen Functionen." He received the degree there in 1890 and shortly after married Theresa Ruprecht of Göttingen, and then returned to Harvard.

Osgood's thesis was a study of Abelian integrals of the first, second, and third kinds, based on previous work by Klein and Max Noether. He expresses in the thesis his gratitude to Max Noether for aid. He seldom mentioned the thesis in later life; on the one occasion that he mentioned it to me he tossed it off with "Oh, they wrote it for me." Nevertheless, it was part of the theory of functions, to which he devoted so much of his later life.

In 1890 Osgood returned to the Harvard Department of Mathematics, and remained for his long period of devotion to the science and to Harvard. At about this time a large number of Americans were returning from graduate work in Germany with the ambition to raise the scientific level of mathematics in this country. There was no spirit of research at Harvard then, except what Osgood himself brought, but a year later Maxime Bôcher (A.B., Harvard, 1888; Ph.D., Göttingen, 1891) joined him there, also a student greatly influenced by Felix Klein, and a man of mathematical background and ideals similar to those of Osgood. They were very close friends both personally and in scientific work until Bôcher's death in 1918.

Osgood's scientific articles are impressive as to their high quality. In 1897 he published a deep investigation into the subject of uniform convergence of sequences of real continuous functions, a topic then as always of considerable importance. He found it necessary to correct some erroneous results on the part of du Bois Reymond, and established the important theorem that a bounded sequence of continuous functions on a finite interval, convergent there to a continuous function, can be integrated term by term. Shortly thereafter, A. Schoenflies was commissioned by the Deutsche Mathematiker-Vereinigung to write a report on the subject of Point Set Theory. Schoenflies wrote to Osgood, a much younger and less illustrious man, that he did not consider Osgood's results correct. The letter replied in the spirit that he was surprised at Schoenflies' remarkable procedure, to judge a paper without reading it. When Schoenflies' report appears (1900), it devoted a number of pages to an exposition of Osgood's paper. Osgood's result, incidentally, as extended to non-continuous but measurable functions, became a model for Lebesgue in his new theory of integration (1907).

In 1898 Osgood published an important paper on the solutions of the differential equation $y' = f(x, y)$ satisfying the prescribed initial conditions $y(a) = b$. Until then it had been hypothesised that $f(x, y)$ should satisfy a Lipschitz condition in y: $|f(x, y_1) - f(x, y_2)| \leq M\,|y_1 - y_2|$, from which it follows that a unique solution exists. Osgood showed that if $f(x, y)$ is merely continuous there exists at least one solution, and indeed a maximal solution and a minimal solution, which bracket any other solution. He also gave a new sufficient condition for uniqueness.

In 1900 Osgood established, by methods due to H. Poincaré, the Riemann mapping theorem, namely that an arbitrary simply connected region of the plane with at least two boundary points, can be mapped uniformly and conformally onto the interior of a circle. This is a theorem of great importance, stated by Riemann and long conjectured to be true, but without a satisfactory proof. Some of the greatest European mathematicians (e.g., H. Poincaré, H. A. Schwarz) had previously attempted to find a proof but without success. This theorem remains as Osgood's outstanding single result.

Klein had invited Osgood to collaborate in the writing of the *Enzyklopädie*, and in 1901 appeared Osgood's article "Allgemeine Theorie der analytischen Funktionen a) einer und b) mehrerer komplexen Grössen." This was a deep, scholarly, historical report on the fundamental processes and results of mathematical analysis, giving not merely the facts but including numerous and detailed references to the mathematical literature. The writing of it gave Osgood an unparalleled familiarity with the literature of the field.

In 1901 and 1902 Osgood published on sufficient conditions in the Calculus of Variations, conditions which are still important and known by his name. He published in 1903 an example of a Jordan curve with the positive area, then a new phenomenon. In 1913 he published with E. H. Taylor a proof of the one-to-oneness and continuity on the boundary of the function mapping a Jordan region onto the interior of a circle; this fact had been conjectured from physical considerations by Osgood in his *Enzyklopädie* article, but without demonstration. The proof was by use of potential theory, and a simultaneous proof by functional-theoretic methods was given by C. Carathéodory.

In 1922 Osgood published a paper on the motion of the gyroscope, in which he showed that intrinsic equations for the motion introduce simplifications and made the entire theory more intelligible.

From time to time Osgood devoted himself to the study of several complex variables; this topic is included in his *Enzyklopädie* article. He published a number of papers, gave a colloquium to the American Mathematical Society (1914) on the subject, and presented the first systematic treatment in his *Funktionentheorie*. He handled there such topics as implicit function theorems, factorization, singular points of analytic transformations, algebraic functions and their integrals, uniformization in the small and in the large.

It will be noted that Osgood always did his research on problems that were both intrinsically important and classical in origin—"problems with a pedigree," as he used to say. He once quoted to me with approval a German professor's reply to a student who had presented to him an original question together with the solution, which was by no means trivial: "Ich bestreite Ihnen das Recht, ein beliebiges Problem zu stellen und aufzulösen."

Osgood loved to teach, at all levels. His exposition was not always thoroughly transparent, but was accurate, rigorous, and stimulating, invariably with emphasis on classical problems and results. This may have been due in some measure to his great familiarity with the literature through writing the *Enzyklopädie* article. He also told me on one occasion that his own preference as a field of research was real variables rather than complex, but that circumstances had constrained him to deal with the latter; this may also have been a reference to the *Enzyklopädie*.

Osgood's great work of exposition and pedagogy was his *Funktionentheorie*, first published in 1907 and of which four later editions were published. Its purpose was to present systematically and thoroughly the fundamental methods and results of analysis, with applications to the theory of functions of a real and of a complex variable. It was more systematic and more rigorous that the French traités d'analyse, also far more rigorous than, say, Forsyth's theory of functions. It was a moment to the care, orderliness, rigor, and didactic skill of its author. When G. Pólya visited Harvard for the first time, I asked him whom he wanted most to meet. He replied "Osgood, the man from whom I learned function theory"—even though he knew Osgood only from his book. Osgood generously gives Bôcher part of the credit for the *Funktionentheorie*, for the two men discussed with each other many of the topics contained in it. The book became an absolutely standard work wherever higher mathematics was studied.

Osgood had previously (1897) written a pamphlet on Infinite Series, in which he set forth much of the theory of series needed in the Calculus, and his text on the Calculus dates from 1907. This too was written in a careful exact style, that showed on every page that the author knew profoundly the material he was presenting and its background both historically and logically. It showed too that Osgood knew the higher developments of mathematics and how to prepare the student for them. The depth of Osgood's interest in the teaching of the calculus is indicated also by his choice of that topic for his address as retiring president of the American Mathematical Society in 1907.

Osgood wrote other texts for undergraduates, in 1921 an Analytic Geometry with W. C. Graustein, which again was scholarly and rigorous, and in 1921 a revision of his *Calculus*, now called *Introduction to the Calculus*. In 1925 he published his *Advanced Calculus*, a masterly treatment of a subject that he had long taught and that had long fascinated him. He published a text on Mechanics in 1937, the outgrowth of a course he had frequently given, and containing a number of novel problems from his own experience.

After Osgood's retirement from Harvard in 1933 he spent two years (1934-1936) teaching at the National University of Peking. Two books in English of his lectures there were prepared by his students and published there in 1936: *Func-*

tions of Real Variables and *Functions of a Complex Variable*. Both books borrowed largely from the *Funktionentheorie*.

Osgood did not direct the Ph.D. theses of many students; the theses he did direct were those of C. W. Mcg. Blake, L. D. Ames, E. H. Taylor, and (with C. L. Bouton) G. R. Clements. I asked him in 1917 to direct my own thesis, hopefully on some subject connected with the expansion of analytic functions, such as Borel's method of summation. He threw up his hands, "I know nothing about it."

Osgood's influence throughout the world was very great, through the soundness and depth of his *Funktionentheorie*, through the results of his own research, and through his stimulating yet painstaking teaching of both undergraduates and graduate students. He was intentionally raising the scientific level of mathematics in America and elsewhere, and had a great part in this process by his productive work, scholarly textbooks, and excellent classroom teaching.

Osgood's favorite recreations were touring in his motor car, and smoking cigars. For the latter, he smoked until little of the cigar was left, then inserted the small blade of a penknife in the stub so as to have a convenient way to continue.

Osgood was a kindly man, somewhat reserved and formal to outsiders, but warm and tender to those who knew him. He had three children by Mrs. Teresa Ruprecht Osgood: William Ruprecht, Freida Bertha (Mrs. Walter Sitz, now deceased), Rudolph Ruprecht. His years of retirement were happy ones. He married Mrs. Celeste Phelpes Morse in 1932, and died in 1943. He was buried in Forest Hills Cemetery, Boston.

SELECTED BIBLIOGRAPHY

1896

Some points in the elements of the theory of functions. *AMS Bull.* 2:296-302.

1897

Introduction to Infinite Series. Cambridge. (2nd ed. reprinted with corrections, 1902; 3rd ed. reprint, 1910; other reprints in 1920, 1928, and 1936. French trans. by A. Sallin: *Sèries Infinies. Exposé théorique et pratique illustré par de nombreux Exemples développés et des Exercices à resoudre empruntés la Géométrie, la Mécanique, la Physique et l'Astronomie,* Paris, 1935.

Non-uniform convergence and the integration of series term by term. *AJM* 19:155-90.

1898

Example of a single-valued function with a natural boundary, whose inverse is also single-valued. *AMS Bull.* 4:417-24.

Selected topics in the general theory of functions. Six lectures delivered before the Cambridge Colloquium, August 22-27, 1898. *AMS Bull.* 5:59-87.

Beweis der Existenz einer Lösung der Differentialgleichung $dy / dx = f(x, y)$ ohne Hinzunahme der Cauchy-Lipschitz'schen Bedingung. *MMP* 9:331-45.

1899

Note über analytische Functionen mehrerer Veränderlichen. *MA* 52:462-64; Zweite Note, *MA* 53(1900):461-64.

1900

Üeber einen Satz des Herrn Schönflies aus der Theorie der Functionen zweier reeller Veränderlichen. *GN* 94-97.

On the existence of the Green's function for the most general simply connected plane region. *AMS Trans.* 1:310-14, 2(1901):484-85.

1901

Sufficient conditions in the calculus of variations. *AM*, s. 2, 2:105-29 (Polish trans., *Wiadomoœci Matematyczne* 5:179-210).

On the existence of a minimum of the integral $\int_{x_0}^{x_1} F(x, y, y')dx$ when x_0 and x_1 are conjugate points, and the geodesics on an ellipsoid of revolution: A revision of a theorem of Kneser's. *AMS Trans.* 2:166-82, 486.

On a fundamental property of a minimum in the calculus of variations and the proof of a theorem of Weierstrass's. *AMS Trans.* 2:273-95; 3(1902):500.

Allgemeine Theorie der analytischen Funktionen: a) einer und b) mehrerer komplexen Grössen. *Encyk. d. Math. Wiss.* II-2:1-114. French trans.: Fonctions analytiques, exposé d'après l'article allemand de W. F. Osgood . . . par P. Boutroux . . . ét Jean Chazy . . . *Encycl. d. Sci. Mathém.* tome 2, v. 2, fasc. 1, 1911, pp. 94-96. Only these pages of the introduction were ever published.

1902

Problems in infinite series and definite integrals; with a statement of certain sufficient conditions which are fundamental in the theory of definite integrals. *AM,* s. 2, 3:129-46.

1903

A Jordan curve of positive area. *AMS Trans.* 4:107-12.

On the transformation of the boundary in the case of conformal mapping. *AMS Bull.* 9:233-35.

1907

Lehrbuch der Funktionentheorie, vol. 1. Leipzig. (Vol. 2, 1924).

1909

A First Course in the Differential and Integral Calculus. New York.

1913

With E. H. Taylor. Conformal transformations on the boundaries of their regions of definition. *AMS Trans.* 14:277-98.

1914

Topics in the theory of functions of several complex variables. *AMS Colloq. Pub.* 7:111-230.

1916

On functions of several complex variables. *AMS Trans.* 17:1-8.

1917

Factorization of analytic functions of several variables. *AM,* s. 2, 19:77-95.

1918

Singular points of analytic transformations. *AMS Trans.* 19:251-74.

1921

With W. C. Graustein. *Plane and Solid Analytic Geometry*. New York.

1922

On the gyroscope. *AMS Trans.* 23:240-64.

ELIZABETH S. RUSSELL

May 1, l913–May 28, 2001

BY JANE E. BARKER AND WILLYS K. SILVERS

ELIZABETH ("TIBBY") BUCKLEY Shull Russell, one of the truly great figures in the field of mammalian developmental genetics, died on May 28, 2001, at her home on Mount Desert Island, Maine, at the age of 88. In a career spanning five decades, spent almost entirely at Jackson Laboratory in Bar Harbor, Russell did pioneering work on pigmentation, blood-forming cells, and germ cells. She also, more than anyone else, championed the importance of employing genetically defined laboratory animals in all branches of biomedical research.

Looking at Tibby's pedigree one could claim she was destined to become an outstanding geneticist. She was born on May 1, 1913, in Ann Arbor, Michigan, the eldest child of Margaret Jeffrey Buckley, a former teacher at Grinnell College with a master's in zoology, and Aaron Franklin Shull, Ph.D., a zoologist and geneticist at the University of Michigan who authored one of the first textbooks on genetics. Her uncle, George H. Shull, also was a prominent geneticist. He pioneered the development of hybrid corn, coining the word "heterosis," and founded the journal *Genetics* in 1916. Her pedigree also included a physicist, another geneticist, a plant physiologist, and a botanical artist, leaving little doubt that she would have ample exposure to science. At the age of six her first self-imposed project was the identification and cataloguing of all the flowering plants near the family's summer home. Her interest in science also was fostered by one of her teachers at the grammar school associated with the University of Michigan. The students were taught to make hypotheses based on scientific questions the teacher posed, to design methods to test the hypotheses, and to evaluate and report the results.

Tibby matriculated at the University of Michigan when she was 16 and graduated, Phi Beta Kappa and first in her class, with an A.B. in zoology at the height of the depression in 1933. At her father's suggestion she obtained a scholarship to Columbia University, where she received her master's in 1934. At Columbia Tibby became captivated by the infant field of physiological genetics. Strongly influenced by a Sewall Wright paper entitled "Physiological and Evolutionary Theories of Dominance," she decided to pursue her training in genetics with Wright at the University of Chicago, where she was supported by a teaching assistantship. Her doctoral dissertation, like many Wright students at the time, was concerned with a study of genetic effects on guinea pig coat colors. Tibby received her Ph.D. in zoology in 1937 and married fellow Wright doctoral student William L. Russell the same year.

The couple moved to Mount Desert Island and the Roscoe B. Jackson Memorial Laboratory (as it was then called); here Elizabeth came to be known as "Tibby," a nickname originally bestowed on her by her husband to differentiate her from two other Elizabeths at the Laboratory. Unfortunately, because of nepotistic rules typical of the times, only William Russell was hired as a staff member of the laboratory. Nevertheless, Tibby was provided space in his lab as an independent, unpaid investigator to study tumorigenesis in *Drosophila melanogaster.* Two publications resulted. In the first (1940) the properties of five benign and one "malignant" tumor were compared and found to be similar (i.e., the putative malignant tumor was not really malignant). The second paper (1942) was concerned with the inheritance of these tumors. While conducting these studies, Tibby was supported as an Elizabeth Pemberton Nourse fellow of the American Association of University Women, beginning what was a lifelong association, including local and state leadership positions with this organization.

Despite raising three boys, Richard, John, and James and a girl, Ellen (all born between the years 1940 and 1946, the year she was finally appointed to the Laboratory's staff), Tibby was able to find time during the 1940s to characterize many of the genetically uniform strains maintained at the laboratory for physical attributes and disease susceptibilities. She also was able to complete a monumental histological study, published in four parts (1946, 1948, 1949) on the effect the major coat color mutations of the mouse have on the physical attributes and distribution of pigment granules in the hair. As far as we are aware this analysis represents the first attempt to define each phenotype of the mouse in terms of the actions and interactions of all the participating factors. It also set the stage for virtually all coat-color studies that followed.

In 1947 Tibby's marriage ended in divorce, with William Russell departing for Oak Ridge National Laboratory in Tennessee, where he and his second wife, Liane Brauch Russell, also went on to become renowned geneticists. Throughout her life Tibby maintained a cordial relationship with the "Oak Ridge Russells." Nineteen forty-seven also was the year of the devastating Bar Harbor fire, a fire that largely destroyed the main laboratory building and wiped out all the mice excepting a few in a fireproof section of the building. Resisting pressure from friends to relocate the laboratory at some major research center, Clarence C. Little, the laboratory's founder and director, with the enthusiastic agreement of the staff, determined to rebuild on the same site. Tibby was chosen to coordinate the retrieval of Jackson Laboratory mice from scientists around the world so that the lost inbred strains could be reestablished.

While this was a long and laborious process, it resulted in huge benefits for the laboratory, as it focused Tibby's attention on animal health and husbandry matters. She realized that even in the normal course of events, as a preventive measure against either another fire or serious epidemic, there was much to be said for having all the inbred strains represented in a completely isolated facility at the Laboratory. Hence, a so-called inbred nucleus was established; a colony from which all the other breeding colonies of mice at the laboratory were no more than a few generations removed. In 1990 this inbred nucleus was moved to a newly constructed building that was appropriately designated the Russell-Dickie Building in honor of Tibby and her colleague, Margaret Dickie.

Tibby also was the first to realize that because the genetic background can greatly influence the expression of pigment genes, especially those associated with white spotting, it was important that any comparison of the effects of these genes, particularly the pleiotropic effects of alleles, be made on the same genetic background. Accordingly, she laboriously transferred all known coat color mutations onto one of the most widely used strains, C57BL/6J. These congenic strains, which have the bonus of being histocompatible, have been widely used.

Of course, most of Tibby's research efforts were involved with investigating the pleiotropic effects of mutations at the so-called dominant spotting or W locus of the mouse.

Although mutations at this locus affect hematopoiesis and gametogenesis, as well as pigmentation, it is not surprising that it was this last affect that attracted her attention. As she tells it, she was in the mouse room when she was shown a new dominant W mutation, which turned out to be W^v (for viable dominant spotting), that had appeared in Little's mouse colony. Because this new mutation had pronounced effects on pigmentation, her specialty, she was offered the opportunity to study it and compare its effects with those of the previously known *W* allele. And so she was "hooked" and on her way! Tibby's first paper on the W-locus appeared in *Genetics* in 1949. The effort was concerned with the relationship between the effects of *W* and W^v substitution on hair pigmentation and on erythrocytes and indicated that there was a very close connection. The pleiotropic effects of W-locus mutations greatly expanded Tibby's approach to the analysis of gene action. It also necessitated that she become a hematologist as well as an expert on gametogenesis. While much of this was accomplished by spending many hours in the library, it was helped enormously by collaborating and learning from established experts in these fields.

Tibby's first analysis of the effects of *W* and W^v on germ cell development appeared in 1954 in the *Journal of Experimental Zoology*. This histological analysis with Jane Coulombre who had been her summer student, demonstrated that the sterility displayed by *W/W*, W^v/W^v and W/W^v genotypes of both sexes was caused by a germ cell defect. In a subsequent paper, published in the *Journal of Embryology and Experimental Morphology* in 1956, Tibby and her colleagues showed that transplantation of 12-16 day post-coitum (dpc) gonads from anemic fetuses to the spleens of histocompatible castrated adults with normal blood parameters did not alter the donor's capacity to produce germ cells.

Clearly, the effect of W-series genes on germ cells was autonomous and occurred early in development. The question remained, however, whether the germ cell deficiency stemmed from an inability of the so-called germinal epithelium to produce germ cells, as some believed, or a deficiency in proliferation of a small primordial germ cell stock originating extra-gonadally and entering the germinal epithelium. To resolve this issue Tibby, who favored the former view, collaborated with Beatrice Mintz, who favored the latter view. Taking advantage of the discovery that because of their high level of alkaline phosphatase, the germ cells of the mouse could be selectively stained red by an azo dye coupling method to visualize this enzyme, Tibby and Bea applied this histochemical technique to 8-12 dpc embryos derived from either wild-type parents or from fertile carriers of *W* or W^v. They were able to compare the formation, localization, migration, and multiplication of germ cells in putative anemic mice with those in normals. What they found and reported in 1957 in the *Journal of Experimental Zoology* was that the germ cells in putative anemic embryos form at 8 dpc, but fail to proliferate normally, have low viability, and are retarded in their migration from their site of origin into the germinal ridges. Not only did these observations establish when the germ cell defect in *W/W*, W^v/W^v and W/W^v genotypes become evident but they also constituted the first experimental proof of the extra-gonadal origin of the germ cells in the mammalian embryo.

One of us (W.K.S.) was exceedingly fortunate to spend two years in Tibby's laboratory in the early 1950s as a graduate student from the University of Chicago, and during this period we demonstrated that the agouti series of alleles acted via the hair follicle. Although I was in Bar Harbor to do my thesis research, I was supported as Tibby's technician and as such helped maintain her color stocks. In those days and, as far as I am aware, throughout her career Tibby weaned once a week with her technician and it was while we were weaning that our agouti locus experiments were conceived. Tibby had called my attention to Sheldon Reed's early experiment on the agouti locus allele, black-and-tan (a^t), and although the results of this experiment were erroneously interpreted, it demonstrated that when neonatal skin grafts are made to neonatal mice, host melanoblasts migrate into graft hair follicles. One afternoon while discussing Reed's findings over the weaning table in the mouse room, it occurred to us that one of the color stocks we were setting up new matings from, was made to order for determining the site of action of lethal yellow (A^y) and nonagouti (*a*). Hence, employing Reed's technique of transplanting skin from one newborn mouse to another, we were able to demonstrate that when nonagouti (*a/a*) melanoblasts migrated into genetically yellow (A^y/-) but non-pigmented skin, they produced intensely pigmented yellow hairs; and conversely when yellow (A^y/ -) melanoblasts migrated into genetically nonagouti (*a/a*) but very lightly pigmented skin, intensely pigmented black hairs were produced. These results demonstrated in definitive and spectacular fashion that it is the agouti locus genotype of the receiving hair follicle that determines the kind of melanin synthesized by the pigment cell. Despite the fact that this study was jointly conceived, that it employed a coat color stock Tibby had originated, and that I was her technician, Tibby had to be convinced that her contributions merited coauthoring the 1955 *Journal of Experimental Zoology* paper that reported the results.

