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.)

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