DOCUMENTS OF THE GENERAL FACULTY

REPORT OF THE MEMORIAL RESOLUTION COMMITTEE FOR KARL AUGUST FOLKERS[1]

The special committee of the General Faculty to prepare a memorial resolution for Karl August Folkers, professor emeritus, chemistry, has filed with the Secretary of the General Faculty the following report.

John R. Durbin, Secretary
The General Faculty

IN MEMORIAM
KARL AUGUST FOLKERS

Karl August Folkers, Ashbel Smith Professor Emeritus of Chemistry, and director, Institute for Biomedical Research, died on December 9, 1997, at Lake Sunapee, New Hampshire. His beloved wife of 60 years, Selma Leona Johnson, preceded him in death in 1992. His son, Richard Karl Folkers, daughter, Cynthia Carol Jamieson, and two grandchildren survived him.

Karl Folkers will be remembered for his many major contributions and assistance to many other investigators over a period of more than six decades of chemical research, especially on the structure, synthesis, and medical use of naturally-occurring, biologically-active compounds, such as alkaloids, antibiotics, B-vitamins, hormones, and coenzymes. His unique roles in structural determination and synthesis of B-vitamins, and the isolation and chemical nature of vitamin $B_{12,}$ provided major advances toward making B-vitamins available for nutritional supplementation. His extensive collaboration with others resulted also in the structure and synthesis of the first hypothalamic hormone, evidence for the last position assignment of substituent groups in coenzyme Q_{10}, the synthesis of coenzyme Q_9, and the structure and synthesis of the isoprenoid precursor, mevalonic acid. His awards and honors covered almost all of those in his field of research. However, he valued most highly his long-term relationships with the many collaborators and friends with whom he worked and consulted, and especially the knowledge that somehow, with others, he contributed to the health and lifespan of individuals benefitting from his work.

Karl August Folkers was born in Decatur, Illinois, on September 1, 1906. His father, August William Folkers, born June 5, 1878, in Eckwarden, State of Oldenburg, Germany, moved to the United States with his parents in 1882. His mother, Laura Susan Black, was born on March 4, 1878, in Reynolds County, Missouri. As an only child, Karl had the benefit of a mother who, as the oldest, assisted in rearing her many brothers and sisters. Karl read books on chemistry, worked with chemistry sets and apparatus before taking the subject in high school, and read about chemistry as a profession early in his life. While working in food service and in the chemistry library at the University of Illinois, he completed his undergraduate degree with a senior thesis directed by Carl (Speed) Marvel, who encouraged him to go to the University of Wisconsin for graduate work. At Wisconsin, on fellowship appointments, Karl worked with Homer Atkins on high-pressure hydrogenation and discovered copper-barium chromite as a catalyst for reduction of esters to alcohols. Upon completing his PhD, his reading on biochemistry led him to do postdoctoral work at Yale University on the synthesis of pyrimidines with Treat B. Johnson, who introduced him to pharmaceutical chemistry. While at Yale, Karl met Selma Leona Johnson (born July 5, 1910, in Philadelphia). Their marriage on July 30, 1932, began their lifelong, caring relationship of mutual support and admiration for each other.

Karl's decision to initiate his professional career at Merck in 1934 was influenced not only by his interest in

[1] Title header corrected on June 5, 2001.

pharmaceuticals but also by the new “pure research” building and activity being created there. His very successful work on isolation and structures of Erythrina alkaloids began when his director, Randolph Majors, handed him a bag of Erythrina seed to see what he could do with it, leaving the problem entirely to him. Karl gave Majors credit for his foresight in promoting vitamin research, and for his advice to be aware of outside research and to visit other laboratories doing good research.

Appointed assistant director of research in 1938, Karl was assigned the group that had just isolated vitamin B_6 (pyridoxine) and had limited the structure to two possible isomers, analogous to the work of the Richard Kuhn group in Germany. Karl and his group completed the final structure and provided the first synthesis of vitamin $B_{6,}$ for which they were corecipients of the 1940 Mead Johnson Company Award of the American Institute of Nutrition.

The total synthesis of pantothenic acid, discovered and partially synthesized by Roger Williams, was achieved in 1939 when Karl's group completed the structure of the lactone moiety with which Williams was working and needed collaboration. Karl received the American Chemical Society Award for meritorious work in pure chemistry in 1941.

Deeply involved in structural studies of penicillin and aware of the status of Vincent du Vigneaud’s difficulty in discerning between two possibilities for the structure of biotin, Karl’s group discovered that the hydrogen in Raney nickel could be used to remove the sulfur in these compounds, which was of great value in structural determination. This allowed a joint publication of the structure of biotin, and Karl and his group then provided 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). From 1945 to 1951 Karl was director of the organic and biochemical research department at Merck and was involved in the isolation and structure of antibiotics, particularly the isolation and structure of streptomycin.

While visiting the University of Maryland, Karl learned of Mary Shorb’s Lactobacillus lactis Dornier test that responded to commercial anti-pernicious anemia extracts from liver. He arranged for her to test a group of samples, including a clinically-active liver extract preparation passed through alumina, which appeared colorless in the shape of the lyophilized water crystals. Fermentation residues from antibiotic production were found to be potent sources of the 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 the structure was outstanding for the large molecule with its cobalt porphyrin-like ring and side chain interacting with cobalt complexed with cyanide. Although the final detailed structure was completed by x-ray diffraction elsewhere, the work of Karl and his group made vitamin B_{12} available, and its identity with the animal growth factor was quickly established. Karl and Mary Shorb were corecipients of the 1949 Mead Johnson Award for their work on vitamin B_{12}.