With her W mutations Tibby also pioneered the field of transplantation of blood-forming tissue. In a 1956 publication in *Science,* as well as in a 1959 contribution to the *Journal of the National Cancer Institute,* Tibby and her associates reported that syngeneic blood forming tissue, derived from livers of 15.5 dpc normal C57BL/6 embryos, could cure the anemia and prolong the life of W/W^v adults when given intravenously into recipients that had received 200r whole-body irradiation. In another 1959 paper with Seldon Bernstein, published in the *Proceedings of the Society of Experimental Biology and Medicine*, prior irradiation was shown to be unnecessary (i.e., because the normal implant had a competitive advantage over the indigenous blood-forming tissue of the host, it replaced the indigenous tissue and produced normal numbers of erythrocytes). These efforts not only revealed there are genetically controlled differences in the functioning of blood-forming tissue but also demonstrated that barring histocompatibility complications, at least some kinds of hereditary anemias might be alleviated clinically by implantation of normal blood-forming tissue.

Inasmuch as Tibby's interest in W required she become an expert hematologist, it is hardly surprising that she became interested in other mouse mutations having effects on erythropoiesis, especially in association with white spotting. This was particularly the case with the mutation Stee*l* (Sl, Sl^d), which also affects germ cell multiplication during the migratory phase. In fact, black-eyed white Sl/Sl^d mice are a phenocopy of W/W^v animals. Hence, once Tibby and her colleagues demonstrated that the implantation of normal blood-forming tissue could cure the anemia of W/W^v mice, attention was focused on curing severely anemic Sl/Sl^d animals by implanting highly congenic +/+ marrow cells. However, all attempts failed. Then, in experiments conducted with E. A. McCulloch's laboratory at the University of Toronto, and employing mice that Tibby had generated, it was found that Sl/Sl^d marrow cells were as effective as +/+ cells in "curing" W/W^v anemia. This observation, reported in *Blood* (1965), indicated that whereas the W defect was intrinsic to hematopoietic cells, Steel's defect was in cells of the hemopoietic microenvironment. Seldon's subsequent demonstration that the anemic condition of Sl/Sl^d mice could be ameliorated if they were grafted with an intact, histocompatible W/W^v spleen also was in accord with this interpretation. As a consequence of these observations Tibby, in a review published in *Advances in Genetics* in 1979, suggested that the normal alleles at the W and Steel loci must interact in some manner, perhaps one was an acceptor and the other bound to it, thus activating the cell. This suggestion turned out to be very prophetic as within the next 11 years both genes were cloned and W (*c-kit*) proved to be the receptor for the Steel (stem cell factor, *scf*) ligand. In fact, *c-Kit* is currently recognized as one the few cell surface markers that identify pluripotent hematopoietic stem cells.

Many of Tibby's research activities in the 1960s were concerned with analyzing mouse hemoglobins, and most of these are cited in a 1974 review (with E. C. McFarland) she published in the *Annals of the New York Academy of Science.* Waelsch and Ranney had described strain-dependent electrophoretic differences in adult mouse hemoglobin in 1957 and Tibby realized these differences would be useful as transplantation markers if they were fixed on the same strain background as her anemic mutants. By that time the 12 different mutations she had accumulated with different heritable blood defects had been moved onto the same homogeneous background as W and Steel. The hemoglobin marker that differed was moved onto the normal parental stock. This marker and others that are more ubiquitously expressed proved to be an enormous boon to transplantation biology. One question that had plagued the W transplantation studies was whether the normal donor provided cells or a substance that stimulated normal blood cell production. By employing the hemoglobin marker Tibby and Seldon (1968) were able to confirm that the normal hematopoietic cells injected into the W mice not only cured the anemia but also permanently replaced their red blood cells.

In collaboration with summer students and visiting investigators Tibby also characterized the adult hemoglobin pattern and that of an embryonic hemoglobin variant in 115 inbred mouse stocks of diverse genetic origin. The adult and embryonic hemoglobins were tightly linked (1976). She and her colleagues subsequently described structural differences in adult hemoglobins from six mouse inbred strains and mapped these near the albino locus. A second locus that determined the solubility of hemoglobin and encoded alpha globin variability was studied in 40 different inbred strains. These experiments were a heroic effort since variability at the beta globin locus had an independent effect on the solubility of the hemoglobin and often stocks had to be generated where this anomaly was avoided. These globin variants were of tremendous importance in the 1970s when Tibby and Barry Whitney (1980) discovered a spontaneous mutation that proved to be a model for alpha thalassemia. Finally, mention also must be made of Tibby and Marcia Craig's (1964) important demonstration that in mice embryonic hemoglobins are expressed only in the large nucleated red blood cells from the yolk sac while adult hemoglobins are produced in the fetal liver. This was a seminal finding since it supported arguments that differential gene expression is dependent on factors intrinsic to ontogenic stages.

Tibby also discovered the first mouse model for muscular dystrophy, which she published with her summer student as senior author (1955). This was followed by her laboratory's observation (1961) that the genetic background on which the dystrophia muscularis (*dy*) mutation was fixed influenced its penetrance and expressivity. This observation presaged secondary genes that modify disease expression; genes that more recently have become suspect in patients carrying an identical DNA alteration but showing marked differences in clinical manifestations.

For many years Tibby also was in charge of all the "retired" animals at the Jackson Laboratory. This not only enabled her to establish life-span data for different strains and some of their F1 hybrids but also because many of these animals were routinely autopsied at advanced ages, information regarding strain differences in susceptibilities to a number of diseases, including different kinds of malignancies. Much of this information served as the basis for Tibby's chapter on "Lifespan and Aging Patterns" in the second edition (1966) of the *Biology of the Laboratory Mouse,* an effort that is still widely cited.

We only have considered some of the highlights of Tibby's scientific achievements. Not to be overlooked, however, is her promotion of the use of genetically controlled laboratory animals in biomedical research. Indeed, her efforts in this regard were carried out with the zeal of an evangelist!

Tibby was elected to the National Academy of Sciences in 1972 and in 1974 she was appointed to its Council, where not surprisingly, she was an active participant in the Institute of Laboratory Animal Resources, waging a vigorous battle in support of the preservation of live animal and plant germ plasm. She also was a member of the American Academy of Arts and Sciences and the American Philosophical Society. In 1974 Tibby was vice-president and president-elect and in 1975-76 president of the Genetics Society of America. In her position as president she chaired a committee charged with drafting a position paper on the sensitive issue of race and IQ. Although this necessitated agreement on the meaning and relevance of IQ among her colleagues, who were from disparate disciplines, the final document was supported with almost no dissent. Tibby also served a five-year term as a member of the advisory council of the National Institute on Aging and subsequently volunteered for their onsite temporal studies of human health. In 1978 she was appointed by the secretary of health, education, and welfare to co-chair a committee assessing the future need for biomedical researchers. Other awards emanating from Tibby's scientific achievements included being a Guggenheim fellow at the California Institute of Technology (1958-59); inclusion among the Ten Outstanding Women of Northern and Eastern Maine (1983); the Women of Achievement Award from Westbrook College (1985); the University of Maine Maryann Hartman Award (1990); election to the Maine Women's Hall of Fame (1991); and honorary degrees from several Maine-based colleges. She also served as a trustee at the University of Maine (1975-83), College of the Atlantic (1977) and Associated Universities, Inc. (1977-83).

Although Tibby was not a dynamic speaker her infectious enthusiasm, along with her wonderful disposition and most important her genuine affection and concern for students, made her the consummate mentor. She loved to teach and was especially effective one-on-one. It is therefore not surprising that from her first summer at the laboratory, when she supervised 12 students, until her retirement 41 years later, numerous summer students, Ph.D. candidates, and postdoctoral fellows were nurtured and supported in their career goals by Tibby. Indeed, if Tibby had one failing, it stemmed from her eagerness to champion the cause of some of the young people who worked in her lab: She sometimes exaggerated their abilities or overlooked some of their weaknesses. Tibby also developed a summer course in mouse genetics that for many years alternated with the Johns Hopkins/Jackson Laboratory human genetics course. After her retirement the two courses fused. Because retirement was mandatory at the age of 65, Tibby became senior staff scientist emeritus in 1978. With papers and reviews yet to publish, she continued to work several days a week at the laboratory and, although this activity declined with time, still attended weekly genetics seminars at the laboratory through the year 2000.

After retiring, Tibby became even more involved in health and education matters. She served on Governor Brennan's Task Force on Education for Maine in the 1980's. As a trustee of the University of Maine, she argued vehemently for local branches of the University so that Maine-born employees who refused to leave the state when their employers moved away could have alternative and more available educational experiences . She also taught genetics and global ecology at the College of the Atlantic, a school in Bar Harbor whose focus is on human ecology.

Although Tibby rarely expressed her religious views, she was a devout Episcopalian who regularly attended church and sang a rich alto in the choir. In 1982, after participating in a radiation biology workshop in Egypt, she extended her trip to Liberia to represent the Episcopal Diocese of Maine during the Anglicanization of the Liberian Diocese, a sister diocese of Maine. The Episcopal Bishop of Maine was a good friend of Cuttington College in interior Liberia and it was here that Tibby, at the ages of 75 and 77, returned to teach embryology and genetics. She barely escaped during the civil war in l990, catching the last plane out following a harrowing trip with loyal students to the capital, Monrovia. On her return to Maine she had several life threatening bouts with malaria before it was cured.

One of Tibby's most amazing achievements was raising four F_1's as a single parent at a time when society was not geared up for it, and not only doing a superb job, but doing it while achieving notoriety in her professional pursuits. And, at least to those of us who were on the scene, it all seemed to be accomplished so enjoyably and effortlessly.

At a gathering in remembrance of Tibby held at the

Jackson Laboratory shortly after her death, her son Jim's remarks to those of us who were present were so poignant, and reflected so accurately her spirit and personality that we believe some of them merit repeating here. He remarked that "of course the house and everything in it were in constant disarray, but that's just Tibby. What mattered was we felt secure. We had a rich cultural environment. We benefited from her love, warmth, and good humor, and her wonderful knack of openness and tolerance. She led us on adventures, whenever possible taking the whole family with her to scientific meetings. She taught us to swim and to canoe. She was a Cub Scout den mother. We raised vegetables and cats, dogs, guinea pigs and, occasionally, hell." He also noted that Tibby "didn't just tolerate our teenage shenanigans and soul searching, she lent support wherever our interests carried us. And as we became adults, she stayed engaged, sought our intellectual companionship, and continued to set an example in her own inimitable way." In a story that was so "typically Tibby," he told of one of her trips to Liberia when she failed to take sufficient funds or to arrange the means to get more from home. As she later recounted it she didn't realize her money was gone until after she'd bought textbooks and lab gear for the school. When Jim asked her how she had survived, she said, 'Oh, it was okay, I sold my camera.' She sounded like a college kid on a roadtrip who suddenly runs out of cash!"

Especially significant were Jim's remarks about one of his last visits with Tibby. "She was asleep—never unusual even in the old days. I looked at her for awhile, propped up in her special bed; she had lost weight, some of her appetite and a great deal of mobility, and here she was near the end of her long, rich, complicated journey. When I held her hand she woke. I kissed her and said, 'How are you, Mom?' She looked right at me and said, 'How are you?' I think that almost said it all. Tibby's interest in and concern for others animated every thing she ever did—and she did a lot."

In the 1970s David Gilmore, Tibby's son-in-law, and Jim redesigned and winterized her summer cottage on Echo Lake in Somesville with floor-to-ceiling windows overlooking the water. It was here that Tibby died peacefully of pancreatic cancer, a disease that had claimed her oldest son, Dick, also a developmental biologist, in 1994. Tibby is survived by her three other children and five grandchildren.

In the summer of 1955 Beatrice Mintz and one of us (W.K.S.) wrote new words to the tune of a song from a very successful Kurt Weill musical of the 1940s, "Lady in the Dark." The song was known as "The Saga of Jennie" and accordingly we called our variation "The Saga of Tibby." Every time I sang it, Tibby, who had a wonderful sense of humor, broke out in smiles and she usually insisted on an encore. It therefore seems fitting to close our tribute with "Tibby's song."

Tibby made her mind up when she was three,
To delve into the mystery of pleiotropy,
So she started with *Drosophila* and as you see,
She ended up with W and W^v.

(Chorus)
Poor Russell, O what a tussle, to get at the common cause,
Of anemia, pigmentation and gonial migration,
Without breaking Mendel's laws.

Tibby made her mind up at seventeen,
To switch the poor old germ cells to a nice red spleen,
So she got herself some castrate hosts without any sex,
But their genotype conferred on them the same old hex.

(Chorus)

Tibby made her mind up at twenty- two,
To study blood formation was the thing to do,
So she radioed for isotopes and got glycine,
And revealed the gory story in the scheme of heme.

(Chorus)

Tibby made her mind up at ninety-eight,
To see the light before she'd sight the pearly gate,
The results are still unpublished but they came out fine,
Yes, Tibby solved the problem at ninety-nine.

SELECTED BIBLIOGRAPHY

1940

A comparison of benign and malignant tumors in Drosophila melanogaster. *J. Exp. Zool.* 84:363-85.

1942

The inheritance of tumors in Drosophila melanogaster with special reference to an isogenic strain of St Sr tumor 36a. *Genetics* 27:612-18.

1946

A quantitative histological study of the pigment found in the coat-color mutants of the house mouse. I. Variable attributes of the pigment granules. *Genetics* 31:327-46.

1948

A quantitative histological study of the pigment found in the coat-color mutants of the house mouse. II. Estimates of the total volume of pigment. *Genetics* 33:228-36.

1949

A quantitative histological study of the pigment found in the coat-color mutants of the house mouse. III. Interdependence among the variable granule attributes. *Genetics* 34:133-45.

A quantitative histological study of the pigment found in the coat-color mutants of the house mouse. IV. The nature of the effects of genic substitution in five major allelic series. *Genetics* 34:146-66.

Analysis of pleiotropism of the W-locus in the mouse: Relationship between the effects of W and W^v substitution on hair pigmentation and on erythrocytes. *Genetics* 34:708-23.

1954

With J. L. Coulombre. Analysis of the pleiotropism at the W-locus in the mouse: The effect of W and W^v substitution upon postnatal development of germ cells. *J. Exp. Zool.* 126:277-95.

1955

With W. K. Silvers. An experimental approach to action of genes at the agouti locus in the mouse. *J. Exp. Zool.* 130:199-220.

With A. M. Michelson and P. J. Harman. Dystrophia muscularis: A hereditary primary myopathy in the house mouse. *Proc. Natl. Acad. Sci. U. S. A.* 41:1079-84.

1956

With L. M. Murray, E. M. Small, and W. K. Silvers. Development of embryonic mouse gonads transferred to the spleen: Effects of transplantation combined with genotypic autonomy. *J. Embryol. Exp. Morphol.* 4:347-57.

With L. J. Smith and F. A. Lawson. Implantation of normal blood-forming tissue in radiated genetically anemic hosts. *Science* 124:1076-77.

1957

With B. Mintz. Gene-induced embryological modifications of primordial germ cells in the mouse. *J. Exp. Zool.* 134:207-37.

1959

With S. E. Bernstein, F. A. Lawson, and P. Smith. Long-continued function of normal blood- forming tissue transplanted into genetically anemic hosts. *J. Natl. Cancer Inst.* 23:557-66.

With S. E. Bernstein. Implantation of normal blood-forming tissue in genetically anemic mice, without x-irradiation of host. *Proc. Soc. Exp. Biol. Med.* 101:769-73.

1961

With R. Loosli, W. K. Silvers, and J. L. Southard. Variability of incidence and clinical manifestation of mouse hereditary muscular dystrophy on heterogeneous genetic backgrounds. *Genetics* 46:291-99.

1964

With M. L. Craig. A developmental change in hemoglobins correlated with an embryonic red cell population in the mouse. *Dev. Biol.* 10:191-201.

1965

With E. A. McCulloch, L. Siminovitch, J. E. Till, and S.E. Bernstein. The cellular basis of the genetically determined hemopoietic defect in anemic mice of genotype *Sl/Sl*^{d}. *Blood* 26:399-410.

1966

Life span and aging patterns. In *Biology of the Laboratory Mouse*, 2nd ed., ed. E. L. Green, pp. 351-72. New York: McGraw-Hill.

1968

With S. E. Bernstein. Proof of whole-cell implant in therapy of *W*-series anemia. *Arch. Biochem. Biophys.* 125:594-97.

1974

With E. C. McFarland. Genetics of mouse hemoglobins. *Ann. N. Y. Acad. Sci.* 241:25-38.

1976

With R. H. Stern and B. A. Taylor. Strain distribution and linkage relationship of a mouse embryonic hemoglobin variant. *Biochem. Genet.* 14:373-81.

1979

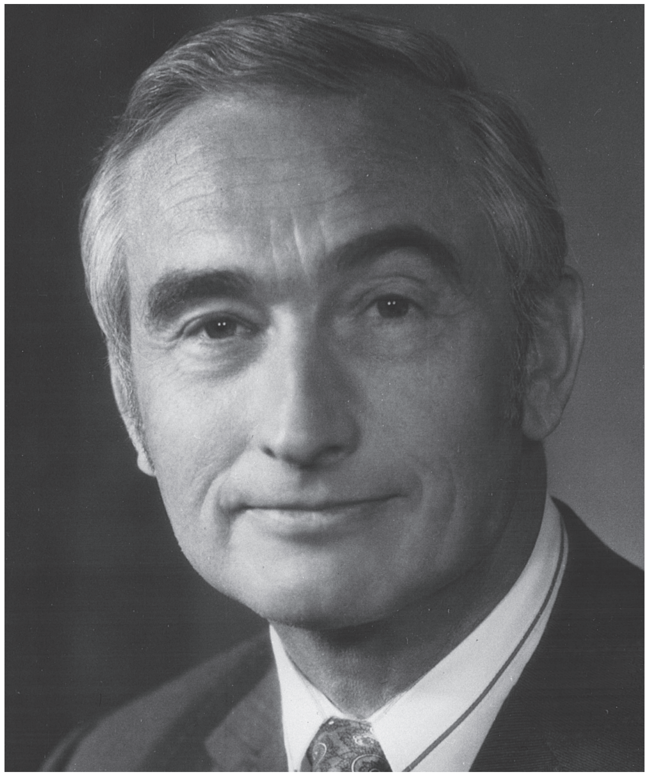
Hereditary anemias of the mouse: A review for geneticists. *Adv. Genet.* 20:357-459.

1980

With J. B. Whitney. Linkage of genes for adult alpha-globin and embryonic alpha-globin-like globin chains. *Proc. Natl. Acad. Sci. U. S. A.* 77:1087-90.

1985

A history of mouse genetics. *Ann. Rev. Genet.* 19:1-28.



Courtesy of Merck & Co., Inc., Whitehouse Station, New Jersey.

Lewis H Sarett

LEWIS HASTINGS SARETT

December 22, 1917–November 29, 1999

BY ARTHUR A. PATCHETT

LEWIS H. SARETT WAS the first chemist to synthesize cortisone. It was a feat of remarkable complexity involving nearly 40 chemical steps from desoxycholic acid and was achieved during World War II as a chemist in the Merck Research Laboratories. This synthesis and subsequent improvements of it ultimately led to cortisone's use in treating rheumatoid arthritis and was the first of Sarett's many contributions to medicine during a 40-year career at Merck. When he retired in 1982 he was senior vice-president for science and technology. He had been a key contributor to Merck's growth, and in later years Sarett was an influential industry spokesman for U.S. science policy.

Lew Sarett was born in Champaign, Illinois, on December 22, 1917. His father was a professor of speech at Northwestern University, a poet, and an outdoorsman. The latter interest led him to locate his family in Laona in northern Wisconsin while he lived in Evanston, Illinois, for one semester of the school year. Lew enjoyed rural life, but the commuting ultimately became too much for his father, and the family moved back to Illinois, where Sarett attended high school in Highland Park. A beginner's chemistry set introduced him to science, and with the encouragement of one of his relatives, Charles Osgood, later to become a curator of the Peabody Museum at Yale, he acquired an interest in fossils. Apparently on his own, Lew became an avid chess player and even in retirement he continued to play chess using a computer as his opponent. One of his characteristics as a chemist and manager was his love of challenges and an ability to devise detailed strategies. These traits were evident in his lifelong enjoyment of chess.

In 1935 Lew enrolled in Northwestern University where he originally thought he might major in mathematics, but the chemistry department, which included Charles Hurd and Ward Evans, was a good one. Sarett had a natural talent for chemistry, more so than for advanced mathematics, so he became a chemistry major. He continued playing chess and, with the encouragement of his father who was an athlete in college, he also took up wrestling. He did well in his chemistry courses and graduated from Northwestern University in 1939 with Phi Beta Kappa honors.

To continue his studies after Northwestern Sarett applied to four graduate schools. Princeton offered him a teaching assistantship, which he accepted on the recommendation of Professor Hurd. Princeton's department was strong in physical chemistry (Henry Eyring, Hugh Taylor and John Turkevich), but Sarett wanted to do synthesis. The choices were Greg Dougherty and Everett Wallis, and the latter's work in steroid chemistry held great appeal. Some of the best chemists of the day were working on steroids. Sarett was caught up in that cutting-edge research, which intensified when the United States entered World War II in December 1941. Sarett's assignment with Wallis was to explore bromination reactions of steroidal ketones with the long-range objective of converting steroids like cholesterol into the female sex hormone estradiol.

Princeton granted Sarett a Ph.D. degree after only two and one-half years so he could begin working in early 1942 at Merck on the synthesis of cortisone. Syntheses of it and penicillin were given high priority in the war effort and consortiums of industrial and academic scientists were created to expedite their production. The cortisone consortium included a group at the Mayo Clinic under E. C. Kendall, and Sarett spent a short time there before working full-time at Merck. Great importance was attached to a cortisone synthesis since supplies from bovine adrenal glands were extremely limited and it was believed (although erroneously) that the hormone increased the endurance of German pilots at high altitudes.

Sarett's synthesis of cortisone from desoxycholic acid required moving the 12-ketone to the 11-position, introduction of an unsaturated ketone in the A-ring and replacement of the bile acid side chain by dihydroxyacetone functionality. Relocating the ketone was achieved using methodology pioneered by Tadeus Reichstein's group in Basel, Switzerland. Sarett degraded the bile acid side chain to a 17-ketone, from which he fashioned a protected dihydroxyacetone side chain in a multi-step process. Bromination and dehydrobromination afforded the unsaturated ketone functionality required in ring A. The Merck process research group led by Max Tishler supplied some of the intermediates required in this synthesis; however, without an assistant, Sarett had gone through nearly 40 steps to produce 18 milligrams of cortisone.

On March 1, 1944, Sarett married Mary Adams Barrie. They lived in Princeton and had two daughters: Mary Nicole Sarett of Skillman, New Jersey, and Katharine Wendy Young of Devon, Pennsylvania. Sarett frequently entertained Merck colleagues at his home and in later years he became a low-handicap golfer.

Shortly after the war ended, Merck management decided to make cortisone available to clinical investigators to see if a use could be found for it. Sarett's partial synthesis had been improved and scaled up by Max Tishler's chemists and by April 1948 almost 100 grams of cortisone were on hand.

When later that year Philip Hench tried cortisone in a female patient with rheumatoid arthritis, her improvement was spectacular, and cortisone was hailed as a wonder drug. Knowledge of its efficacy led to urgent clinical requests for the compound. With justifiable confidence in Merck chemistry, George Merck convinced U.S. government officials that Merck could in reasonable time supply all that was needed. While Tishler's group improved the bile acid process still further and established its commercial viability, Lew Sarett and his group accomplished a total synthesis of cortisone, which he announced in 1952. Although it did not go into production, Sarett was very proud of that achievement, which the *Annual Reports of the Chemical Society* said was the best synthetic chemistry contribution of that year. Sarett's cortisone achievements brought him acclaim in the academic community. He was offered a faculty position at MIT, but he turned it down to accept expanded responsibilities at Merck as head of medicinal chemistry.

Cortisone's leadership position in the treatment of arthritis was overtaken by prednisolone following its discovery in 1955 by scientists at the Schering Corporation. They had been working on alternative methods of making cortisone; instead, they discovered that an additional double bond in the A-ring of cortisol modestly increased its potency, and more importantly, this change markedly reduced the sodium retention properties of cortisol. The realization that a natural hormone's efficacy and therapeutic index could be improved by chemical manipulation had profound consequences in the steroid field and in drug design more generally. Josef Fried and his group at Squibb enhanced cortisone's potency by introducing a 9α-fluorine group. Sarett's group showed 16α-methyl steroids had advantages in both potency and sodium retention. Putting all of these structural features together, Sarett's group produced *Decadron*, which to this day is the high-potency clinical standard among anti-inflammatory steroids.

As head of medicinal chemistry at Merck, Sarett became an industry leader in drug design. He evolved rules for the minimum systematic development of screening leads and elaborated receptor concepts to rationalize the anti-inflammatory activities of cortisone analogs. His department in Rahway, New Jersey, also had responsibility for Merck's animal health products. That business had begun several years earlier with Tishler's development of sulfaquinoxaline for coccidiosis. Sarett and his group led by Ed Rogers and Horace Brown produced the coccidiostats *Amprol* and *Nicarbazin* and the anthelmintic *Thibenzole*. They were market leaders for many years.

Most importantly, Sarett continued to innovate therapy for arthritis. When manipulations of the steroid nucleus failed to improve the therapeutic index of *Decadron*, he and Ralph Hirschmann devised steroidal conjugates that were selectively activated in the inflamed joint. These compounds unfortunately lacked oral activity and so were not developed, but this work was a dramatic early example of drug latentiation that is still a viable way to maximize safety.

Ultimately, addressing the shortcomings of steroids required a fundamental change in strategy. *Aspirin* had been in use for many years, so there was precedent for nonsteroidal arthritic drugs. The problem was how to discover new therapeutic mechanisms or improve the potency of aspirin. Under Sarett's leadership Merck scientists took up that challenge. A reliable animal assay for anti-inflammatory activity was developed by Charles A. Winter, and T. Y. Shen headed the chemistry effort. Together with their colleagues this team and Sarett in a remarkable burst of creativity produced *Indocin*, *Clinoril*, and *Dolobid*. With *Decadron* these drugs became mainstays of therapy and have been used to alleviate the pain and disabilities of millions of rheumatoid and osteoarthritis patients.

In 1969 Sarett was made president of the Merck Sharp and Dohme Research Laboratories, a position that he held until 1976. During that time Merck became a leader in vaccine research. Maurice Hilleman's group in its West Point laboratories produced a triple vaccine for measles, mumps, and rubella, and *Pneumovax* was introduced, affording protection against 14 strains of pneumonia.

Sarett had a longstanding interest in natural products and one of his legacies was to strengthen Merck capabilities in fermentation product research. An early achievement was the identification of a methoxycephalosporin in 1972 from which Burton Christensen and his associates produced *Mefoxin*. This injectable antibiotic had excellent activity against a group of organisms resistant to existing antibiotics. For several years it became one of the leading antibiotics in hospital use.

Most importantly, in 1976, the year of his retirement as president of the Merck Research Laboratories, the broad-spectrum antibiotic thienamycin and the antiparasitic drug avermectin were discovered. Their development in subsequent years led to *Imipenem* and *Ivermectin*. The former is one of the antibiotics of last resort in hospital use today. The latter is widely used to treat roundworms in cattle and sheep and prevent heartworm infections in dogs and river blindness in humans.

Sarett also organized the New Lead Discovery Department first under Ralph Hirschmann and then under Arthur

Patchett in 1972. Sarett was ahead of his time in recognizing a need to generate compounds in large numbers for biological testing. That department, whose structure and mission were established by Sarett, produced several of Merck's biggest products in the 1980s and 1990s, including *Vasotec*, *Prinivil*, and *Mevacor*.

When Sarett was promoted to corporate management in 1976, he was the inventor or coinventor of 178 U.S. patents. His scientific honors were numerous and included:

1951	Northwestern Alumni Associate Award of Merit
	Merck Board of Directors Scientific Award
	Leo Hendrik Baekeland Award of the American Chemical Society (North Jersey Section)
1959	Julius W. Sturmer Memorial Lecture Award
1964	William Scheele Lecture Award, Stockholm, Sweden
	American Chemical Society Award for Creative Research in Synthetic Organic Chemistry
	Synthetic Organic Chemical Manufacturers Association Medal for Creative Research in Synthetic Organic Chemistry
1966	New Jersey Patent Award, New Jersey Council for Research and Development
1972	Chemical Pioneer Award of the American Institute of Chemists
1975	National Medal of Science
1976	Perkin Medal Award of the Society of Chemical Industry

From 1976 to 1982 Sarett was Merck senior vice-president for science and technology and directed the strategic planning activities of all the company's divisions worldwide.

He had corporate responsibility for licensing new products and technologies and built relationships with companies and academic groups. He also became a leading spokesman for Merck and the industry on national science policy, including service on the General Accounting Office's advisory group regarding the Food and Drug Administration (1978), a Commerce Department subcommittee on research support and industrial innovation (1978-79), and a U.N. advisory group on science and technology development (1978-82). He was also a member of the Task Force on Science and Technology for President-elect Reagan and served on the Science and Technology Panel of the Reagan transition team. Sarett testified seven times during 1980-82 before committees of the U.S. Senate and House of Representatives about the interrelationships of governmental policy and innovation in the pharmaceutical industry.

During his tenure as senior vice-president for science and technology, Sarett was asked if he would like to be director of the National Institutes of Health, but Merck President Henry Gadsden asked him to remain at Merck, and somewhat reluctantly Sarett turned down the NIH possibility.

He became a member of the National Academy of Sciences in 1977 and a member of the Institute of Medicine in 1978. Other honors included:

1977	Honorary doctor of science, Bucknell University
1980	Election to the National Inventors Hall of Fame Industrial Research Institute Medal
1981	Gold Medal Award of the American Institute of Chemists
1982	Proctor Medal of the Philadelphia Drug Exchange

Throughout his career Sarett was an active participant and advisor to numerous professional organizations. Among these activities were the following:

1966-69	Chair, Basic Science Advisory Committee, National Cystic Fibrosis Research Foundation
1967-68	Consultant, Department of Defense, Chemotherapy of Malaria and Schistosomiasis
1968-70	Member, Board of Trustees, Cold Spring Harbor Laboratory for Quantitative Biology
1969-71	Member, Advisory Council, Department of Chemistry, Princeton University
	Member, Editorial Advisory Board, *Chemical and Engineering News*
1969-82	Representative, Pharmaceutical Manufacturers Association
1971-75	Member, Governing Board, Association of Princeton Graduate Alumni
1972-73	Chair, Directors of Industrial Research

He also became a member of the Industrial Advisory Committee of the University of California, San Diego, in 1971; a member of the Center for Public Resources Task Force on Developing Countries' Health in 1979; and a member of the Pharmaceutical Manufacturers Association's Commission on Drugs for Rare Diseases in 1981.

Sarett retired from Merck in 1982 several months ahead of his sixty-fifth birthday and mandatory retirement as a corporate officer. An overflow crowd of admirers packed the Baltusrol Country Club in Springfield, New Jersey, on July 23, 1982, to express their gratitude and to wish him well. Among the speakers was his long-time mentor and colleague Max Tishler. With great pride he described Sarett's contributions to chemistry, to the growth and welfare of

Merck, and to the shaping of public science policy. It was a memorable night and a breadth of achievements unequaled in Merck chemistry was honored.

Sarett's first marriage ended in divorce and he remarried on June 28, 1969. His second wife was Merck microbiologist Pamela Thorp, and they were together for the remaining 30 years of his life. They had two children: Will H. Sarett of Bonney Lake, Washington, and Renee M. Sarett of Norwich, Vermont. Like Sarett, Pamela Thorp had grown up in Wisconsin and when he retired from Merck, they decided to relocate from Skillman, New Jersey, to a rural area. Their choice was to build a home in Viola, Idaho, where they could have fruit trees, tend garden, and Sarett would be well located for occasional hunting trips. The surrounding countryside was beautiful and the University of Idaho was nearby. He was offered a position in its chemistry department, but he declined feeling that he had been away from the laboratory for too many years. Instead, he joined the advisory committee of a venture capital company, New Enterprise Associates, and became active in the West Coast biotech industry. With years of experience he knew how to develop drugs and this knowledge was an important asset for biotech companies to draw upon; following his retirement from Merck he served on the boards of directors of more than 15 of them, including *Affymax*, *Amylin*, *Immunex*, and *Genentech* Development Corporation. He enjoyed working with innovators, and the entrepreneurial spirit of these smaller organizations brought back pleasant memories of his early days at Merck.

Lew Sarett died in Viola at age 81 of complications from advanced colitis. In addition to his wife and four children he was survived by five grandchildren. As Max Tishler said of him at his retirement dinner "both by words and by his accomplishments he added a sense of excitement to invention in industrial laboratories."

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SELECTED BIBLIOGRAPHY

1943

With P. N. Chakravorty and E. S. Wallis. Studies on the bromination of steroid ketones. *J. Org. Chem.* 8:405-16.

1946

Partial synthesis of pregnene-4-triol-17(β), 20(β), 21-dione-3, 11 and pregnene-4-diol-17(β),21-trione-3,11,20 monoacetate. *J. Biol. Chem.* 162:601-32.

Partial synthesis of dehydrocorticosterone acetate. *J. Am. Chem. Soc.* 68:2478-83.

1947

With E. S. Wallis. The chemistry of steroids. *Annu. Rev. Biochem.* 16:655-88.

1948

A new method for the preparation of 17(α)-hydroxy-20-ketopregnanes. *J. Am. Chem. Soc.* 70:1454-58.

1952

With G. E. Arth, R. E. Beyler, and others. Stereospecific total synthesis of cortisone. *J. Am. Chem. Soc.* 74:4974-76.

1958

With G. E. Arth, D. B .R. Johnston, J. Fried, and others. 16-Methylated steroids. I. 16-Methylated analogs of cortisone, a new group of antiinflammatory steroids. *J. Am. Chem. Soc.* 80:3160-61.

With G. E. Arth, J. Fried, D. B. R. Johnston, and others. 16-Methylated steroids. II. 16α-Methyl analogs of cortisone, a new group of anti-inflammatory steroids, 9α-halo derivatives. *J. Am. Chem. Soc.* 80:3161-63.

With R. Hirschmann, J. M. Chemerda, K. Pfister, and others. Synthesis of cortisone 21-phosphate. *J. Am. Chem. Soc.* 80:6300-6303.

1959

With J. H. Fried and G. E. Arth. Alkylated adrenal hormones. Synthesis of 6α-methyl cortical steroids. *J. Am. Chem. Soc.* 81:1235-39.

1960

With E. F. Rogers, R. L. Clark, A. C. Cuckler, and others. Antiparasitic drugs. III. Thiamine-reversible coccidiostats. *J. Am. Chem. Soc.* 82:2974-75.

1961

With H. D. Brown, W. C. Campbell, A. C. Cuckler, and others. Antiparasitic drugs. IV. 2-(4-Thiazolyl)benzimidazole, a new antihelmintic. *J. Am. Chem. Soc.* 83:1764-65.

With R. E. Beyler and others. Bis(methylenedioxy) steroids. V. General method for protecting the dihydroxyacetone side chain. *J. Org. Chem.* 26:2421-25.

1963

With A. A. Patchett and S. Steelman. The effects of structural alteration on the antiinflammatory properties of hydrocortisone. *Prog. Drug Res.* 5:11-154.

With G. E. Arth and others. Aldosterone antagonists. 2′,3′-Tetrahydrofuran-2′-spiro-17-(4-androsten-3-one) and related compounds. *J. Med. Chem.* 6:617-18.

1964

With R. Hirschmann, S. L. Steelman, R. Silber, and others. Approach to an improved anti-inflammatory steroid. Synthesis of 11β,17-dihydroxy-3,20-dioxo-1,4-pregnadien-21-yl 2-acetamido-2-deoxy-β-D-glucopyranoside. *J. Am. Chem. Soc.* 86:3903-3904.

1965

Progress in chemotherapy of inflammation. *Farm. Revy.* 64:525-43.

1966

With T. Y. Shen. Indolyl aliphatic acids. U.S. Patents 3,242,162; 3,242,163; and 3,242,193.

1971

International symposium on inflammation and its therapy—experiences with indomethacin. Florence, April 1-4, 1971. Introduction. *Arzneimittelforsch.* 21:1759-61.

1974

Impact of regulations on industrial R and D—FDA regulations and their influence on future R and D. *Res. Manage.* 17:18-20.

1976

Private research in the public eye. Perkin Medal address, Feb. 28, 1976. *ChemTech.* 6:506-508.

1977

With J. Hannah, W. V. Ruyle, T. Y. Shen, and others. Discovery of diflunisal. *Br. J. Clin. Pharmacol.* 4(Suppl. 1):7-13.

1978

With J. Hannah, W. V. Ruyle, T. Y. Shen, and others. Novel analgesic-antiinflammatory salicylates *J. Med. Chem.* 21:1093-1100.

1979

The impact of natural product research on drug discovery. *Prog. Drug Res.* 23:51-62.

1983

Research and invention. *Proc. Natl. Acad. Sci. U. S. A.* 80:4572-74.

Courtesy of Lawrence Berkeley National Laboratory, Berkeley, California.

EMILIO GINO SEGRÈ

January 30, 1905–April 22, 1989

BY J. DAVID JACKSON

EMILIO GINO SEGRÈ made important contributions to atomic and nuclear physics and discovered two new elements. He shared the Nobel Prize in physics with Owen Chamberlain in 1959 for the discovery of the antiproton. Segrè was born in Tivoli, Italy, on January 30, 1905 (recorded officially as February 1). He died suddenly in California on April 22, 1989. His youth, spent growing up in a well-to-do Jewish family in Tivoli, was apparently a happy time. After high school he entered the University of Rome, initially majoring in engineering but later in physics. He pursued graduate studies and attained his doctorate in 1928. Military service consumed 1928-29. He then returned to the University of Rome and began research in atomic spectroscopy under Enrico Fermi.

In the period 1929-32 he was an assistant to O. M. Corbino, while also holding a traveling Rockefeller Foundation Fellowship that permitted him to visit and work with O. Stern in Hamburg and P. Zeeman in Amsterdam. In 1932 he became the equivalent of an assistant professor under Fermi. In 1934 the Fermi group switched from atomic spectroscopy to nuclear physics to work on the interactions of neutrons with matter, making Rome the center of research with this new tool for nuclear transformations.

Segrè was appointed to the physics professorship in Palermo in 1936. That year he visited Berkeley and persuaded Ernest Lawrence to give him various discarded parts made radioactive by exposure in the cyclotron. In collaboration with the Palermo chemist Carlo Perrier he discovered the element technetium (atomic number $Z = 43$), not known in nature because all of its isotopes are radioactively unstable.

In 1938, on a visit to the United States, Segrè decided to emigrate because of the increasing anti-Semitism and the threat of war in Europe. He became a visitor at Lawrence's Radiation Laboratory and continued work on radioisotopes. Eventually, he became a research associate and after the start of World War II a lecturer in the Berkeley Physics Department. He was a co-discoverer of astatine ($Z = 85$), another element not known in nature. He worked with Glenn Seaborg and others on the fission properties of ^{239}Pu under slow neutron bombardment after its discovery in 1941. He also invented chemical methods of isolating nuclear isomers together with Seaborg.

In 1943 Segrè went to Los Alamos where his group's most important contribution was discovery and measurement of the spontaneous fission rate of plutonium. The rate proved sufficiently high that the cannon design used for the ^{235}U bomb could not be used with plutonium. The risky implosion design was then urgently pursued to a successful conclusion for a ^{239}Pu bomb.

After the war Segrè returned to Berkeley as professor of physics and group leader at the Radiation Laboratory. Two key members of his Los Alamos team Owen Chamberlain and Clyde Wiegand joined him, Chamberlain on the faculty and Wiegand as a laboratory staff scientist. Among early postwar research were investigations of isomerism and the modification of the rate of electron capture by a nucleus caused by a change in the chemical environment of the atom. As higher-energy particle beams became available Segrè and his colleagues began study of high-energy proton and neutron bombardment of nuclei, particularly hydrogen, at the 184-inch synchrocyclotron. With the completion in 1955 of the bevatron, an accelerator whose energy was chosen to produce antiprotons (if they existed), several groups began searches that culminated in success that summer for Chamberlain, Segrè, Wiegand, and Ypsilantis. The discovery of the antiproton removed any lingering doubts about the particle-antiparticle symmetry of nature. The achievement was recognized by the award of the Nobel Prize in physics to Chamberlain and Segrè in 1959.

In addition to his accomplishments in research Segrè is the author or editor of a number of books: texts, handbooks, popularizations of the history of physics, and a biography of Fermi. For 20 years he served as editor of the *Annual Review of Nuclear Science*. He was elected to numerous learned societies, including the National Academy of Sciences in 1952, and received many honorary degrees.

EARLY YEARS

Emilio Segrè's childhood, indeed his whole life, is described in detail in his autobiography.[1] Only a brief sketch is given here. He was born in Tivoli, Italy, on January 30, 1905, into a prosperous Jewish family originally from northern Italy. His father ran a papermaking and hydroelectric plant; his uncles were academics, lawyers, and engineers. He had a happy, even pampered, childhood, playing in the famous gardens of Villa d'Este and attending elementary school and the first years of high school (*ginnasio*). In 1917 the family moved to Rome, where Emilio attended a new high school (*ginnasio*, then a *liceo*), graduating in 1922 at age 17 with a specialization in engineering. Private tutoring and instruction from cousins led to early mastery of German and English.

He entered the University of Rome, beginning with a two-year general course for scientists and engineers and then entering the School of Engineering. He soon switched to the Physics Institute, did the equivalent of graduate studies, and received his doctorate in 1928, with a thesis titled "Anomalous Dispersion and Magnetic Rotation." During these university years Segrè's friends included Ettore Majorana, a fellow student; Edoardo Amaldi; and Franco Rasetti, a colleague of Fermi's and a bit older. In addition to mountain climbing with Segrè, Rasetti was instrumental in introducing Emilio to Fermi in 1927. Under the tutelage of Rasetti (experiment) and Fermi (theory) and the paternal oversight of O. M. Corbino, director of the institute, Segrè developed laboratory skills and gained much theoretical knowledge before getting his doctorate after only one year as a physics student.

In 1928-29 Segrè did his compulsory military service (officers' training school in 1928), spent a six-month hiatus back at the Physics Institute, and then received a commission as a second lieutenant in the antiaircraft artillery stationed near Rome. In early 1930 he was discharged into the reserve. While in the military he managed to study some advanced treatises and visit the institute occasionally to keep in touch. He became an assistant to Corbino in 1930. Segrè's early life, especially in its intersection with Fermi's, is described by Laura Fermi.[2]

Emilio Segrè was a complicated man. He had high standards and expected others to measure up. He appeared proud, aloof, and somewhat intimidating, but underneath he was welcoming and generous in his support of younger physicists, always ready with helpful advice. He was cultured in the European tradition, able to speak several languages and to quote at length from Latin classics, Dante, nineteenth-century British poets, and Victor Hugo or Schiller. He was a great outdoorsman who accomplished very impressive climbs in the Alps in his youth and took up fly-fishing in America. He was also an accomplished hunter of wild mushrooms.

It is convenient to summarize here the major personal events in Segrè's life. In 1936 he married Elfriede Spiro. They had three children: Claudio born in Palermo in 1937 and two daughters, Amelia born in Berkeley in 1942 and Fausta born in Los Alamos in 1945. Claudio's autobiography[3] gives a son's view of the Segrè family life. The Segrès emigrated to the United States in 1938. Emilio's mother was captured by the Nazis in 1943 and died at their hands. His father escaped capture but died of natural causes in 1944. After Elfriede's death in 1970 Segrè married Rosa Mines, a Uruguayan friend of Elfriede's, in 1972. Segrè collapsed and died on April 22, 1989, at age 84 while on his regular walk with his wife near their home in Lafayette, California. Rosa Segrè died from injuries received in a freak accident in Tivoli in 1997.