Enlarged by a merger of Merck with Sharpe and Dohme, including Lemuel Wright and Helen Skeggs, the Folkers 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 made possible direct approaches to the control of cholesterol biosynthesis associated with heart disease.

In 1958, Karl and his Merck group confirmed the structure of coenzyme Q_{10} proposed by Fred Crane and his colleagues at the University of Wisconsin, demonstrated that CoQ_{10} from beef and human heart were identical, and synthesized CoQ_9. Coenzyme Q, which he felt should be named vitamin Q, became one of Karl’s major research interests for the remainder of his life.

Karl, after moving through several changes in his responsibilities 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), resigned from Merck in 1963 to accept the position of president and chief executive officer at Stanford Research Institute. He held this position until 1968.

During this period, the institute increased its staff over 50 percent, doubled its revenues, and successfully

completed a land and new building program. Karl continued his research, particularly on the biosynthesis of coenzyme Q and its role in genetic dystrophy in mice.

In 1968, Karl accepted an appointment as professor of chemistry and pharmacy at The University of Texas at Austin, and as director of his newly-established Institute for Biomedical Research. 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. Karl and his group provided the structural proof and synthesis of this first hypothalamic hormone, TRH, in 1969.

For his role in the structure and synthesis of the first hypothalamic hormone, Karl was corecipient with Shally and Bowers of the 1969 Van Meter Prize of the American Thyroid Association. Bowers and Folkers continued extensive research on hypothalamic hormones and their analogs for over two decades, with the leutinizing releasing hormone, LHRH, and its analogs receiving major attention. Studies on the activities of these analogs as antagonists and agonists of LHRH and their toxicities provided the basis for design of several analogs with potential medical use. The synthesis of inhibitory analogs of substance P provided the means by which insight into the role of this long-known peptide hormone could be effectively studied, and extended to worldwide cooperative studies in this general area of research on peptide hormones.

Karl's Institute for Biochemical Research worked with Dr. John Ellis on extending his observation that vitamin B_6 alleviated the carpal tunnel syndrome in his patients. Double-blind, cross-over placebo controlled studies not only confirmed the effectiveness of vitamin B_6, but also provided data that deficiencies of the coenzyme of vitamin B_6 in erythrocyte transaminase required twelve weeks of supplementation of vitamin B_6 to become saturated in patients. Subsequently, a patient with deficiencies of both vitamin B_6 and riboflavin was found to respond significantly to riboflavin and completely to both vitamins. Karl attributed the need for riboflavin to its coenzyme role in synthesis of the vitamin B_6 coenzyme. Such biochemical evidence for the cause of disease was a driving force in his research work.

Karl's search for medical uses for coenzyme Q resulted in the observation that inadequate biosynthesis does occur in tissues of patients with many different disorders and can result from deficiencies of certain vitamins. With many collaborators, it was demonstrated that benefits result from coenzyme Q administered to patients with muscular dystrophy, periodontal disease with deficiencies in gingival tissue, hypertension, and cardiomyopathy with life-extending effects in advanced stages. Potential benefits were also observed in cancer patients. His laboratory developed the means of determining coenzyme Q in one drop of blood, making the search for deficiencies easily available.

Karl's Institute for Biomedical Research (IBR) involved undergraduate and graduate students, postdoctoral fellows, and many outstanding collaborators from throughout the world. The Folkers' maintained close relationships with them all from their Austin home or from their Lake Sunapee home in the summer.

After the death of his wife on August 12, 1992, Karl's health, but not his research activity, began to decline. For the last two years of his life, he actively directed, with the aid of his colleague Richard Willis, his Institute for Biomedical Research from his Lake Sunapee summer home. He remained actively involved in research through his final day.

Karl created the Folkers Foundation to support biochemical research on causes of human disease. His lifelong pursuit of discoveries that would identify such causes and improve the life and health of those afflicted by various diseases would be continued in the work pursued by the Foundation, which will generate a fitting and permanent legacy of the life of Karl Folkers.

Karl, with his collaborators, published more than 700 papers in scientific journals and presented an equally large list of invited lectures and papers at scientific meetings. For his outstanding work, he received honorary doctoral degrees in science from Philadelphia College of Pharmacy and Science (1962), Uppsala University, Sweden (1969), University of Wisconsin (1970), University of Illinois (1973), and an Honorary Degree in Medicine and Surgery, University of Bologna, Italy (1989).
Other awards include: 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); American Chemical Society-Priestly Medal (1986); President's National Medal of Science (1990); Karl Folkers Centennial Research Award (first), Rutgers University (1992); Infinity Award, American Academy of Anti-Aging Medicine (1996).

Karl helped organize, and chaired, many international research conferences, including several for the Gordon Research Conferences, for which he 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 (president in 1962), and on various advisory committees for the National Academy of Science (elected a member in 1948) and many American and foreign universities in scientific areas. He was elected as an honorary member of Societa Italiana de Scienze Pharmaceutiche (1969) and Phi Lambda Upsilon (1966), as one of the Honorary Fellows of the American Institute of Nutrition (1982), and as a Foreign Member, Royal Swedish Academy of Engineering Sciences (1966).

This memorial resolution was prepared by a special committee consisting of Professors William Shive (chair), Bob G. Sanders, and Richard A. Willis, and will be incorporated with additional material for publication in Biographical Memoirs, National Academy of Sciences.

Distributed to the Dean of the College of Natural Sciences, the Executive Vice President and Provost, and the President on March 13, 2001. Copies are available on request from the Office of the General Faculty, FAC 22, F9500. This resolution is posted under "Memorials" at: http://www.utexas.edu/faculty/council/.