FIRST RESEARCHES

In 1928-29 Segrè had already begun publication of his research results. First were two papers jointly with Amaldi, one on anomalous dispersion in atoms and the other on the theory of the Raman effect. A third paper, by Segrè alone, explained the anomalous dispersion in band spectra of molecules caused by the accumulation of absorption lines near the head of a band. The experimental work of Segrè, Amaldi, and Rasetti focused on the Raman effect until 1931. But in the fall of 1930, pursuing an idea entirely his own, Segrè examined so-called forbidden ($S \leftrightarrow D$) transitions in alkali spectra. By studying the Zeeman effect in absorption he showed that the forbidden lines were the result of electric quadrupole radiation. This important proof of a hitherto neglected form of atomic deexcitation was published as a short letter[4] in *Nature* in November 1930. Pursuing his studies of forbidden spectra, Segrè went to Amsterdam to work in Pieter Zeeman's laboratory and later on a Rockefeller Foundation Fellowship to Otto Stern's laboratory in Hamburg and again to Amsterdam in September 1932. Fermi and Segrè collaborated in a theoretical study of atomic hyperfine structure, published in 1933,[5] that shows that hyperfine structure arises from the purely electromagnetic interactions of the nuclear magnetic moment with the electron's spin and orbital magnetic moments.

SLOW NEUTRONS

In 1933 Fermi and his colleagues began to shift emphasis from atomic spectroscopy to nuclear physics and Fermi devoted more and more of his time to experiment. The group studied the work of Rutherford, copied nuclear apparatus, and learned radiochemistry. By 1934, when artificial radioactivity was discovered by the Joliot-Curies, the Rome group was ready to participate. Fermi immediately saw the great advantage of using neutrons rather than charged particles to cause transmutations. Under his leadership the group (Amaldi, D'Agostino, Fermi, Rasetti, Segrè) used a radon-beryllium source to bombard every available element in the periodic table in a search for new artificial radioactivities. Segrè was charged with finding the elements for bombardment, an experience that paid off in later years. During 1934 the Rome group was amazingly productive, publishing new results almost weekly.[6,7] They discovered (n, p) and (n, α) reactions, as well as (n, γ) or perhaps $(n, 2n)$ reactions that made radioactive isotopes of the target element. The brilliant achievements of the Rome group were dimmed only slightly by their not unnatural error of mistaking the fission of thorium and uranium for the production of transuranic elements. In late 1934 the use of paraffin to surround a target led to the discovery that moderation of the neutrons' energies enhanced manyfold their effectiveness in production of radioactive isotopes of the targets. The field of radiative slow neutron capture was born.

PALERMO AND TECHNETIUM

In the late fall of 1935 Segrè won the competition for the professorship of physics at the University of Palermo, where he joined a modest number of colleagues in other fields of science and began to modernize the physics instruction and build up his small research laboratory. In the summer of 1936 Segrè and his wife visited the United States, first New York at Columbia University, where he had spent time the previous summer, and then Berkeley at Lawrence's Radiation Laboratory. He persuaded Lawrence to let him take back to Palermo some discarded cyclotron parts that had become radioactive. He hoped that there might be something interesting to be found in their long-lived radioactivity.

Back in Palermo, he found that his samples contained a variety of known radioactivities that had been deposited on them from bombardment of different targets. One was ^{32}P, an activity with a two-week half-life, with which he began a collaboration with the local professor of physiology in tracer studies of metabolism. In early 1937 Lawrence sent him a molybdenum foil that had been part of the deflector in the cyclotron. For Segrè this was a godsend. The atomic number of molybdenum is $Z = 42$. The foil had been bombarded with deuterons, a hydrogen isotope of mass 2 consisting of a neutron and a proton. By then (d, p) and (d, n) reactions were recognized, in which one or the other of the projectile's nucleons is captured by the target nucleus. In the (*d, n*) process, the proton is captured to create a nucleus with $Z = 43$. Alternatively, the (*d, p*) process could lead to a radioactive isotope of molybdenum that undergoes beta decay to produce $Z = 43$. In 1934, when he was the procurer of elements for Fermi, Segrè sought element 43, known as masurium, from his chemical supplier and was told that the supplier had never seen a sample of it. Now, he suspected that its alleged discovery in the mid-1920s had been a mistake.

Segrè enlisted his experienced chemist colleague Carlo Perrier to attempt to prove through comparative chemistry that the molybdenum activity was indeed $Z = 43$, an element not existent in nature because of its instability against nuclear decay. With considerable difficulty they finally succeeded in isolating three distinct decay periods (90, 80, and 50 days) that eventually turned out to be two isotopes, ^{95}Tc and ^{97}Tc, of technetium, the name given later by Perrier and Segrè to the first man-made element.[8,9]

Rightly proud of having filled a gap in the periodic table by their discovery of technetium, Segrè apparently was disturbed by lack of recognition in Italy and by perceived hindrances to his career caused by academic and national politics in Rome. The edge to his personality, visible in later years, and his tendency to criticize, were not moderated by these events.[10] Without knowing his mind at the time, one can imagine that he viewed the discovery of technetium as research of Nobel-prize quality and smarted internally from lack of what he felt was sufficient recognition. Such speculations aside, he began seriously in 1937 to look elsewhere for a position, at least in part because of the hints, and more, of trouble for Jews.

BERKELEY (1938-1942)

Pursuing their researches on samples from Lawrence's laboratory, Perrier and Segrè wished to look for short-lived technetium radioactivities not present in samples received through the mails. In the summer of 1938 Segrè came without family to Berkeley to investigate short-lived radioactivities from cyclotron bombardments. He was initially a visitor at the Radiation Laboratory, expecting to return to Italy at the end of the summer, but the situation in Europe was deteriorating rapidly. Before the summer's end Segrè decided to stay in the United States. His wife and son joined him in October 1938, and Lawrence appointed him a paid research associate. In 1939 together with Glenn T. Seaborg he developed chemical methods to isolate nuclear isomers.[11] He continued studies of technetium, with further proof of $Z = 43$ from the energies of internal conversion electrons from a six-hour isomeric transition in ^{99}Tc. After the discovery of fission in 1939 by Hahn and Strassmann research at the Radiation Laboratory focused on the high end of the periodic table. When the 60-inch cyclotron began operating in 1940, Segrè, Corson, and MacKenzie bombarded bismuth with alpha particles to create $Z = 85$ (astatine), another element missing in the periodic table. After the discovery of plutonium in early 1941 Segrè collaborated with Seaborg, Kennedy, and Wahl on the isolation of the isotope ^{239}Pu by slow neutron bombardment of uranium and then studied its chemistry and nuclear fission properties. Segrè's position in the collaboration was rather bizarre because of government restrictions on aliens concerning topics viewed as sensitive. Matters became even more complex with the entry of the United States into the war.

For four and one-half years (1938-43) Segrè held a series of term appointments as research associate in

Lawrence's laboratory. In the fall of 1940, with regular faculty off on defense work, he was appointed lecturer in the Berkeley Physics Department (January 1941 to September 1942), teaching advanced undergraduate and graduate courses in modern physics. During 1942 Segrè was busy with war-related work, identifying and monitoring the effectiveness of the pilot mass spectrometer experiments aimed at large-scale separation of uranium isotopes, studying spontaneous fission of heavy elements, measuring the fission cross section of uranium. In some of this work Segrè was joined by two students, Clyde Wiegand and Owen Chamberlain, who with others went to Los Alamos with Segrè in 1943.

LOS ALAMOS

In the spring of 1943 Segrè accepted Oppenheimer's invitation to join the atomic bomb project at Los Alamos. There he headed a group including Chamberlain and Wiegand to measure the spontaneous fission rates of ^{235}U and ^{239}Pu. The delicate measurements, which required construction of a remote laboratory away from all possible radioactive backgrounds, proved crucial to the design of a ^{239}Pu bomb. The plutonium spontaneous fission rate, though small, is sufficiently large that the (relatively) slow cannon design of the first ^{235}U bomb could not be used with plutonium. (The spontaneous fission proved to be mostly from the "contaminant" isotope ^{240}Pu, not from ^{239}Pu.) The laboratory had to develop the unproven and risky but more rapid implosion design from concept to reality, and it did.

In 1944, while at Los Alamos, Segrè and his wife Elfriede became U.S. citizens. At the end of the war he entertained a number of offers before accepting a professorship at Berkeley. He returned in early 1946 and began official university duties in March. R. T. Birge, then chair of the Physics

Department, gives a blow-by-blow account from a chair's point of view of the successful effort to have Segrè come (return) to Berkeley.[12]

BERKELEY (1946-1954)

Having left Berkeley in 1943 as a lecturer on a temporary appointment, Segrè returned as a full professor with a regular campus appointment as well as affiliation with the Radiation Laboratory. He set up a research group at the laboratory with Clyde Wiegand as a graduate student and later as an essential staff member. He was joined in 1948 by Owen Chamberlain, who was appointed to the faculty after receiving his Ph.D. at the University of Chicago. Initially Segrè's research continued with projects stemming from work at Los Alamos and others interrupted by his war work. One of these was the modification of a nuclear lifetime by alteration of the chemical environment, specifically the electron capture rate in ^{7}Be.[13]

In 1948 Segrè's group began experiments on nucleon-nucleon scattering with the 90-MeV neutron and proton beams produced from deuterons accelerated in the 184-inch synchrocyclotron. The data on elastic neutron-proton scattering showed the first evidence for strong exchange forces in the nucleon-nucleon interaction. As the energy of the available beams increased to 300-350 MeV in the period 1948-55 the group made a detailed study of elastic proton-proton scattering of increasing sophistication. Thomas Ypsilantis, then a graduate student, pushed the development and use of polarized beams. These extensive data from single-, double-, and triple-scattering experiments were subjected to a phase-shift analysis by Henry Stapp, Ypsilantis, and Nicholas Metropolis, using computers at Los Alamos. They stand as the most complete description of proton-proton interactions at those energies ever assembled.

As this stage of his career Segrè's style was more managerial and less hands-on than some group leaders. He provided overall direction, argued for funds, gave advice, and was the final arbiter on the science to be pursued. But he was comfortable leaving the details of execution to his trusted associates, Chamberlain, Wiegand, and Ypsilantis (after his Ph.D., an assistant professor on campus).

ANTIPROTON

The discovery of the antiproton by the Segrè group occurred in 1955. From the early 1930s, when Carl Anderson established that electrons had oppositely charged partners of the same mass and spin (called positrons) as predicted by Dirac, the suspicion was that all known particles probably had antiparticle partners. However, the waters were muddied by the existence of the neutron with approximately the same mass as the proton and the magnetic moment of the proton, so different from Dirac's prediction for spin 1/2 particles. Thus, while physicists were on the lookout for antiprotons (same mass and spin, opposite charge to a proton), there was some doubt as to whether the charge conjugation symmetry of electrons and positrons applied to strongly interacting particles such as the proton and neutron. With the discovery after the war of various unstable particles, the evidence for charge conjugation symmetry mounted. Lawrence and colleagues designed the bevatron to have a beam of 6-GeV protons, nicely sufficient to produce proton-antiproton pairs (if they existed) in collisions of protons with a stationary nucleon target.

Planning of experiments began as the machine was under construction. When the bevatron began operation in 1955, several Berkeley groups with different techniques competed in the search for antiprotons. Deflection in a known magnetic field permits identification of the sign of charge and the particle momentum. The Segrè-Chamberlain group chose a Cherenkov detector, supplemented by time-of-flight, for a velocity measurement to combine with the momentum to determine the mass. A novel mass spectrometer was built and the Cherenkov detector was constructed by Chamberlain and Wiegand. In the final stages a crucial veto Cherenkov detector was added to eliminate the otherwise overwhelming number of negative pions relative to the antiprotons in the momentum-analyzed beam. The experimental apparatus was assembled during the early summer while Segrè was absent at Brookhaven. Soon after the run began in August antiproton events began to appear. The first experiment was completed in short order; the publication announcing the discovery[14] was received on October 24 by *Physical Review*. Gerson Goldhaber, a member of the Segrè group, and collaborators exposed emulsions to the beam selected by the counter experiment and found annihilation stars in which there was clearly much more than 1 GeV of energy released in the form of pions and recoiling fragments. These annihilation events confirmed the negatively charged particle as the proton's antiparticle. For the discovery of the antiproton Chamberlain and Segrè were awarded the Nobel Prize in physics for 1959.

The circumstances surrounding the discovery of the antiproton were not without controversy. Claims were raised that key ideas for the experiment had been stolen. Even within the group, feelings of injustice prevailed. The discovery paper has four authors (Chamberlain, Segrè, Wiegand, and Ypsilantis). The process of nomination and selection for Nobel Prizes is arcane, to say the least, but the practice of no more than three persons to share any one prize seems inviolate. There are those who feel that Wiegand was as deserving as any one to share the prize. Why he was not included is not publicly known. Wiegand's own recount of the initiation, construction, and operation of the 1955 experiment at a symposium in Berkeley in 1985 on the thirtieth anniversary of the discovery gives a glimpse of his own views.[15] For his own part Segrè undoubtedly felt that as group leader responsible for marshaling the resources and fighting successfully to get the experiment scheduled, he deserved a significant share of the glory, regardless of who had actually taken the data. He now had the accolade that had eluded him 20 years earlier.[16]

BERKELEY (1956-1989)

The antiproton discovery was followed by studies of its properties and interactions, as well as those of the antineutron. In subsequent experiments Chamberlain and Wiegand worked independently of Segrè, with Chamberlain rejoining the Segrè group after a few years but on an equal footing in what became the Segrè-Chamberlain group. In the early 1960s Ypsilantis, with Wiegand and students, mounted an ambitious counter experiment to study pion-pion interactions through pion production by pions. Theorists had described the electromagnetic form factors of the proton and neutron in terms of a spin-one resonance between pions with an energy in the range of 500-600 MeV. The experiment was designed to find such a resonant state. In the event the resonance proved to be at 760 MeV, near the upper limit of the apparatus. The discovery of the rho meson, as the state was called, was accomplished by others using hydrogen bubble chambers. The counter experiment confirmed the bubble chamber results but could add little.[17] Segrè blamed the theorists for their incorrect prediction of the resonant energy.

Segrè's life changed as it does for most upon receiving the Nobel Prize. He became increasingly involved in travel, guest lectures, and committee service, but he was only 54 and stayed as co-head of the research group, now more in an advisory role than as a participant. He had excellent physical intuition and made many helpful suggestions to advance the group's program. He retired in 1972, but remained active with traveling and writing taking much of his time. He retained an enduring curiosity about new developments in physics and often sought out a colleague to explain their significance.

Segrè served as editor or author of a number of books both before and after retirement. In the immediate postwar years he edited an influential three-volume handbook on experimental nuclear physics.[18] He served as chairman of the editorial board overseeing the publication of the collected papers of Enrico Fermi.[19] In 1964 he authored a text on nuclei and particles,[20] and in 1970 a biography of Fermi.[21] His lectures on the history of physics were transformed into two appealing and accessible books.[22,23] His autobiography[1] appeared posthumously in 1993. He served for 20 years (1958-77) as editor of the *Annual Review of Nuclear Science*. A few years after stepping down as editor he gave an account of his life in physics in a prefatory chapter in the *Annual Review*.[24]

ACADEMIC LIFE

Segrè's academic life in teaching and university service was as full as his life as a research scientist, at least in his Berkeley years. His autobiography makes little mention of teaching during his years in Rome. He tells of how Corbino, after smoothing his transition from engineering to physics by giving him a phantom grade in a laboratory course, assigned him to teach the course after he received his Ph.D. It seems that Segrè's position in the Physics Institute was primarily in research.

As mentioned above, Segrè taught courses in the Berkeley Physics Department in 1941-42. Departmental records show that he taught upper-division optics, quantum mechanics, and atomic physics, and graduate thermodynamics and statistical mechanics. Upon his return in 1946 he taught fairly regularly the undergraduate quantum mechanics and nuclear physics courses. The latter led to preparation of the textbook *Nuclei and Particles*.[19] In the 1970s he turned to the history of twentieth-century physics and later to that of the seventeenth through the nineteenth centuries. In subsequent years, even well into retirement, he continued to lecture from time to time on historical topics in an undergraduate special topics course. The two books emerging from these lectures have already been mentioned.[22,23]

In departmental and university affairs Segrè took an active role. He was a regular at the weekly departmental colloquium, often with a probing question at the end. He took very seriously the intellectual health of the department and its future development. He was a shrewd judge of character and ability. He played a strong role in departmental faculty meetings, even after retirement, when rules permitted emeriti to speak but not vote. At least one chair remarked that Emilio invariably came into his office the day of a faculty meeting to discuss the agenda and advise on how the chair should conduct the meeting. He himself served as departmental chair in 1965-66 in Burton Moyer's absence. In the wider arena he served regularly on a variety of committees of the Academic Senate. Perhaps most important was his service for four years (1961-65) on the powerful Budget Committee, which has little to do with budgets but everything to do with appointments and advancements of faculty on the Berkeley campus.

His professional service through advice to governmental agencies both in the United States and abroad was extensive and in some cases recognized with appropriate honors. In 1974 Segrè was honored by the Italian Parliament with an ad hominem chair at the University of Rome. He served one year before reaching the mandatory retirement age.

PH.D. STUDENTS

During his time at Berkeley Segrè was responsible for training 30 Ph.D. students, many of whom went on to distinguished careers. A list of those he could recall when writing his autobiography appears in Footnote 16 (p. 317 of Note. 1). To mention only a few, he supervised the research for part of the thesis of Chien-Shung Wu (Ph.D., 1940), resulting in a short joint publication,[25] but because he was a research associate, not a faculty member, his name does not appear in her official records. Madame Wu, a fine experimenter, went to Columbia. She is best known for the experimental discovery of parity violation in weak decay processes. The first Ph.D. on the postwar list is Herbert F. York (Ph.D., 1949), who went on to have a distinguished career in laboratory, governmental, and university service. In later years are Thomas J. Ypsilantis (Ph.D., 1955) and Herbert M. Steiner (Ph.D., 1956). Ypsilantis eventually went to Europe and played a major role in scattering experiments and detector development at CERN and in Paris. Steiner became a member of the Segrè-Chamberlain group at the Radiation Laboratory and then a faculty member in the Berkeley Physics Department. He served as departmental chair from 1992 to 1995.

CODA

Proud and opinionated, Segrè showed remarkable common sense in matters of substance. One vignette is illustrative. By 1970 the nuclear weapons branch of the Radiation Laboratory at Livermore, already essentially autonomous, had grown so large that its budget dwarfed that of the original Berkeley site. Edward Teller argued that Livermore should become a totally independent entity because in his mind the Berkeley lab was a hindrance to Livermore in seeking government funds. McMillan, the director of the whole Radiation Laboratory, called a meeting in Berkeley to discuss the idea of separation. Influential senior physicists argued that Livermore should remain formally part of the overall laboratory for the converse of Teller's argument for separation. They feared that Berkeley's funding would suffer if Livermore were to cut free. Among the younger physicists the sentiment was for separation. After listening to the arguments, Segrè spoke up. He said, "Logic argues for separation of the weapons work from the pure science in Berkeley. If funding suffers, so be it." Senior colleagues, who believed Segrè to be cautious and conservative, were taken aback by his statement. It seemed to carry the day. Shortly thereafter, the university regents formally separated the two laboratories giving them the names recommended by McMillan: Lawrence Berkeley Laboratory and Lawrence Livermore Laboratory. Funding to the Berkeley lab did not suffer.

EMILIO SEGRÈ VISUAL ARCHIVES

A legacy of Emilio Segrè is the Emilio Segrè Visual Archives of the American Institute of Physics. Located in College Park, Maryland, as part of the Center for the History of Physics, the Segrè Visual Archives is the result of a donation by Rosa Segrè after Emilio's death, subsequently augmented by a bequest from her on her death in 1997. The American Institute of Physics already had a sizable collection of photographs, but Rosa Segrè's gifts permitted the institute to preserve and organize its collection. Segrè was a skillful amateur photographer. Many of his photographs are in the archives.

SEGRÈ'S AUTOBIOGRAPHY has obviously been of great help, but the written and informal recollections and views of others have been equally valuable. I thank especially Herbert M. Steiner for his helpful comments and attention to historical accuracy. Spencer Weart kindly supplied the background on the creation of the Emilio Segrè Visual Archives at the American Institute of Physics.

NOTES

1. E. Segrè. *A Mind Always in Motion: The Autobiography of Emilio Segrè.* Berkeley: University of California Press, 1993.
2. L. C. Fermi. *Atoms in the Family.* Chicago: University of Chicago Press, 1954.
3. C. Segrè. *Atoms, Bombs, and Eskimo Kisses: A Memoir of Father and Son.* New York: Viking, 1995.
4. E. Segrè. *Nature* 126 (1930):882.
5. E. Fermi and E. Segrè. *Z. Phys.* 82(1933):729-49.
6. These communications were published in Italian in *La Ricerca Scientifica,* the journal of the Consiglio Nazionale delle Ricerche. A listing of the many of them is given in Footnote 22, pp. 305-306 of Note 1.
7. E. Fermi, E. Amaldi, O. D'Agostino, F. Rasetti, and E. Segrè. *Proc. R. Soc. Lond. A* 146 (1934):483-500 (a summary paper communicated by Lord Rutherford).
8. C. Perrier and E. Segrè. *Rend. Lincei,* 6th ser., 25(1937):723-30; 27 (1937):579-81.
9. A popular account (in English), Cinquant'anni dalla scoperta del tecnezio (The adventurous history of the discovery of technetium) appears in E. Segrè. *Atti Accad. Lig. Sce. Lett* . XLVI (1989):84-95.
10. For Segrè's self-assessment, see Note 1, p. 150, lines 6-12.
11. E. Segrè, R. S. Halford, and G. T. Seaborg. *Phys. Rev.* 55(1939):55.
12. R. T. Birge. History of the Physics Department (informal departmental document), vol. V, ch. XVIII, pp. 11-16.
13. E. Segrè and C. E. Wiegand. *Phys. Rev.* 75(1949):39-43. Erra-

tum 81(1951):284. R. F. Leininger, E. Segrè, and C. Wiegand. *Phys. Rev.* 76 (1949):897-98.

14. O. Chamberlain, E. Segrè, C. Wiegand, and T. Ypsilantis. *Phys. Rev.* 100 (1955):947-50.

15. There is a footnote about Wiegand's 1985 presentation by a puzzled Segrè in Footnote 9, p. 316 of Note 1.

16. Segrè was also disappointed not to share in the 1951 Nobel Prize in chemistry awarded to McMillan and Seaborg for his contributions to the work on plutonium. See Note 1, p. 299.

17. L. B. Auerbach, T. Elioff, W. R. Johnson, J. Lach, C. E. Wiegand, and T. Ypsilantis. *Phys. Rev. Lett.* 9(1962):173-76.

18. E. Segrè (ed.). *Experimental Nuclear Physics*, 3 vols. New York: Wiley, 1953-59.

19. E. Fermi. *Collected Papers*, 2 vols. Chicago: University of Chicago Press, 1962-65.

20. E. Segrè. *Nuclei and Particles.* New York: W. A. Benjamin, 1964 (2nd ed., 1977).

21. E. Segrè. *Enrico Fermi, Physicist.* Chicago: University of Chicago Press, 1970.

22. E. Segrè. *From X-Rays to Quarks: Modern Physicists and Their Discoveries.* San Francisco: W. H. Freeman, 1980.

23. E. Segrè. *From Falling Bodies to Radio Waves: Classical Physicists and Their Discoveries.* San Francisco: W. H. Freeman, 1984.

24. E. Segrè. Fifty years up and down a strenuous and scenic trail. *Ann. Rev. Nucl. Part. Sci.* 31(1981):1-18.

25.E. Segrè and C. S. Wu. *Phys. Rev.* 57(1940):552.

SELECTED BIBLIOGRAPHY

1930

Evidence for quadrupole radiation. *Nature* 126:882.

1931

With C. J. Bakker. Der Zeemaneffekt von Quadrupollinien bei den Alkalien. *Z. Phys.* 72:724-33.

1933

With E. Fermi. Zur Theorie der Hyperfeinstruktur. *Z. Phys.* 82:729-49.

1934

With E. Amaldi, O. D'Agostino, E. Fermi, and F. Rasetti. Artificial radioactivity produced by neutron bombardment. *Proc. Roy. Soc. Lond. A* 146:483-500.

With E. Amaldi, E. Fermi, B. Pontecorvo, and F. Rasetti. Azione di sostanze idrogenate sulla radioactività provocata da neutron. *Ric. Sci.* 5:282.

1935

With E. Amaldi, O. D'Agostino, E. Fermi, B. Pontecorvo, and F. Rasetti. Artificial radioactivity produced by neutron bombardment II. *Proc. Roy. Soc. Lond. A* 149:522-58.

With E. Amaldi. Einige spektoskopische Eigenschaften hochangeregter Atome. *Zeeman Verhandelingen*, pp. 8-17. 's Gravenag: Martinus Nijhoff.

1937

With C. Perrier. Alcune proprietà chimiche dell'elemento 43. *Rend. Lincei,* 6th ser., 25:723-30; 27:579-81. Some chemical properties of element 43. *J. Chem. Phys.* 5:712-16; 7:155-56.

1939

With R. S. Halford and G. T. Seaborg. Chemical separation of nuclear isomers. *Phys. Rev.* 55:321-22.

1940

With D. R. Corson and K. R. MacKenzie. Possible production of radioactive isotopes of element 85. *Phys. Rev.* 57:459; 58:672-78.

With C. S. Wu. Some fission products of uranium. *Phys. Rev.* 57:552.

1945

With C. S. Wu. Radioactive xenons. *Phys. Rev.* 67:142-49.

1947

Possibility of altering the decay rate of a radioactive substance. *Phys. Rev.* 71:274 (abstract).

1948

With J. Hadley, E. L. Kelly, C. E. Leith, C. Wiegand, and H. F. York. Angular distribution of n-p scattering with 90-MeV neutrons. *Phys. Rev.* 73:1114-15.

1949

With C. E. Wiegand. Experiments on the effect of atomic electrons on the decay constant of Be^7. *Phys. Rev.* 75:39-43. Erratum 81(1951):284.

1950

With E. L. Kelly, C. E. Leith, and C. Wiegand. Experiments with 260 MeV neutrons. *Phys. Rev.* 79:96-98.

1951

With O. Chamberlain and C. Wiegand. Experiments on proton-proton scattering from 120 to 345 MeV. *Phys. Rev.* 83:923-32.

1952

Spontaneous fission. *Phys. Rev.* 86:21-28.

1954

With O. Chamberlain, R. Tripp, C. Wiegand, and T. Ypsilantis. Experiments with high-energy polarized protons. *Phys. Rev.* 93:1430-31.

1955

With O. Chamberlain, C. Wiegand, and T. Ypsilantis. Observation of antiprotons. *Phys. Rev.* 100:947-50.

1956

With E. Amaldi, G. Baroni, C. Castagnoli, O. Chamberlain, W. W. Chupp, C. Franzinetti, G. Goldhaber, A. Manfredini, and C. Wiegand. Antiproton star observed in emulsion. *Phys. Rev.* 101:909-10.

With O. Chamberlain, D. V. Keller, H. M. Steiner, C. Wiegand, and T. Ypsilantis. Antiproton interaction cross sections. *Phys. Rev.* 102:1637-40.

1964

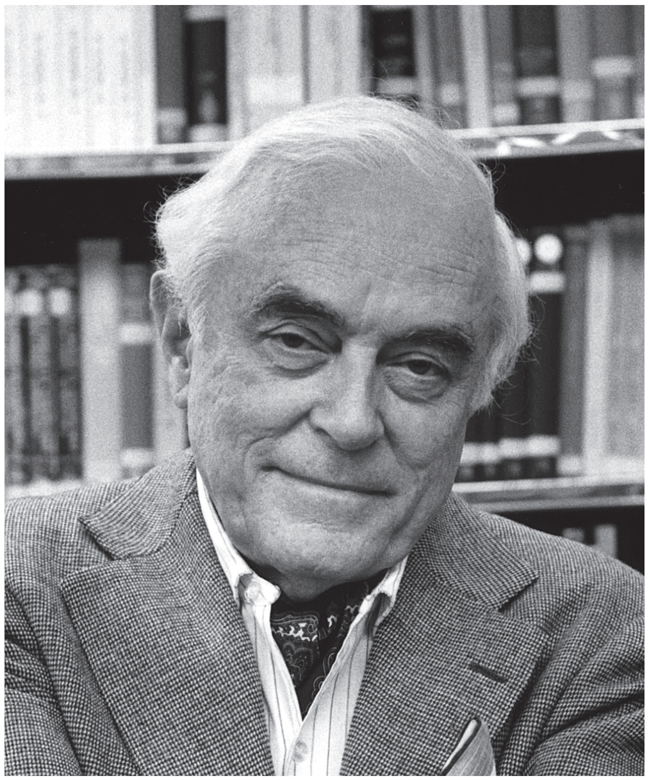
Nuclei and Particles. New York: W. A. Benjamin (2nd ed., 1977).

1980

From X-Rays to Quarks: Modern Physicists and Their Discoveries. San Francisco: W. H. Freeman.

1984

From Falling Bodies to Radio Waves: Classical Physicists and Their Discoveries. San Francisco: W. H. Freeman.



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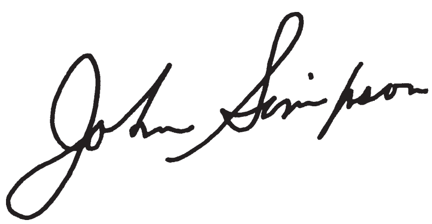


JOHN ALEXANDER SIMPSON

November 3, 1916–August 31, 2000

BY EUGENE N. PARKER

JOHN SIMPSON WAS A visionary experimental nuclear and cosmic ray physicist, a prolific inventor, a vigorous booster of colleagues and university, and was deeply committed to communicating science and its implications to the public and political leaders. His eyes were continually on the next generation of science as he worked with the present tasks, anticipating the next leap forward. Thus his specific scientific measurements invariably had profound implications.

Simpson began his professional career in 1943 as a group leader on the Manhattan Project. He recognized the social and human implications of nuclear energy for both sustained and explosive release, and he and many others of the project began serious discussion of the future of nuclear energy and the human relation to it. Such group discussions were forbidden under the wartime regulations imposed on the project, but the ideas were developed and shared among the concerned scientists nonetheless. The upshot was that John Simpson became a founding member and first chairman of the Atomic Scientists of Chicago, formally founded August 7, 1945, the day after the United States dropped the atomic bomb on Hiroshima. He was a cofounder of the *Bulletin of the Atomic Scientists* later in 1945. The doomsday clock on the cover of the bulletin is familiar to all. Henry

Luce, publisher of *Time* and *Life* magazines, was sufficiently impressed with the thoughts and concerns of the Atomic Scientists of Chicago that he provided them with two full pages in the October 20, 1945, issue of *Life* to spell out the implications of the atomic bomb and possible rational courses of action in response to the implications.

In 1945 Simpson joined the faculty of the University of Chicago as an instructor in the Physics Department. He remained at the university throughout his career, active in his research to within a few weeks of his death on August 31, 2000, from pneumonia contracted in the hospital following successful heart surgery. Simpson's first act as a new instructor was to take a leave of absence to work as an unofficial advisor to Senator Brian McMahon of Connecticut. The product of this collaboration was the McMahon Act of 1946, placing the control of atomic (nuclear) energy in civilian hands rather than leaving it under the military jurisdiction that spawned its creation. It was a milestone in the history of atomic energy. Simpson was just 30 years old at the time of the McMahon Act. Born on November 3, 1916, in Portland, Oregon, Simpson earned an A.B. degree in physics from Reed College in 1940. His graduate training was in physics at New York University, where he earned an M.S. in 1942 and a Ph.D. in 1943 before joining the Manhattan Project. His research advisor was Prof. Serge Korff.

One of Simpson's first contributions was the invention of a gas flow α-particle proportional counter for measuring plutonium yields in the presence of high intensity fission products. It must be appreciated that α-particles (helium nuclei) emitted in the radioactive decay of plutonium, and other transuranic elements, have but little penetrating power. A sheet of paper stops them. They do not penetrate the thin window of particle counters, so the trick was to pipe the plutonium-bearing gas through the counter itself.

Simpson patented the device, which was the first of the 15 patents that now bear his name, ranging from the multiwire proportional counter to a device that assists in improving reading speed and accuracy. During his professional career he kept a file of his many (unpatented) ideas (e.g., a modification of the profile of a clarinet reed to provide different tone qualities). He was an accomplished clarinetist and saxophonist, already recognized in high school with an award for his virtuosity.

COSMIC RAYS

When Simpson returned to the University of Chicago in 1946, his scientific curiosity turned to cosmic rays. At this point it is desirable to say a few words about the scientific problem posed by cosmic rays then and now, for the fact is that Simpson's immense contribution to science lies in that little known field. The basic nature of cosmic rays was only in the process of being established in 1946, and their origins were a matter of speculation. It was recognized, from the variation of the cosmic ray intensity with geomagnetic latitude and from the east-west asymmetry of their arrival at the surface of Earth, that cosmic rays are mostly charged particles, as distinct from energetic photons, with the majority of the particles positively charged. It was not long before photographic emulsions, carried on balloons to the top of the atmosphere, showed that the incoming cosmic ray particles are indeed mostly protons, with a small but surprising distribution of heavier nuclei.

It must be appreciated that these incoming "primary" cosmic rays are not the cosmic rays found down here in the lower atmosphere. The primary particles collide with the nuclei of the air atoms in the topmost tenth of the atmosphere (the first 100 gm/cm^2) producing a spray of gamma rays, mesons, electrons and positrons, protons and neutrons. It is these secondary particles that are observed at the surface of Earth. It should also be appreciated that the magnetic field of Earth is horizontal at the equator, so an incoming proton can reach the atmosphere only by moving across the magnetic field. That cross motion deflects the proton so much that a minimum energy of about 15 GeV is required for vertical arrival at the top of the atmosphere. This energy restriction declines smoothly to zero at the magnetic poles, where the field extends vertically outward into space. Thus, the observed cosmic ray intensity is greater at the high than at the low geomagnetic latitudes—the so-called latitude effect. By 1946 the work of S. E. Forbush had identified time variations in the cosmic rays, closely correlated with outbursts of activity on the Sun and the associated magnetic storms here at Earth. Solar activity generally had the effect of diminishing the intensity of the cosmic rays arriving at the surface of Earth.

Today we know that the cosmic rays are created throughout the galaxy by such energetic phenomena as supernovae and that the cosmic rays in the large represent a tenuous relativistically hot gas, with dynamical pressure comparable to the magnetic fields and other gases in interstellar space and in the galactic halo. The story of the development of the modern cosmic ray concept is to a large degree the story of Simpson's scientific investigations. The interesting thing is that he accomplished this work in a way that boosted the scientific accomplishments and careers of those around him—graduate students, research associates, and fellow faculty. For instance, in 1955 he gave me a job as a research associate in what is now the Enrico Fermi Institute of the University of Chicago. My subsequent progress up through the academic ranks was in no small way a consequence of his continuing support. This was only typical of his general approach to his work, his colleagues, and the university.

Returning to the scientific narrative: Simpson chose to begin his investigations with a study of the cosmic ray neutrons in the lower atmosphere, whose existence had been established before World War II by Serge Korff. Almost all of the cosmic ray measurements up to that time used Geiger counters and ionization chambers, responding largely to the mesons. Simpson discovered that the latitude effect seen with neutrons is about 20 times greater than observed with ionization chambers, and it was soon apparent that the time variations are much greater, too (1949, 1951). The neutrons are produced mostly by incoming cosmic ray protons of 15 GeV or less, while the mesons are produced mostly by protons above about 15 GeV. Simpson recognized the potential of the neutrons and the lower energy cosmic ray particles for probing the causes of the time variations. That is to say, the strong time variation of the lower energy cosmic rays is a thumbprint of whatever is happening out in space.

A stable ground-based neutron detector was needed, so Simpson invented the neutron monitor. This instrument was bulky, with layers of both lead shielding and paraffin moderator, but it was inexpensive, stable, and could be built large to obtain any desired counting rate. It had the big advantage that the diurnal atmospheric corrections required little more than the local barometric reading. Ionization chambers, for instance, must include the height (temperature) of the atmosphere in the corrections, as a consequence of the decay of the downward propagating mesons. Simpson recognized the importance of determining the energy dependence of the time variations, so he established neutron monitor stations at Chicago, Illinois; Climax, Colorado; Sacramento Peak, New Mexico; Mexico City, Mexico; and Huancayo, Peru. The Peruvian station responded only to cosmic rays above 15 GeV, while the Chicago station responded to cosmic rays above about 2 GeV, with the other three stations distributed between.

TIME VARIATIONS

The energy dependence of the time variations soon showed that the reduction of the cosmic rays during times of solar activity arose from the partial disappearance of cosmic ray particles at the lower energies (1954, 1955). This demolished the idea, popular at the time, that the abrupt Forbush-type decrease, occurring at the time of a geomagnetic storm, was a consequence of the storm modification of the geomagnetic field in such a way as to make it more difficult for cosmic ray particles to arrive at Earth. The other popular notion was that interplanetary space is a hard vacuum, and electrostatic fields in space, with potential differences of a billion volts and more, decelerate the cosmic rays. Passing through such a potential difference would reduce the energy of each particle by the same amount, and that did not produce the energy dependence found from the neutron monitors.

Simpson explored the global variation and time variation of cosmic rays around the world with neutron monitors and other detectors carried on Air Force B-25's, B-29's, and Globemasters, on Navy ships to and from the Antarctic, and with helium-filled balloons going to the top of the atmosphere. The neutron monitor stations were intercalibrated, and there were many other cosmic ray detectors up and running elsewhere, too.

So it was that the giant cosmic ray flare of February 23, 1956, emitting an immense burst of protons up to 25 to 30 GeV, provided the first direct glimpse of the state of things in interplanetary space. Briefly, the leading edge of the burst of energetic particles arrived promptly at Earth from the direction of the Sun. Over the next 10 minutes or so the whole space around Earth was filled with solar energetic particles, providing a roughly isotropic sea, which soon began to decay away, very approximately going over into the declining form $t^{-3/2}$ for the next several hours.

This behavior and the precise timing suggested that the inner solar system (out to about Mars) is enclosed by a disordered magnetic field beyond Mars that greatly impedes the free escape of energetic particles. The abrupt arrival of the first particles from the direction of the Sun indicated that any magnetic fields between Earth and the Sun must be relatively smooth and more or less in the radial direction (1956). This was the first evidence that interplanetary space is filled with a magnetic field and hence contains a plasma in which the field is embedded. It suggested that the cosmic ray variations are a consequence of variations of the magnetic field and plasma, and it was the beginning of the concept that ultimately led to recognition of coronal expansion and the supersonic solar wind and heliosphere.

By this time there was an active scientific community interested in such topics as solar activity, cosmic ray variations, and geomagnetic storms. The international community got together for the International Geophysical Year (IGY) in 1957-58. Simpson was one of the 12 discipline scientists responsible for organizing and coordinating the international program. The neutron monitor was adopted as the standard for cosmic ray measurements worldwide. Indeed the fundamental role of the neutron monitor is evidenced today by the 23 nations that use them at 51 centers around the world. These centers are part of a network of stations that monitor space weather under the auspices of the National Science Foundation. The IGY was a huge success, with its tightly coordinated worldwide observations providing a general picture that had never before been possible.

SPACE MISSIONS

Simpson realized at this point in time the necessity for sending instruments into space. It was general public knowledge that the development of rocket technology was approaching the capability of launching spacecraft into orbit around Earth. The launch of *Sputnik* by the Soviet Union in the fall of 1957 provided an efficacious prod to rocket development in the United States. At the end of 1957 Simpson went to Lawrence Kimpton, chancellor of the University of Chicago, and outlined the scientific situation and his plans for the future. Kimpton responded with $5,000 to get the project off the ground. Together with Peter Meyer, Simpson started work immediately on the development and construction of small lightweight particle detectors suitable for going into space; his first particle detector was launched into space on *Pioneer 2* in 1958. Rocket failures on the *Ranger 1* and *2* launches delayed things momentarily, so the second instrument to go into space was on *Pioneer 5* in 1960.

It was clear to Simpson that the limited weight and power available on spacecraft made it necessary to invent small detectors that could determine the mass, charge, and energy of the individual energetic particles passing through the instrument. Only with such detailed knowledge of the cosmic ray particles would it be possible to infer their origin. Attention turned first to silicon crystals, and a long program of development in collaboration with A. J. Tuzzolino and others ensued. By 1980 the art of particle detection and measurement had advanced to the point where it was possible to resolve the individual isotopes of nuclei, eventually all the way up through Fe and Ni, at the same time measuring their kinetic energy (1969, 1996, 1997). This technology is now generally employed in the space program for studies of galactic cosmic rays, solar cosmic rays, and energetic particles trapped in planetary magnetic fields.

An offshoot into plastic detectors led to the dust flux monitor instrument (DFMI) developed by Simpson and A. J. Tuzzolino in the 1980s. It is a novel pyroelectric scheme involving a thin sheet of plastic that has been polymerized in the presence of a strong electric field perpendicular to the plane of the plastic; the final sheet is electrically polarized and carries a positive electric charge on one surface and a negative charge on the other. A dust particle or heavy nucleus penetrating though the sheet vaporizes a small area, thereby releasing the charges. The electrical signal indicates the location and size of the hole in the plastic and can be calibrated to give information on the speed and size of the particle (1985, 1989). This device was first carried into space on the Soviet *Vega 1* and *2* spacecraft to Halley's comet in 1986. The ability to handle up to 0.5×10^5 hits per sec made the DFMI indispensable for studying the cometary dust cloud close to the comet and using the results of *Vega 1* to judge how close to send *Vega 2*. Simpson was awarded the Gagarin Medal for Space Exploration in 1986 for his contribution to the success of the *Vega* mission. His instruments were the only ones from the United States to encounter Halley's comet.

A more recent DFMI is carried on the Cassini mission to Saturn, where it will investigate the dust environment of Saturn's gravel rings. DFMI's are flown on the Air Force's unclassified *Advanced Research and Global Observation Satellite* and on the *ARGUS* spacecraft in low Earth orbit, where it monitors the space dust of both natural and human origins. It is evident that the DFMI has joined the silicon detectors and the neutron monitor in the stable of scientific workhorses.

LABORATORY FOR ASTROPHYSICS AND SPACE RESEARCH

Now, going back to pick up the narrative around 1960: The growing complexity of space instrumentation and the analysis of data returned from space by the instrumentation led Simpson to recognize that a closely coordinated infrastructure was a necessity. So in 1962 he and Prof. Peter Meyer established the Laboratory for Astrophysics and Space Research (LASR) within the Enrico Fermi Institute of the University of Chicago. The direct interest to NASA and its future space missions induced NASA to fund a building for LASR, which was completed in 1964. LASR made it possible to consolidate the instrument development and space research under one roof, at the same time providing a home for theoretical research directly or loosely connected with the results of the ongoing space experiments. Equally important in Simpson's eyes was the immersing of the students in all aspects of space research.

Simpson believed in the innate ability of his graduate students, and he saw to it that they shared in the responsibilities of instrument development, operation, and data analysis. The outstanding success of so many of his students in their subsequent professional careers attests to the validity of his assessment. In the course of his academic career he supervised the research of 34 doctoral students, but times were changing. The classical university laboratory, where professor and student worked through the experiment, was giving way by the mid-1960s to the extended space project, stretching beyond the years that a student could reasonably spend in graduate school. So Simpson turned to another training pattern for his students, in which a student does not follow through with all phases of a single space mission but rather gets some experience by working for a time with the laboratory development of an instrument and then moving on to the calibration, perhaps of an instrument about to be launched into space, finally analyzing the accumulated data from a space mission launched at an earlier date.

SPACE EXPLORATION

Exploration of interplanetary space and the planets throughout the solar system was soon underway, with expectations of finding magnetic storms and trapped energetic protons and electrons in the magnetic fields of Jupiter, Saturn, and presumably Uranus and Neptune, in analogy to the active magnetic field of Earth. The magnetic fields and shock waves in interplanetary space were a new subject, of course, and conditions were surely different beyond the orbit of Mars, where the interplanetary magnetic field becomes more nearly azimuthal. So there was high anticipation of surprises and new discoveries all around. Simpson and his students and coworkers built the first cosmic ray (energetic particle) detectors to visit Mars (in 1965), Jupiter (in 1973), Mercury (in 1974), and Saturn (in 1979). The 1973 mission to Jupiter made the first detection of the relativistic (3-30 MeV) electron population emitted by Jupiter, first recognizing the electrons within the Jovian magnetosphere and ultimately detecting the escaping electrons at distances of 1 AU and more. The electron escape from Jupiter is synchronized with the rotation of Jupiter (period of 9 hours, 55 minutes, 30 seconds), so that the electrons are readily identified at large distances from Jupiter by their pulse (1974, 1977).

It was Simpson's detection of the fixed energetic particle populations around Mercury that first established that the magnetic fields observed at Mercury belong to the planet itself, rather than being carried from the Sun by the impacting solar wind (1974). Then Simpson and others detected a tiny gap in the distribution of energetic particles trapped in the magnetic field of Saturn, indicating the presence of a previously undetected small moon of Saturn orbiting at that position in space and absorbing the particles that would otherwise be found there (1980). The moon was subsequently identified optically.

Besides the purely exploratory discoveries, there were several known effects that needed to be mapped throughout the solar system. For instance, the outward sweep of the magnetic fields carried in the solar wind partially excludes the galactic cosmic rays from the solar system. So it is important to measure the outward increase of the cosmic ray intensity, and ultimately to determine the intensity of the full cosmic ray intensity in interstellar space (1973, 1985). Such distant investigations are limited by the mechanics of rocket launches from the orbiting Earth in the plane of the ecliptic. Thus, space far away from the ecliptic was unexplored until a carefully orchestrated swing by Jupiter tossed the *Ulysses* spacecraft over the poles of the Sun. Simpson (1959) was involved with the development of the mission from the beginning of the concept. He ultimately served as the principal investigator of the international team that provided the diverse individual particle detectors harnessed together to measure the wide range of energetic particle populations to be encountered on the journey. As expected, the polar regions, above about 35° magnetic latitude, produce only high-speed solar wind (500-800 km/sec) at solar minimum, with the polar magnetic fields of the Sun stretched radially out through space.

The speculation that the galactic cosmic rays penetrate freely into the Sun along this radial field was found to be incorrect. Evidently, with so many small-scale transverse fluctuations in the field, the cosmic ray intensity is reduced almost as much as near the ecliptic. Then the *Ulysses* cosmic ray measurements showed the puzzling fact that the 26-day variations, produced by the magnetic fields of the rotating Sun caught up in the interacting slow and fast solar wind streams near the ecliptic, are present over the poles of the Sun, where there is only the fast solar wind (1995, 1996). This discovery indicates that the cosmic ray particles disperse widely over heliocentric latitude, which suggests extensive wandering of the field lines relative to the mean field. This whole phenomenon has yet to be fully understood.

PARTICLE ACCELERATION

It is remarkable that wherever one looks around the solar system and wherever one can probe the galaxy, there are vigorous populations of fast particles, from cosmic rays to trapped particle belts in the magnetic fields of planets. The mechanisms responsible for accelerating these particles above the general thermal background pose a fundamental problem in classical physics. The intense bursts of solar cosmic rays from impulsive flares had for many years emphasized that the acceleration process is remarkably efficient (10-50 percent). So Simpson's detection of bursts of energetic particles associated with the passage of shock waves in the solar wind was an important conceptual step (1976, 1982), emphasizing that the shock transition is an efficient accelerator of particles. Subsequent theoretical studies of the acceleration of particles in a shock front have shown just how efficient the acceleration can be.

Another discovery by Simpson eventually led to the realization that plasma waves can also be efficient accelerators. It began with Simpson's (1970) discovery that impulsive flares at the Sun produce energetic particles among which ^{3}He is ten or more times abundant relative to ^{4}He than normal. Subseequently, others observed instances in which ^{3}HE actually outnumbered ^{4}HE. L. A. Fisk showed that this very selective acceleration can be understood in terms of the plasma waves created by current instabilities, and M. Temerin and J. Roth more recently have shown that ion cyclotron waves are another possibility, both processes being remarkably efficient under the right circumstances.

Simpson was particularly interested in the ultimate acceleration problem (i.e., the origin of the galactic cosmic rays) created somewhere else in the galaxy, far beyond the outer reaches of the solar wind and heliosphere. He realized that the detailed isotopic composition of the heavier elements among the cosmic rays should give some idea of their place of origin.

Then Simpson's original interest in the modulation of the galactic cosmic ray intensity by the solar wind became part of the galactic program because it was ever more interesting to know just how high was the cosmic ray intensity out in interstellar space. He and his associates carried out extensive studies of the gradual outward increase of the cosmic ray intensity. His instruments on *Pioneer 10* and *11* indicated an increase of about 1 percent per AU (1973). The net reduction of the low energy cosmic rays (~100 MeV/nucleon) here in the inner solar system is particularly striking. The intensity goes up and down by about a factor of 10 with the 11-year cycle of solar activity. Then Simpson (1975) found that during the activity minimum of 1972 the abundance of cosmic ray helium was peculiarly enhanced at very low energies. It did not drop off with declining energy like the protons, more or less linearly toward zero energy. It was as if an independent source of low energy helium (20-50 MeV/nucleon) was able to get through at that time of minimum solar suppression. These helium nuclei, as well as heavier nuclei (e.g., C, N, O), are now referred to as the anomalous cosmic rays. The theoretical work of Pesses, Jokipii, and Eichler showed that these rays are produced in great numbers in the termination shock of the solar wind. These particles first enter the solar wind as free-falling interstellar neutral atoms, passing freely through the magnetic fields and tenuous solar wind, ultimately being ionized by solar UV somewhere in the general vicinity of the orbit of Jupiter. Upon ionization (becoming a singly charged ion) they are immediately picked up by the solar wind, within which they have a relative velocity comparable to the speed of the wind (about 1 KeV per nucleon compared to the 1 eV thermal energy of the solar wind particles). So they are selectively accelerated to energies of the order of 100 MeV as they pass through the termination shock.

COSMIC RAYS IN THE GALAXY

Finally, then, turning attention to the galactic cosmic rays: The isotopic studies revealed that ^{10}Be is almost entirely missing from among the cosmic rays. One would expect to see modest abundances of ^{3}He and Li, Be, and B as a consequence of collisions of such common massive cosmic ray nuclei as C, N, and O with the nuclei of interstellar atoms knocking chunks out of the heavier nuclei. Indeed, studies of these spallation nuclei show them to be present in about the expected ratios, with the cosmic rays having passed through about 5 gm/cm^2 since being accelerated. A mean interstellar number density of 1 or 2 atoms/cm^3 throughout the gaseous disk of the galaxy would indicate a travel time of about 2×10^6 years. The ^{10}Be nuclei are different, in that they are unstable, with a half-life of 2.6×10^6 years. Simpson pointed out that their scarcity indicates they have been around for about 2×10^7 years, which can only mean that the cosmic rays pass freely between the gaseous disk and the extended magnetic halo of the galaxy, where the ambient gas density is more like 10^{-2} atoms/cm^3 or less (1975, 1977). One infers from this that the magnetic halo is made up largely of lobes of the disk magnetic field inflated outward by the continuing production of cosmic rays (by supernovae, for example) in the disk. Subsequent evaluations of other unstable nuclei confirm the general 2×10^7 year cosmic ray residence time within the magnetic fields of the galaxy. So the study of isotopes provides insight into the galactic range of the cosmic rays.

More recently the isotopic studies have led to the conclusion that the cosmic rays do not represent a sample of nuclei taken from a supernova but rather are close to the expected relative abundances of interstellar atoms. From this one infers that the cosmic rays are accelerated in interstellar space by shock waves from nearby supernovae. The shock waves propagate out ahead of the supernova ejecta, and little or no matter from the ejecta is accelerated to cosmic ray energies. So again the isotopic studies add a piece to the general picture.

IN CONCLUSION

This brief survey of Simpson's contributions to the cosmic ray picture is intended to show how much his work contributed to the present day picture of this vast and powerful galactic phenomenon. The limited space really can do justice neither to the full span of Simpson's work nor to the many others who have worked and contributed to the field.

To say a little more about Simpson's role in the scientific community: He was elected to the National Academy of Sciences in 1959. He was made distinguished service professor at the University of Chicago in 1968, holding first the Ryerson chair and then, from 1974 the first to be appointed to the Compton chair. He became emeritus in 1986. He was awarded the Bruno Rossi Prize by the American Astronomical Society in 1991 for contributions to high-energy astrophysics and the Henryk Arctowski Medal of the National Academy of Sciences in 1993. In June 2000 he was awarded the William Bowie Medal, the highest award by the American Geophysical Union, in recognition of his extensive explorations of the cosmic rays and other energetic particles that continually bombard our planet.

In 1974 he used funds that came with the Compton chair to initiate the weekly Compton Lectures for the public. It is an honor among the junior scientific staff of the Enrico Fermi Institute to be appointed the Compton lecturer for an academic quarter. The lectures are invariably excellent, and the response from the public has been gratifying. In 1982 he established the Universities Space Science Working Group in Washington, D.C., representing the space science laboratories in their dealings with NASA and Congress. He was the first chairman, and the group has enabled the scientific community to be heard more effectively by the Washington bureaucracy.

John Simpson is survived by his wife, Elizabeth, and by his children, Mary Ann and John, from his first marriage.

SELECTED BIBLIOGRAPHY

1949

With R. B. Uretz. On the latitude dependence of nuclear disintegrations and neutrons at 30,000 feet. *Phys. Rev.* 76:569.

1951

Change of cosmic ray neutron intensity following solar disturbances. *Phys. Rev.* 81:639.

1954

Cosmic radiation intensity-time variations and their origin. III. The origin of 27-day variations. *Phys. Rev.* 94:426.

1955

With P. Meyer. Changes of the low energy particle cut-off and primary spectrum of cosmic radiation. *Phys. Rev.* 99:1517.

1956

With P. Meyer and E. N. Parker. The solar cosmic rays of February 1956 and their propagation through interplanetary space. *Phys. Rev.* 104:768.

1959

With B. Rossi, A. R. Hibbs, R. Jastrow, F. L. Whipple, T. Gold, E. N. Parker, N. Christofolis, and J. A. Van Allen. Round table discussion chaired by J. A Simpson. *J. Geophys. Res.* 64:1691

1960

With C. Y. Fan and P. Meyer. Preliminary results from the space probe *Pioneer V*. *J. Geophys. Res.* 65:1861.

1969

With G. M. Comstock and C. Y. Fan. Energy spectra and abundances of the cosmic ray nuclei He to Fe from the OGO-1 satellite experiments. *Astrophys. J.* 155:609.

1970

With K. C. Hsieh. The relative abundances and energy spectra of ^{3}He and ^{4}He from solar flares. *Astrophys. J. Lett.* 162:L191.

1972

With A. Mogro-Campero. Enrichment of very heavy nuclei in the composition of solar accelerated particles. *Astrophys. J. Lett.* 171:L5.

1973

With R. B. McKibben, J. J. O'Gallagher, and A. J. Tuzzolino. Preliminary *Pioneer 10* intensity gradients of galactic cosmic rays. *Astrophys. J. Lett.* 181:L9.

1974

With D. L. Chenette and T. F. Conlon. Bursts of relativistic electrons from Jupiter observed in interplanetary space with time variations of the planetary rotation period. *J. Geophys. Res.* 79:3551.

With J. H. Eraker, J. E. Lamport, and P. H. Walpole. Electrons and protons accelerated in Mercury's magnetic field. *Science* 185:160.

1975

With G. M. Mason and M. Garcia-Munoz. The anomalous ^{4}He component in the cosmic ray spectrum at 50 MeV per nucleon during 1972-74. *Astrophys. J.* 202:265.

With M. Garcia-Munoz and G. M. Mason. The cosmic ray age deduced from ^{10}Be abundance. *Astrophys. J. Lett.* 201:L141.

1976

With C. W. Barnes. Evidence of interplanetary acceleration of nucleons in corotating interaction regions. *Astrophys. J. Lett.* 210:L91.

1977

With D. L. Chenette, T. F. Conlon, and K. R. Pyle. Observations of Jovian electrons at 1 AU throughout the 13 month Jovian synodic year. *Astrophys. J. Lett.* 215:L95.

With M. Garcia-Munoz and G. M. Mason. The age of galactic cosmic rays derived from the abundance of ^{10}Be. *Astrophys. J.* 217:859.

1980

With T. S. Bastian, D. L. Chenette, R. B. McKibben, and K. R. Pyle. The trapped radiations of Saturn and their absorption by satellites and rings. *J. Geophys. Res.* 85:5731.

1982

With B. Tsurutani, E. J. Smith, and K. R. Pyle. Energetic protons accelerated at corotating shocks: *Pioneer 10* and *11* observations from 1 to 6 AU. *J. Geophys. Res.* 87:7389.

1985

With R. B. McKibben and K. R. Pyle. Changes in the radial gradients of low energy cosmic rays between solar minimum and maximum: Observations from 1-31 AU. *Astrophys J. Lett.* 2289:L95.

With A. J. Tuzzolino. Polarized polymer films as electronic pulse detectors of cosmic dust particles. *Nucl. Instrum. Methods Phys. Res.* A236:187.

With M. A. Perkins and A. J. Tuzzolino. A cometary and interplanetary dust experiment on the *Vega* spacecraft missions to Halley's comet. *Nucl. Instrum. Methods Phys. Res.* A239:310.

1989

With A. J. Tuzzolino. II. Instruments for measurement of particle trajectory, velocity, and mass. *Nucl. Instrum. Methods Phys. Res.* A279:625.

1995

With R. B. McKibben, M. Zhang, S. Bame, and A. Balogh. *Ulysses* out-of-ecliptic observations of "27-day" variation of high energy cosmic ray intensity. *Space Sci. Rev.* 72:403.

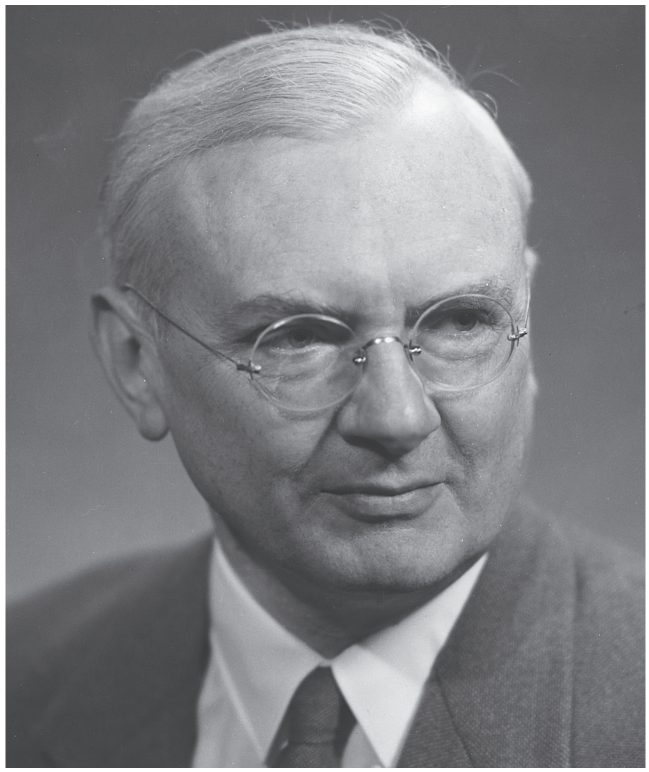
1996

With R. B. McKibben, J. J. Connell, C. Lopate, and M. Zhang. Observations of galactic cosmic rays and anomalous helium during *Ulysses* passage from south to north solar pole. *Astron. Astrophys.* 316:547.

With M. DuVenois, M. Garcia-Munoz, K. R. Pyle, and M. Thayer. Isotopic composition of galactic cosmic ray elements from carbon to silicon: The CRRES satellite investigation. *Astrophys. J.* 466:457.

1997

With C. J. Connell. Isotopic abundances of Fe and Ni in galactic cosmic ray sources. *Astrophys. J. Lett.* 475:L61.



Official United States Navy Photograph.

RICHARD TOUSEY

May 18, 1908–April 15, 1997

BY WILLIAM A. BAUM

RICHARD TOUSEY WAS THE leading pioneer in solar research from space. Using a V-2 rocket in 1946, he and his collaborators at the Naval Research Laboratory were the first to record the spectrum of the Sun in the ultraviolet, which is blocked from reaching instruments on Earth's surface (or even on the highest balloons) by gases in Earth's atmosphere. This solar spectrum was, in fact, the very first astronomical observation to be made successfully from above Earth's atmosphere, and it marked the dawn of the space age. Using rockets and Earth-orbiting spacecraft, Tousey devoted the next three decades to increasingly sophisticated studies of the Sun and Earth's atmosphere, resulting in a number of important firsts. In private life, Tousey was interested in baroque music, harpsichords, hiking, sailing, and bird watching. He was a soft-spoken person with a probing mind and a strong sense of purpose.

Richard Tousey was born on May 18, 1908, in Somerville, Massachusetts, the son of Coleman and Adella Hill Tousey. From the time he was a child Richard had a great fondness for nature and the outdoors, where he liked to hike and where he developed a lifelong interest in ornithology. His family usually spent summers on the Atlantic coast, first south of Boston and later on the coast of Maine, where they particularly enjoyed sailing. According to family lore, Richard's mother feared her children might be at risk of encountering a mountain lion in the Maine woods, but she felt that they were safe at sea. The family also traveled to Europe and went hiking in the Alps. At home in Boston, Richard took an early interest in ham radio and got his license at the age of 12, the youngest person to do so in Boston at that time. He spent hours tapping Morse code to radio amateurs in distant countries, and he had a collection of cards from those who had received his transmissions. He also developed and printed his own photographs.

Tousey majored in physics and mathematics at Tufts University from which he graduated summa cum laude in 1928. From there he entered graduate school at Harvard, earning an M.A. in physics in 1929 and a Ph.D. in physics in 1933 under Professor Theodore Lyman, who 20 years earlier had discovered the fundamental emission line of atomic hydrogen at 1216 A in the ultraviolet (the Lyman-alpha line), which today we know to be an important component of the radiation field of the Universe. As a graduate student Tousey designed a specialized vacuum spectrograph for determining the optical constants of fluorite, a very clear crystal that is transparent far down into the ultraviolet and has optical properties useful in lenses and optical instruments. His thesis was titled "An Apparatus for the Measurement of Reflecting Powers with Application to Fluorite at 1216 A."

While at Harvard, Tousey was a Whiting fellow (1929-31), a Tyndall scholar (1931-32), and a Bayard Cutting fellow (1932-33). He thus finished his Ph.D. at the depth of the Great Depression, but he had an opportunity to stay on at Harvard as an instructor in physics until 1936, supported in part during the last year by another Bayard Cutting Fellowship. Taking his Harvard research apparatus with him, Tousey then returned to Tufts in 1936 as a research instructor in physics, a position he held until 1941, when he took a leave of absence to enter wartime research at the Naval Research Laboratory in Washington, D.C.

In 1932, while still in graduate school, Tousey married Ruth Lowe, who shared his interest in classical music, especially baroque music. They assembled a collection of wire-stringed keyboard instruments that included three harpsichords (one of which they found in the basement of a church in Oxford, England), a virginal, a clavichord, and a piano. In the 1940s and 1950s professional musicians frequently gathered at Tousey's home for a chamber music soiree and for one of Ruth's excellent home cooked meals. Richard played the piano or the harpsichord, and Ruth played the viola or the violin. Their daughter, Joanna, attended the Eastman School of Music on a scholarship, went to Paris as Jean-Pierre Rampal's first Fulbright scholar, obtained a master's degree and later a doctorate at the University of Michigan, and established a career as a professional flautist. In the late 1940s Tousey tinkered (and interested me in doing so, too) with the recording of live music, using vacuum-tube amplifiers and wire recorders. By today's standards the sound fidelity was poor, and the wire had a frustrating tendency to break rather often.

Tousey maintained his outdoor interests throughout his life. Although not especially athletic, he tended to walk quite fast. And he particularly enjoyed sailing. It was in fact while anchored at Bucks Harbor, Maine, that Tousey first became acquainted with E. O. Hulburt, the director of research at the Naval Research Laboratory (NRL), a connection that resulted in Tousey spending most of his career at NRL. In addition to their love of sailing, Tousey and Hulburt shared some personality traits; both were unusually tranquil, undemonstrative, and soft-spoken. I do not recall either one ever raising his voice or speaking rashly.

In 1941 Hulburt asked Tousey to join him in wartime research at NRL. Part of that research pertained to the visibility of stars in the daytime sky, because of the need at that time for the celestial navigation of military aircraft by day as well as by night. That project included determining the brightness and polarization of the daytime sky at high altitudes. Another part of the wartime research at NRL pertained to the nighttime visibility of objects, particularly the effects of night myopia and dark adaptation. Tousey also worked on the visibility of near infrared light sources because of the need to maintain security against visual detection of sources used with infrared military systems. Tousey's interests in physiological and atmospheric optics continued throughout his career, and they account for about one third of his scientific publications. Along with various colleagues Tousey also did extensive work on ultraviolet transmitting and reflecting materials, and the data published from that work are standard references for the properties of those materials.

When World War II ended in 1945, Tousey had an opportunity at NRL to do the fundamental scientific research for which he became best known and which is described in the sections that follow. He was elected to the National Academy of Sciences in 1960. Other honors and milestones of his career included the 1960 Frederic Ives Medal of the Optical Society of America, 1963 Henry Draper Medal of the National Academy of Sciences, 1963 Navy Award for Distinguished Achievement in Science, 1963 George Darwin Lectureship of the Royal Astronomical Society, 1964 Eddington Medal of the Royal Astronomical Society, 1964-1966 vice presidency of the American Astronomical Society, 1966 Henry Norris Russell Lectureship of the American Astronomical Society, and the 1974 NASA Exceptional Scientific Achievement Award.

Richard Tousey retired from NRL on June 30, 1978, but remained connected as a consultant. Ruth Tousey died in 1994, and Richard died of pneumonia on April 15, 1997, at Prince Georges Hospital Center in Maryland at the age of 88.

DAWN OF THE SPACE AGE

It was Tousey's group at NRL that obtained the very first successful astronomical observation ever made from above Earth's atmosphere. In 1946 they recorded the ultraviolet spectrum of the Sun down to 2100 A with an instrument mounted in a high-altitude rocket. It was an historic first, and Tousey's ingenuity was the key to its success. As one of those involved, I can offer a first-hand account.

At the end of the war in 1945 a team of German rocket scientists headed by Werner von Braun was brought to the United States together with about 100 unused German V-2 rockets and a supply of parts. The V-2 was a huge liquid-fuel missile about 2 meters in diameter and 14 meters tall that weighed 13 metric tons at launch and traveled to its target area on a high parabolic trajectory above most of Earth's atmosphere. (V-2 stands for *Vergeltungswaffe Zwei*, or Vengeance Weapon 2, and Germany launched many V-2s against targets in England in 1944-45.)

Although sounding rockets for upper-atmosphere research had been under development in the United States, nothing compared with the V-2 for payload capacity and attainable altitude. The V-2 could not only reach more of Earth's upper atmosphere but also offered the tantalizing possibility of exploring the ultraviolet spectrum of the Sun, which had never been seen below about 2900 A; that part of the solar spectrum is blocked by ozone and oxygen from reaching instruments on the ground or in balloons. Space aboard V-2 rockets for installing scientific instruments was made available to several research organizations, including NRL, and launches began in April of 1946 at White Sands Proving Ground in New Mexico. David DeVorkin's 1992 book, *Science with a Vengeance* (Springer-Verlag), not only documents the history of V-2 science but also conveys the excitement and the sense of exploration we all felt.

It was Tousey's ingenious scheme for catching sunlight and feeding it into the spectrograph that was key to the success of his group in recording the first ultraviolet spectrum of the Sun. The V-2 rocket not only rotated about its axis during flight, but it also yawed and tumbled, and the technology for keeping an instrument pointed at a target in the sky (in this case the Sun) was not yet developed. So Tousey devised the use of a tiny sphere of lithium fluoride (2 mm in diameter), mounted much like the ball of a ballpoint pen, that acted as a fish-eye lens to catch the Sun over a wide field of view and produced a tiny astigmatic image of the Sun in place of an entrance slit to the spectrograph. Although transparent in the ultraviolet down to Lyman-alpha (1216 A), lithium fluoride is a brittle crystal and is slightly water soluble; so the making and handling of the tiny sphere was a formidable challenge. Spectra were recorded on a strip of 35-mm film with a fluorescent coating on the front to make it ultraviolet sensitive and an electrically conducting coat on the back to preclude static electricity when the film was moved. The exposed film was wound into a cassette of armor-piercing steel about the size of a coffee mug so as to survive rocket impact. For the first NRL launch in June of 1946 Tousey's spectrograph was mounted in the conical nose of the V-2 warhead, but the massive warhead buried itself in a deep crater and was never recovered. At the suggestion of von Braun later spectrographs were mounted in one of the tail fins, because the V-2 could be blown apart during re-entry into the atmosphere, causing the lighter parts to be scattered about on the surface of the desert, where retrieval was more likely.

NRL's second V-2 launch on October 10, 1946, was successful, the spectrograph functioned, and the film cassette was recovered. It was a dramatic moment in a darkroom at NRL 10 days later when the film was developed and we had our first peek at the solar ultraviolet spectrum down to about 2100 A. The result, which was reported in November 1946 in *The Physical Review*, was only a modest first step, but it marked the beginning of science in space.

All together NRL spectrographs were flown on 10 V-2 rockets during 1946-48, of which 4 flights were successful. Ozone in the upper atmosphere is the principal absorber of extraterrestrial ultraviolet in the 2100-2900 A range, and oxygen is the main culprit at shorter wavelengths. Tousey's group used the V-2 solar spectra recorded at a series of altitudes to derive for the first time nearly the whole vertical profile of the ozone layer. After 1948 American-made sounding rockets began to replace the V-2s. In 1949 Tousey's group flew two spectrographs in an Aerobee rocket near sunset, when the slant path through the atmosphere was long, so as to improve the accuracy of the upper part of the ozone profile and thereby relate it to a theoretical model for the production of ozone due to solar irradiation of oxygen in that altitude range. These studies, led by Tousey, became the definitive work on the ozone layer. Later, Tousey's group used rocket-borne photoelectric detectors and monochromatic filters to obtain the first direct measurements of the vertical distribution of the nighttime airglow (e.g., the altitudes at which various luminescences are produced).

But solar Lyman-alpha remained the elusive Holy Grail that Tousey sought. Prior to December 1952 spectra had failed to reach that far into the ultraviolet. What would be the form and intensity of this most important line of the most abundant of all elements? On V-2 flights between 1948 and 1950 Kenichi Watanabe and Tousey had succeeded in proving the existence of solar Lyman-alpha by means of a device that, during flight, exposed a thermoluminescent phosphor behind lithium fluoride and calcium fluoride windows. The lithium fluoride was transparent to Lyman-alpha, whereas the calcium fluoride was not. The intensity of Lyman-alpha inferred from that experiment was later confirmed by data obtained from spectra.

AFTER INSTRUMENTS COULD BE AIMED

The first spectrographic detection, albeit near threshold, of solar Lyman-alpha was obtained in December 1952 by a University of Colorado group using a biaxial Sun tracker to keep their instrument pointed at the Sun. Tousey, always eager to adopt any advance in technology, attached an NRL spectrograph to one of Colorado's biaxial Sun trackers and recorded well-exposed spectra of the solar Lyman-alpha feature in February 1954. It was found to be an intense emission line with wide wings. Tousey had made several improvements in solar spectrograph design, aimed at achieving higher spectral resolution and more ultraviolet throughput. Because the Colorado Sun tracker eliminated the need for a wide field of view, the lithium fluoride sphere could be replaced by an entrance slit.

As a result of these advances in instrumentation Tousey's group also succeeded in recording more than a thousand absorption lines of the solar photosphere, mostly longward of 2000 A, and they found nearly 200 emission lines in the extreme ultraviolet down to 977 A. In fact, NRL spectra obtained in 1955 showed that the solar spectrum shortward of 2000 A is composed principally of emission lines from the chromosphere. In 1959, using a pre-disperser to largely eliminate stray light of longer wavelengths, Tousey's group obtained a clean spectral profile of the broad Lyman-alpha feature. They also obtained an excellent image of the Sun in Lyman-alpha light (i.e., a spectroheliogram) for comparison with images obtained simultaneously at longer wavelengths with ground-based instruments.

In April 1960 Tousey's NRL colleagues Herbert Friedman and Richard Blake photographed the first X-ray image of the Sun in wavelengths shorter than 60 A by an amusingly simple device; for a lens they used a pinhole covered with a filter of aluminized Mylar. In 1961 Tousey's group pushed the limit of the solar spectrum down into the soft X-ray region (specifically to 171 A) by using a spectrograph with grazing-incidence optics, together with an unbacked aluminum foil to reduce scattered light by blocking all radiation longer than about 800 A. That yielded the first identification of the Fe XVI coronal lines in the solar spectrum. Then in September 1963 they succeeded in pushing the limit of the solar spectrum down to 30 A.

Also in 1963 Tousey's group was the first to photograph the Sun's outer white-light corona without the help of a solar eclipse. This was accomplished with an externally occulted coronagraph in a rocket, and the photographs showed a long straight streamer extending to 10 solar radii. A number of subsequent flights were made, including some only a day or two apart in 1968 and 1969, from which it became evident that surprisingly large changes in the corona can occur within only a day or two, a phenomenon that ground-based photographs of coronae during solar eclipses had not revealed.

ORBITING SOLAR OBSERVATORIES

To monitor variations in solar radiation on various time scales really requires an instrumented satellite, not rockets. The National Aeronautics and Space Administration (NASA) selected Tousey to be the principal investigator for both an extreme ultraviolet spectroheliograph and a white-light coronagraph to be carried aboard spacecraft of the *Orbiting Solar Observatory* (OSO) series. The main goals of Tousey's NRL group were to find out (1) how solar flares produce effects in Earth's atmosphere that cause radio blackouts and (2) how flares and solar variability relate to the 11-year sunspot cycle. In 1965 an NRL spectroheliograph aboard OSO-2 monitored three solar ultraviolet emission lines by mechanically scanning the images with tiny Bendix photomultipliers. Although the OSO spacecraft provided solar pointing with a short-term stability of better than 5 arcsec, the image resolution of the scanning scheme was rather coarse, yielding only about 30 pixels across the Sun's diameter. Even so, the results showed where the active regions on the Sun were.

Tousey's coronagraph was flown on OSO-7 and was outstandingly successful. It provided nearly daily monitoring of the white-light solar corona from October 1971 to July 1974. This made it possible to record transient changes in the corona on a wide range of timescales. The first great transient to be observed was in December 1971, when clouds of solar plasma were observed traveling out through the corona at 1000 km/sec.

SKYLAB AND THE APOLLO TELESCOPE MOUNT

Tousey was named principal investigator for four solar experiments to be done aboard an Earth-orbiting facility called *Skylab*, which was part of NASA's manned space program following the Apollo lunar landing program. The *Skylab* project began in 1965 and *Skylab* was launched into orbit with a Saturn V rocket on May 14, 1973. The modus operandi of space research had changed dramatically from the era of the V-2 rockets in the 1940s, when experimenters made their own instruments, took them (plus a tool kit) to the launch site, and personally installed them into a rocket. Responsibility for the management and funding of American space research had been assigned to NASA when that agency was created in 1958. By the 1970s space science projects had become very complex bureaucratic enterprises involving contractors, subcontractors, managers, committees, science teams, engineers, design specifications, design reviews, mission planning, proposals, contracts, budgets, grants, cutbacks, changes of course, and cancellations. The tortuous evolution of NASA plans for solar research, from the OSO series to *Skylab*, was only a small part of that story, but it took nearly a decade and is recounted by Tousey in the April 1977 issue of *Applied Optics*. He wrote,

> We have weathered crisis after crisis, found solutions to seemingly unsolvable problems, and learned a great deal in many new fields, especially about large scale engineering methods. I believe that we now understand a little better how engineers think; and on the other hand, I hope that the engineers have learned something of the stringent requirements of scientific experimentation and have come to understand the way scientists think. It has been a fascinating and highly rewarding experience.

Tousey evidently accepted these trends with equanimity.

Aboard *Skylab* a number of solar instruments, including Tousey's, were attached to a stabilized platform, called the Apollo telescope mount (ATM), which was able to keep instruments aimed precisely at a desired point on the Sun, regardless of disturbances, such as those caused by crew movement. The four *Skylab*/ATM instruments for which Tousey had leadership responsibility included the extreme ultraviolet spectroheliograph (S082A), the ultraviolet spectrograph (S082B), the photoelectric spectroheliograph, and the grazing-incidence solar spectrograph (S020). To eliminate stray white light that would otherwise overwhelm the ultraviolet Tousey developed large-area aluminum films, only a few micrometers thick, that could be placed near the focal planes of the *Skylab* spectrographs and that had good ultraviolet transmittance. These very thin films were floated off their glass substrate onto a coarse mesh screen, which provided enough support for the films to survive the *Skylab* launch.

Skylab observations were made during three astronaut visits of 29, 59, and 84 days. The project ended in February 1974, nine months after launch. Tousey rarely used superlatives, but in 1977 he wrote, "the ATM observations alone were of extraordinary value, and in quantity they were staggering." Tousey retired from NRL the following year, but continued to participate in the analysis of the *Skylab* results. In collaboration with Charles Brown (NRL) and Charlotte Moore Sitterly (U.S. Bureau of Standards) he worked on line identifications in the high-resolution solar spectrum obtained from *Skylab*. Images of the spectra as well as tables of line identifications were published by NRL, as were spectroheliograms of remarkably high resolution.

THIS BIOGRAPHICAL MEMOIR is based partly on my personal recollections, partly on Tousey's scientific publications, and partly on input from other people. I am especially indebted to Professor Donald Osterbrock of the University of California, Santa Cruz; Joanna Tousey of the Tucson Symphony and Arizona Opera; Martin Koomen of NRL; and Herbert Gursky of NRL for supplying or calling attention to helpful background material. My personal debt to Richard Tousey is large: Working with him on the quest for the solar ultraviolet spectrum in the 1940s led me to devote my career to astronomical research, a career that took me from NRL to new challenges at Mount Wilson and Palomar observatories, later at Lowell Observatory, and finally where I am now at the University of Washington in Seattle.

SELECTED BIBLIOGRAPHY

1946

With W. A. Baum, F. S. Johnson, J. J. Oberly, C. C. Rockwood, and C. V. Strain. Solar ultraviolet spectrum to 88 kilometers. *Phys. Rev.* 70:781-82.

1951

With F. S. Johnson and J. D. Purcell. Measurements of the vertical distribution of atmospheric ozone from rockets. *J. Geophys. Res.* 56:583-94.

1952

With F. S. Johnson, J. D. Purcell, and K. Watanabe. Direct measurements of the vertical distribution of atmospheric ozone to 70 kilometers altitude. *J. Geophys. Res.* 57:157-75.

1953

With M. J. Koomen. The visibility of stars and planets during twilight. *J. Opt. Soc. Am.* 43:177-83.

1954

With N. Wilson, J. D. Purcell, F. S. Johnson, and C. E. Moore. A revised analysis of the solar spectrum from 2990 to 2635 A. *Astrophys. J.* 119:590-612.

1955

With F. S. Johnson, H. H. Malitson, and J. D. Purcell. Emission lines in the extreme ultraviolet spectrum of the Sun. *Astrophys. J.* 127:80-95.

1958

Rocket measurements of the night airglow. *Ann. Geophys.* 14:186-95.

With I. S. Gulledge, M. J. Koomen, and D. M. Packer. Visual thresholds for detecting an Earth satellite. *Science* 127:1242-43.

1959

With J. D. Purcell and D. M. Packer. Lyman-alpha photographs of the Sun. *Nature* 184:8-10.

1960

With J. D. Purcell. The profile of solar hydrogen Lyman-alpha. *J. Geophys. Res.* 65(1):370-72.

With H. H. Malitson, J. D. Purcell, and C. E. Moore. The solar spectrum from 2635 to 2085 A. *Astrophys. J.* 132:746.

1961

Solar spectroscopy in the far ultraviolet. *J. Opt. Soc. Am.* 51:384-95.

1962

Techniques and results of extraterrestrial radiation studies from the ultraviolet to X rays. In *Space Age Astronomy,* eds. A. J. Deutsch and W. B. Klemperer, pp. 104-14. New York: Academic Press.

1964

With J. D. Purcell, W. E. Austin, D. L. Garrett, and K. G. Widing. New photographic spectra of the Sun in the extreme ultraviolet. In *Space Research IV,* ed. P. Muller, pp. 703-18. Amsterdam: North Holland Publishing.

The spectrum of the Sun in the extreme ultraviolet. *Q. J. Roy. Astron. Soc.* 5:123-44.

1967

Highlights of twenty years of optical space research. *Appl. Opt.* 6:2044-70.

Some results of twenty years of extreme ultraviolet solar research. *Astrophys. J.* 149:239-52.

1968

With J. D. Purcell and M. J. Koomen. Extreme ultraviolet heliograms and the Sun's corona. *Space Research VIII,* vol. I, eds. A. P. Mitra and L. G. Jacchia, pp. 450-57. Amsterdam: North Holland Publishing.

1973

With others. A preliminary study of the extreme ultraviolet spectroheliograms from Skylab. *Sol. Phys.* 33:265-80.

1975

With M. J. Koomen, C. R. Detwiler, G. E. Brueckner, and H. W. Cooper. White light coronagraph in OSO-7. *Appl. Opt.* 14:743-51.

1977

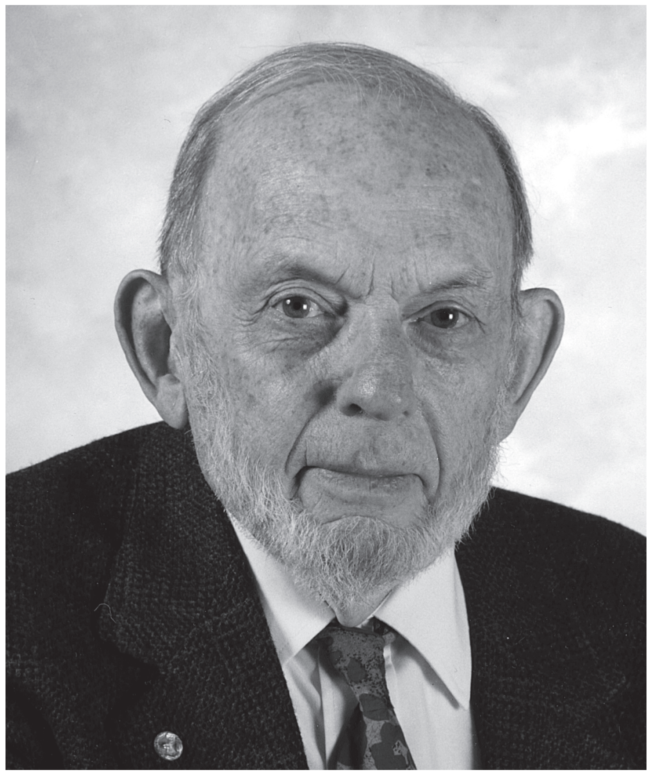
Apollo telescope mount on Skylab: An overview. *Appl. Opt.* 16:825-36.

With J.-D. F. Bartoe, G. E. Brueckner, and J. D. Purcell. Extreme ultraviolet spectroheliograph ATM experiment S082 A. *Appl. Opt.* 16:870-78.

With J.-D. F. Bartoe, G. E. Brueckner, and J. D. Purcell. Extreme ultraviolet spectrograph ATM experiment S082 B. *Appl. Opt.* 16:879-86.

With W. R. Crockett, N. P. Patterson, J. D. Purcell, and R. J. Schumacher. NRL-ATM extreme ultraviolet solar image TV monitor flown on Skylab. *Appl. Opt.* 16:893-97.

With D. L. Garrett. Solar XUV grazing incidence spectrograph on Skylab. *Appl. Opt.* 16:898-903.



John R. Winckler

JOHN RANDOLPH WINCKLER

October 27, 1916–February 6, 2001

BY KINSEY A. ANDERSON

JOHN RANDOLPH WINCKLER was a gifted experimental physicist who made major discoveries in solar, magnetospheric, auroral, and atmospheric physics. He designed and built experimental apparatus for flight on balloons, sounding rockets, and Earth-orbiting spacecraft. Some instruments were exquisite in their simplicity, others highly complex. However, all fit the needs of Winckler's scientific objectives. Early in his research career he ingeniously adapted systems used by the U.S. Navy to detect submarines during World War II to retrieve scientific data from high-altitude research balloons. His first major scientific discovery was to show that electrons with energy in the range of tens to hundreds of kiloelectron volts accompanied bright, active aurora. A few months later with L. E. Peterson he observed and measured an intense and short-lived burst of photons in the energy range of tens to hundreds of kiloelectron volts. The burst was coincident with a bright and active solar flare. This discovery added a new dimension to the study of high-energy particle phenomena occurring on the Sun.

He made many investigations of the geomagnetically trapped energetic particles including "active" experiments.[1] This work required a major technical effort in order to develop instrumentation carried on rockets that could deliver short but intense packets of electrons onto geomagnetic field lines that extended out to great distances from the Earth. The results confirmed and extended several theoretical predictions of charged particle trapping in Earth's magnetic field.

In 1986 John Winckler became professor emeritus and gave up all but a very small amount of extramural research funding. Combining aesthetic inclinations with his scientific insights, he turned to studies of the night sky. Spending many nights at an observatory away from city lights, he was able to demonstrate with fast imaging techniques that some lightning strokes were directed from cloud tops to the ionosphere. His quantitative, high time-resolution measurements stimulated much experimental and theoretical activity among atmospheric research groups across the United States.

THE EARLY YEARS

John Randolph Winckler was born on October 27, 1916, in North Plainfield, New Jersey. Important early influences during his childhood and youth came from his father, an accomplished violinist and amateur photographer. A grandfather was skilled in metal and woodworking. The family, including the young John Winckler, made many outings in surrounding hills and along the streams of eastern New Jersey. These were occasions to observe and study the plant and animal life, and for the grandfather to make paintings and drawings of plants and landscapes. One night during Winckler's youth his father pointed skyward to a display of the aurora borealis. During his professional career Winckler would contribute to the understanding of physical processes that produce the visual auroral displays. The aesthetic appreciation for the natural world Winckler developed in those early years would later become unified with his scientific interests.

As a schoolboy he became interested in the new medium of radio and learned to build AM receivers. To better receive distant radio broadcasts he strung an antenna from the attic of the house to a tall tree. While in high school he built a radio for the family's living room. Winckler's wife, Louise, recalls having seen it. She remembers it as a large object occupying a considerable amount of floor space. During these school years Winckler developed his interest in photography and set up a darkroom to develop and print photographs in the basement of the family home.

John Winckler graduated from high school in 1933 during the Great Depression. His father retained employment as an accountant in a bank during those years. The bank was one of the few in the area that did not close its doors. According to Winckler's children, there had not been a tradition of higher education in his family so Winckler did not immediately go on to college or university although it was financially possible to do so. He then worked at a variety of jobs in and around North Plainfield from 1933 to 1936. According to members of his family, one of these jobs was at a Bell Telephone facility, where his talent and experience with AM radio could be utilized. During these post-high-school years he continued his interest in music and sang at weddings and other occasions. He gave some thought to having a career as a musician. Years later his great baritone voice sometimes would be heard throughout the physics building at the University of Minnesota. While pursuing his musical interests he met concert pianist Louise McDowell. They married in 1943 and raised a family of four daughters and one son.

In 1937, as the United States economy began to improve, Winckler secured employment at a Johns Manville research and development facility. He worked there until 1942. Early in his Johns Manville employment Winckler's intelligence and ingenuity were recognized by one of the engineers who suggested that Winckler obtain higher education. Winckler enrolled in Rutgers University, receiving a bachelor of science degree in 1942, nine years after graduating from high school. During the Rutgers years Winckler continued on at Johns Manville. The work there resulted in his first publication in a scientific journal. It bears the title "Spherical Furnace Calorimeter for Direct Measurement of Specific Heat and Thermal Conductivity." The article was solely authored by Winckler, and its publication appeared about one year after his graduation from Rutgers.

He was then admitted to Princeton University's graduate study program. During the years 1943 and 1944, while studying and carrying out research at Princeton, Winckler held a position with the U.S. Office of Research and Development. Family members believe that the U.S. military, rather than drafting Winckler into active service, preferred to have him continue his studies of supersonic air flow at a time when development of supersonic aircraft was beginning. The title of his Ph.D. thesis was "Interferometric Study of an Axially Symmetric Air Jet"; his advisor was R. Ladenberg. The results of this research were published in *Physical Review* and in *Review of Scientific Instruments*. After receiving his doctor of philosophy degree from Princeton in 1946 he was appointed instructor in physics.

GALACTIC COSMIC RAY STUDIES

After World War II scientists who had worked on radar, nuclear weapons, and other projects having a technical or scientific basis were returning to universities and research laboratories. Physics department planners were seeking areas of basic research to explore using the new techniques and instrumentation developed during wartime. Older areas of research that could be revitalized by the new knowledge and techniques also received attention. One such area of interest was the nature of galactic cosmic rays. At this time little was known about the fundamental character of this physical phenomenon.

Shortly after the end of World War II Princeton University began an experimental cosmic ray program in its Palmer Laboratory. There John Winckler designed and built a system for balloon flight to measure the cosmic ray particle intensity as a function of geomagnetic latitude and its dependence on azimuthal and zenith arrival angles. He took much care to eliminate spurious effects that otherwise could prevent an accurate determination of the cosmic ray intensity. His cosmic ray "telescope" consisted of three trays, each containing 10 Geiger-Mueller tubes. A three-fold coincidence was registered when one or more tubes in each of the three trays gave an output within the resolving time of the electronic circuits. The presence of a center tray reduced the number of spurious coincidence counts, and other measures were taken to insure accuracy of the results. The geometric factor was about 22 cm^2 steradians, quite large for that time. Winckler credited H. V. Neher of the California Institute of Technology for recognizing the value of a counter telescope having the largest possible geometric factor.

Winckler had set up a facility to manufacture and test the Geiger-Mueller tubes for 21 flight systems plus a number of spare tubes. The number of tubes including spares would have been approximately 800.[2] To retrieve data from the flight instruments launched from shipboard, Winckler had ingeniously adapted surplus U.S. Navy equipment originally designed to detect German submarines operating off the coast of the eastern United States. His apparatus was the most complex cosmic ray flight system designed and was successfully flown on balloons up to that time (1947-48).

About 21 flight units were taken aboard the U.S. Navy's seaplane tender, the USS *Norton Sound*. The ship left Port Hueneme, California, in early July and sailed generally southwest to Jarvis Island, near the equator and south of Honolulu, covering the range of geomagnetic latitude 40° to 0°. Only one of the 17 flight units that were launched failed to provide the desired scientific results, a remarkable record of success for those early days of high-altitude experimentation. Three identical cosmic ray telescopes were operated continuously onboard the ship to monitor the sea-level cosmic ray intensity. Winckler credited the Princeton Naval Observatory and professors J. A. Wheeler and G. T. Reynolds for "major support of the effort." In his comprehensive history of cosmic ray research, unpublished at the time of this writing, John E. Naugle gives an assessment of Winckler's latitude survey: "Winckler's experiment is of historical interest because it demonstrated the best data that could be obtained using only Geiger counters and showed the need for more sophisticated instruments for future research on the cosmic radiation."

At this time scientists at several other universities in the United States were also attracted to the problem of galactic cosmic rays as a promising research area. One of these was the University of Minnesota. Winckler accepted their offer of an assistant professorship in the Physics Department, arriving there late in 1949. He continued his program to understand the discrepancies between his measurements and the predictions of geomagnetic theory. One likely source of error was that cosmic ray protons and heavy ions made nuclear interactions in the atmosphere, producing secondary particles. Some of these secondaries would move upward and leave the atmosphere—the "splash albedo." A fraction of these particles would be deflected by the geomagnetic field and re-enter the atmosphere. Measurement of this secondary component would improve quantitative knowledge of the primary cosmic ray number-energy spectrum. He and his graduate students pursued this line of research for a time, using Cerenkov detectors flown on balloons for the first time in order to determine the direction of motion of fast particles at altitudes of about 30 km. This provided him with the flux of upward moving fast particles that would have been counted but not discriminated against by counter telescopes using Geiger-Mueller tubes. By 1950 other groups were combining Cerenkov and scintillation detectors and finding the combination to be a powerful technique for determining the atomic number and velocity of energetic particles arriving at Earth. Moreover, solid-state detectors soon would be introduced. The cosmic ray problem was beginning to be seen in the broader framework of high-energy astrophysics.

THE INTERNATIONAL GEOPHYSICAL YEAR, 1957-1958

The cosmic ray group at the University of Minnesota also included Professor Edward P. Ney and Phyllis Freier. These two scientists were codiscoverers, along with H. Bradt and B. Peters of the University of Rochester, of nuclei having atomic number equal to or greater than 2 in the galactic cosmic rays. With Winckler's arrival the University of Minnesota group was ready for new research initiatives.

From 1955 scientific bodies throughout the world were planning the International Geophysical Year and funding for research projects was becoming available. Freier, Ney, and Winckler developed a proposal to monitor the galactic cosmic radiation intensity during the 18-month period that began on July 1, 1957. Their idea was to keep cosmic ray detectors at an altitude of about 30 km for a substantial fraction of this interval using constant altitude polyethylene (Skyhook) balloons. Each balloon would remain at high altitude from several hours to an entire day. They proposed a payload consisting of three traditional cosmic ray instruments: a Neher-type integrating ionization chamber, a single Geiger-Mueller tube, and a small stack of nuclear emulsions. The latter would record the tracks of heavy cosmic ray nuclei with atomic number 2 and greater. The payload would also include an atmospheric pressure measuring device to obtain the amount of residual atmosphere and a camera to record the ground track of the balloon. The IGY committee accepted the Freier, Ney, and Winckler proposal. The Minnesota project was one of the larger scientific enterprises accomplished during the IGY.

Winckler oversaw the design, fabrication, testing, and calibration of the ion chambers and Geiger-Mueller tubes. He devised the data recording and telemetry systems carried on each balloon and played a major role in organizing the required logistic support for the project. He chose the times when balloon launches would be made and supervised the launch operations for most of the flights. A total of 83 such flights were made during the IGY period. Most launches were made from the Minneapolis, Minnesota area, others from locations in the Midwestern United States, Texas, Alaska, Guam, and Cuba.

Winckler thought it appropriate to launch a balloon carrying the Minnesota standard IGY payload on the very first day of the IGY. The instrument package left Winckler's hands at 0107 GMT. The balloon reached its maximum altitude and floated there collecting data for 20 hours. During the night a brilliant auroral display appeared over Minneapolis. The Geiger counter and the ionization chamber registered large and rapidly fluctuating fluxes of X rays. Winckler and colleagues interpreted the X rays as *bremsstrahlung* produced by electrons with energies ranging from 10 to 100 kiloelectron-volt incident on the atmosphere above the balloon. This result was unexpected, although in 1955 James Van Allen's rockoon group had detected "soft" electrons, but the energy of those electrons was not sufficiently high to produce X rays having tens to hundreds of kV energy observed over Minneapolis on July 1, 1957. Van Allen's discovery of geomagnetically trapped energetic particles was still several months in the future and Gold's general concept of the magnetosphere arrived in 1959. In retrospect Winckler's balloon observations can be seen as one of the earliest observed manifestations of Earth's magnetospheric energetic particle dynamics.

In 1959 Peterson and Winckler published a paper describing a burst of photons in the energy range 200 to 500 kiloelectron volts. It lasted about 20 seconds and was coincident with a bright solar flare. At this time it was known that following great solar flares, nucleons having energies of tens of millions of electron volts to as much as a billion electron volts occasionally appeared in interplanetary space. The result of Peterson and Winckler added a new dimension to solar high-energy particle phenomena.

The intensive coverage of the IGY flights led to an unexpected finding not related to solar phenomena. During two flights in 1958 launched from Minneapolis the detectors responded to "layers of radioactivity observed near the tropopause at Minneapolis, Minnesota." Working with Professor Homer Mantis, a professor of meteorology also at the University of Minnesota, upper-air trajectories were constructed showing that the "radioactivity was produced by nuclear bomb debris about one week old."[3] The air masses could be traced back to sites where Soviet nuclear explosive devices were known to have been detonated.

Winckler made many important contributions to knowledge and understanding of energetic solar nucleonic particles over the years 1959 through 1967. Using his talent and experience in design and construction of instruments that could operate unattended under severe environmental conditions, he provided many instruments for NASA spacecraft beginning with early NASA scientific missions. He contributed to the exploration of the geomagnetically trapped particle populations beginning in 1959 and continued those studies through 1980. Of particular importance were the studies he and colleagues made from data taken on geostationary satellites during periods when they were located above the night side of Earth over the period 1968 to 1980.

With coauthors he published several examples of solar high-energy photon emissions associated with solar flares following the first observed energetic photon burst made with Peterson in 1959. Of particular interest was the observation of a 16-second periodicity in the emission of solar X rays and solar microwave emission (with Parks).

Largely as a result of his discoveries during the International Geophysical Year, John Winckler became well known to researchers in European laboratories. He was invited to the solar physics branch of the Observatoire de Paris on several occasions and to the Centre d'Etude Spatiale de Rayonnement in Toulouse, France. He was invited to the Soviet Union on several occasions to present papers at the Leningrad Seminars, and he visited laboratories in and around Moscow at their invitation.

CONTRIBUTIONS TO THE TECHNOLOGY OF HIGH-ALTITUDE RESEARCH BALLOONS

After the Second World War large-volume balloons (~3000 m^3 and larger) were fabricated from thin (0.025 to 0.007 mm) polyethylene film. The basic design of these balloons was due to Jean Picard. The General Mills Corporation was among the first to fabricate these aerostats. Cosmic ray researchers were quick to make use of the polyethylene balloon to carry payloads having mass of tens and even hundreds or more kilograms to altitudes of about 30 km, where they would remain at a more or less constant altitude for 10 or more hours. Because of catastrophic failures resulting in the loss of scientific payloads and in property damage, an activity was initiated at the University of Minnesota's Department of Physics to improve performance of high-altitude balloons. The effort was led by professors Charles Critchfield, Edward Ney, and John Winckler. The project was supported by the U.S. Air Force, Army, and Navy, and its activities were classified during the years 1951-56. (All project documents were declassified in 1958.) The interest to the U.S. military in high-altitude, constant-level balloons was to place down-looking cameras in the balloon payloads, launch the balloons in Europe, and let the high-altitude balloons drift across the Soviet Union. The cameras would then be retrieved in "friendly" lands or waters. When U-2 aircraft became available, the University of Minnesota balloon project was swiftly cancelled.

The aim of the project at the University of Minnesota was to put all aspects of high-altitude balloon flight on a sound scientific and engineering basis. It would be necessary to understand the thermodynamics of balloon flight during both day and night and to develop better launch techniques, especially for heavy payloads. A major cause of balloon failure was thought to be large, circumferential tensions in the balloon film. Charles Critchfield and graduate student Leland Bohl calculated a balloon shape that would greatly reduce these tensions. Testing the design required full inflation of the balloons with an air-helium mixture. The test program was carried out in a large hangar in North Carolina used in World War II to house and maintain the blimps patrolling the eastern Atlantic seaboard for German submarines. At Winckler's request one of his graduate students designed and built a tensiometer to measure stresses in a biaxially stressed film. The student then carried out the circumferential and tangential measurements from the bottom of the balloon to its top and around several circles of latitude. Winckler shared responsibility for the flight testing of balloon shape designs with Professor Edward P. Ney. On a handwritten note found in his papers Winckler states that over his career he had full or shared responsibility for "more than 500 launches." His records show that he made approximately 150 balloon flights carrying purely scientific payloads. The inference is that Winckler and Ney conducted about 350 balloon launches under the technology development program over the years 1951 to 1956.

In addition to the large polyethylene balloons the project had designed a smaller balloon of Mylar film called the Tetroon. It was used for carrying small payloads to measure atmospheric parameters such as temperature and intensity of infrared radiation. Having trained the launch crews, Winckler or Ney did not have to personally supervise all launches, particularly the smaller balloons. Winckler also took on a major responsibility for the design and development of the instrumentation carried on all balloon flights—he was throughout his career an ingenious designer of electronic and mechanical devices. But his underlying interest was always to look more deeply into the workings of the natural world.

EXPLORING THE MAGNETOSPHERE WITH ARTIFICIAL ELECTRON BEAMS: THE ECHO PROJECT[4]

In the late 1960s John Winckler began a program of rocket experiments he called the "electron echo series." The initial aim was to verify the theory of electron motions in the Earth's magnetosphere, as Winckler did not entirely trust theoretical calculations that had never been tested against experiment. The basic idea was to fire a beam of electrons from a rocket above the atmosphere so that it would be reflected in the Southern Hemisphere and return to the rocket. The electron drift theory, largely due to Hannes Alfvén, predicted that the electrons would return to a point east of the injection point by an amount depending on the electron energy and on the electric and magnetic fields in the magnetosphere. Each electron echo flight raised new issues, and the next flight was planned to solve them.

The first experiment to fire an electron beam from a rocket had been carried out by Wilmot Hess at the NASA Goddard Space Flight Center. Hess's objective was to provide an accurately known injection to calibrate the auroral luminosity that it would produce. Winckler's first electron echo experiment, launched from Wallops Island, Virginia, on August 13, 1970, was successful, and echoes (electron reflections) were detected. In all subsequent experiments electrons were reflected in the Southern Hemisphere by convergence of the Earth's magnetic field, but from Wallops Island they were backscattered by the atmosphere, as the reflection point lies within the atmosphere.

In the next experiment Winckler turned to exploring the Earth's magnetic field in the vicinity of the auroral zone, which was thought to occur on the boundary between the "open" field lines connected to the interplanetary magnetic field and closed field lines that return to Earth. Electron Echo II was launched from Fort Churchill on Hudson Bay, Canada, on September 25, 1972. No echoes were detected, indicating that those field lines there were "open." All five subsequent experiments were launched from the Poker Flat Research Range, near Fairbanks, Alaska, with the overall intention of exploring the Earth's magnetic field and comparing the data with various models. Poker Flat is magnetically south of Ft. Churchill and the field lines there are "closed." In Echo 7 Winckler and Nemzek showed that the experiment also could measure electric fields, even electric fields parallel to the magnetic field, a very challenging experimental problem. Winckler also found that the ionospheric plasma was considerably heated by plasma instabilities produced by the electron beams. The later Echo experiments carried wave and plasma oscillation analyzers in their payloads.

Winckler's successful injection of electron beams from a rocket led other groups to start their own programs. Many of these experiments had little to do with reflecting an electron beam from the southern conjugate point but were trying to understand the heating of the local plasma and the generation of plasma waves and radiation. Such waves and radiation had been observed from Echo I, and the mechanisms involved are still not completely understood.

The Echo project was a major undertaking for a relatively small research group working within a university academic department. The machine and electronics shops, though not extensive, had highly skilled personnel. They contributed greatly to the success of the project, but equally important was the small group of graduate students who fully participated in the construction and conduct of the experiments and the data interpretation.

CLOUD-TOP-TO-IONOSPHERE LIGHTNING

In 1986 John Winckler became professor emeritus and ceased working on large NASA research projects. He continued his interest in the aurora and made casual auroral observations from backyard and lakeside, but often went to the O'Brien observatory operated by the University of Minnesota at a relatively dark site northeast of the twin cities of

Minneapolis and St. Paul. There he fashioned a simple light bucket consisting of an aluminum tube with a photomultiplier tube placed at its bottom. Pointed toward the dark sky the photometer recorded rapid flashes of light. Pursuing this result, Winckler arranged three such light buckets off the zenith with their axes 120° apart. Making use of the polarization of the light flashes due to Rayleigh scattering, he was able to determine the direction from which the light flashes were coming. He concluded that many of the flashes were due to lightning strokes from thunderstorms in the general direction of Florida.

Winckler then sought to image night-sky light flashes at high time and spatial resolution. He had a high-performance charge coupled device television camera remaining from the Echo project, but it was in need of renovation that would cost $7,000. He had a small amount of funds remaining from his NASA project, and the chairman of the University of Minnesota Physics Department provided additional funds for repair of the camera. With its repair Winckler began to make images of the night sky. During the night of July 5-6, 1989, he pointed the camera toward a thunderstorm on the northern horizon. When he viewed the individual TV frames he found twin flashes of light lasting about 0.03 second and extending from cloud top to about 20 km above the ground. He concluded that tropospheric electrical phenomena could extend into the ionosphere. Several weeks later he confirmed the July result while observing thunderstorm activity to the south of his observing site. To analyze the frames of the TV records, Winckler had personally assembled the necessary equipment in his home. He also used his home laboratory to produce camera-ready copy for his publications at a savings to himself of several thousand dollars.

The work of Winckler and his students on upward lightning galvanized several atmospheric research groups into developing major programs, some including suitably instrumented aircraft, to further investigate the phenomenon of cloud-to-ionosphere lightning. Funding agencies soon began to receive proposals of up to $1 million to support research on cloud-to-ionosphere lightning. Winckler's total investment had been no more than $20,000. Several of the groups starting up research programs turned to Winckler for advice on designing observing programs.

From his home, the O'Brien Observatory, and lakeside camp sites—always facing northward for the best viewing—he continued to photograph auroras with still and movie cameras. Many friends and colleagues throughout the world received prints of these superb photographs, often on "Season's Greetings" cards. In this way he continued his long-time interest in combining aesthetics with science.

IN ADDITION TO his contribution to the section on John Winckler's Echo project, Professor Paul Kellogg made many helpful comments on other parts of this memoir. Frank McDonald and John Naugle also made helpful suggestions.

HONORS AND AWARDS

1962	American Institute for Aviation and Astronautics, Space Science Award
1965-66	Guggenheim fellow, France
1972	Doctor honoris causa, Universite Paul Sabatier, Toulouse, France
1978	Arctowski Medal, National Academy of Sciences
1985	Soviet Geophysical Committee International Geophysical Year Commemorative Medal
1991	NASA Medal for Exceptional Scientific Achievement
1996	Member, National Academy of Sciences

NOTES

1. Active magnetospheric experiments include introduction of ion clouds into the magnetosphere and injection of fast electrons along geomagnetic field lines.

2. When Winckler arrived at the University of Minnesota, he set up a Geiger-Mueller tube fabrication facility there. Each of his early graduate students underwent the rite of measuring the count rate versus applied voltage of dozens of Geiger-Mueller tubes to ensure each one had a broad count-rate "plateau."

3. *J. Geophys. Res.* 65(1960):R3515-19.

4. Except for the last paragraph, this section was written by Professor Paul J. Kellogg of the University of Minnesota.

SELECTED PUBLICATIONS

1943

Spherical furnace calorimeter for direct measurement of specific heat and thermal conductivity. *J. Am. Ceram. Soc.* 25:339-49.

1948

Interferometric studies of faster than sound phenomena. Part I. Gas flow around various objects in a free homogeneous, supersonic air stream. *Phys. Rev.* 73:1359-77.

1950

With T. Stix, K. Dwight, and R. Sabin. A directional latitude survey of cosmic rays at high latitude. *Phys. Rev.* 79:656-69.

1957

With K. A. Anderson. High-altitude cosmic-ray latitude effect from 51° to 65° N geomagnetic latitude. *Phys. Rev.* 108:148-54.

With L. E. Peterson. Large auroral effect on cosmic-ray detectors observed at 8 g cm-2 atmospheric depth. *Phys. Rev.* 108:903-4.

1958

With L. E. Peterson. Short gamma-ray burst from a solar flare. *Phys. Rev. Lett.* 1:205-206.

With L. E. Peterson, R. Arnoldy, and R. Hoffman. X-rays from visible aurorae at Minneapolis. *Phys. Rev.* 2nd series 110:1221-31.

1959

With E. P. Ney and P. J. Kellogg. Geophysical effects associated with high altitude explosions. *Nature* 183:358-60.

Balloon observations of solar cosmic rays on March 26, 1958. *J. Geophys. Res.* 64:685.

1960

With H. T. Mantis. Balloon observations of artificial radioactivity at the base of the stratosphere. *J. Geophys. Res.* 65:3315.

1964

With R. L. Arnoldy. Comparison of the total cosmic radiation in deep space and at the Earth during the March-April 1960 events. *J. Geophys. Res.* 69:1697.

1968

With K. A. Pfitzer. Acceleration of energetic electrons observed at the synchronous altitude during magnetospheric substorms. *J. Geophys. Res. Space Phys.* 73:5792-97.

1971

With R. A. Hendrickson and R. W. McEntire. Electron Echo experiment: A new magnetospheric probe. *Nature* 230:564-66.

1974

With R. A. Hendrickson and R. W. McEntire. Electron Echo experiment 1: Comparison of observed and theoretical motion of artificially injected electron in the magnetosphere. *J. Geophys. Res.* 16:2343-53.

1975

With G. Israelson. Measurements of 3914 angstroms light production and electron scattering from electron beams artificially injected into the ionosphere. *J. Geophys. Res.* 80:3709-12.

1976

With R. A. Hendrickson. Echo III: The study of electric and magnetic fields with conjugate echoes from artificial electron beams injected into the auroral zone ionosphere. *Geophys. Res. Lett.* 3.

1980

The application of artificial electron beams to magnetospheric research. *Rev. Geophys. Space Sci.* 18:659-82.

1984

With J. E. Steffen, P. R. Malcolm, K. N. Erickson, Y. Abe, and R. L. Swanson. Ion resonances and ELF wave production by an electron beam injected into the magnetosphere: Echo 6. *J. Geophys. Res.* 89:7565-71.

1985

With R. L. Arnoldy and C. Pollock. The energization of electrons and ions by electron beams injected in the ionosphere. *J. Geophys. Res.* 90:5197-5210.

1989

With R. J. Nemzek and J. R. Winckler. Observation and interpretation of fast sub-visual light pulses from the night sky. *Geophys. Res. Lett.* 16:1015-18.

1990

With R. C. Franz and R. J. Nemzek. Television image of a large upward electrical discharge above a thunderstorm. *Science* 249:48-51.

1993

With R. C. Franz and R. J. Nemzek. Fast low level pulses from the night sky observed with the Skyflash program. *J. Geophys. Res. D* 98:8775-83.

1995

Further observations of cloud-ionosphere electrical discharges above thunderstorms. *J. Geophys. Res.* 100:14335-45.

1996

With W. A. Lyons, T. Nelson, and R. J. Nemzek. New high-resolution ground-based studies of sprites. *J. Geophys. Res.* 101:6997-7004.