Karl August Folkers (1906–1997)

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Karl August Folkers was one of the most imaginative and productive organic chemists who worked in the field of biological chemistry during the past century. Most of his major contributions were made during the period in which he was associated with the Merck Company in Rahway, New Jersey beginning in 1934. The decade following his appointment at Merck was noteworthy for the intense worldwide activity that biologists devoted to the isolation and identification of growth factors for animals, birds and bacteria, many of which turned out to be vitamins. Folkers’ laboratory became a center for the purification, structural determination and synthesis of a large number of factors, including vitamin B-6 (pyridoxine, pyridoxal and pyridoxamine), pantothenic acid, biotin, vitamin B-12, mevalonic acid and ubiquinone (coenzyme Q). Folkers was admitted to the American Institute of Nutrition (now ASNS) in 1954 and was elected a Fellow in 1982.

Beginnings

Karl Folker’s first paper at Merck was a report on the preparation of apocodeine from codeine. Immediately thereafter he undertook the preparation and structural determination of a variety of Erythrina alkaloids, work that lasted 10 years and produced 23 papers. This program overlapped other studies of the B-complex vitamins that began in 1938 when he became Assistant Director of Research at Merck with an expanded research group. In 1930, Folkers and his co-investigators determined the structure of pyridoxine (1) followed by its synthesis (2). In 1944 they carried out the synthesis of pyridoxal and pyridoxamine (3). In 1940, Folkers’ group synthesized pantothenic acid (4), in 1943, biotin (5), and in 1955, lipoic acid (6).

Early research activities at Merck

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The search for the anti-pernicious anemia factor (vitamin B-12), in which Folkers was a major player, began in 1926 when Minot and Murphy showed that beef liver contained a factor that produced a remission in patients with pernicious anemia (7). Edwin Cohn, a physical chemist at the Harvard Medical School, was enlisted by Minot to begin the fractionation of bovine liver for concentrates that were tested in patients with pernicious anemia. It soon became clear to Cohn that the active principal was not associated with the major components of the liver, namely, proteins, fats or carbohydrates. The biological activity was associated with a residue that appeared after proteins had been coagulated and the lipids removed by alcohol-ether extraction. Such a product (called Fraction G) had a potency in humans of ~10 times that of whole liver when given orally and 25 times if given parenterally. This fraction, furthermore, was devoid of the known vitamins. Fraction G became the starting point for subsequent attempts to isolate the anti-pernicious anemia factor. By 1935, Dakin and West (8) reported purification of the anti-pernicious factor of ~100-fold by a combination of precipitation with Reinecke salt and ammonium sulfate fractionation. Fifty milligrams of this material gave vigorous reticulocyte response and regeneration of red cells in pernicious anemia patients in relapse.

In 1942, Folkers decided to try his luck at purifying the anti-pernicious factor. He arranged a collaboration with Randolph West, a hematologist at Columbia University, who had worked previously with Dakin, to carry out clinical assays on liver fractions he would supply. He was fully aware of the difficulties that many investigators both in the United States and in Europe were having with this problem, but he also was aware that more discriminating methods to purify the factor such as chromatography had not been used thus far. Therefore, he assembled a team of chemists to attack this problem. No publications on this subject emanated from the Merck laboratories in the six-year interval between the origination of this fraction and the crystallization of vitamin B-12 in 1948.

Folkers was no doubt spurred on by the report in 1946 by Emery and Parker from the Glaxo laboratory in the UK (9) that by using phenol extraction of liver concentrates followed by adsorption on charcoal, they had obtained a purer sample of this factor. This fraction, furthermore, was devoid of the known vitamins. Fraction G became the starting point for subsequent attempts to isolate the anti-pernicious anemia factor. By 1935, Dakin and West (8) reported purification of the anti-pernicious factor of ~100-fold by a combination of precipitation with Reinecke salt and ammonium sulfate fractionation. Fifty milligrams of this material gave vigorous reticulocyte response and regeneration of red cells in pernicious anemia patients in relapse.

During the period in which vitamin B-12 was being purified at Merck (from 1942 to 1948), Folkers and his co-workers also published 22 papers on the streptomycines antibiotics, especially the chemistry of streptomycin and neomycin. Among other things, it was learned that Streptomyces griseus fermentation mash was a good source of vitamin B-12. They showed that crystals derived from this bacterial fermentation were identical to those obtained from liver (18). In fact, bacterial fermentation became the major commercial method of producing vitamin B-12 for industry and the medical profession.

Structural studies followed the isolation of vitamin B-12 at Merck and in the laboratory of Alexander Todd in Cambridge. The cobalt atom was identified by both groups. The "nucleotide"-like moiety (phosphoribosyl-5,6-dibenzimidazole) was identified by the Merck group (19). The central corrin ring system of pyrroles analogous to the porphyrin system was identified by the Cambridge group (20), and the precise structure of the corrin ring system was determined by X-ray diffraction by Dorothy Hodgkin's group at Oxford (21). The final structure was published by Hodgkin and colleagues in 1956 (22).

After their conquest of vitamin B-12, Folkers and his group at Merck were looking for other worlds to conquer. The strategy that worked in the case of vitamin B-12, i.e., identify a factor with biological activity in animals, assay it in a microbiological system and isolate the unidentified factor by column chromatography, seemed applicable to other unknown factors. In 1948, Novak and Hauge at the Purdue University Agricultural Experiment Station reported that distiller-dried solubles contained an unidentified growth factor for rats that they called vitamin B-13 (23). Thanks to the work of R. J. Williams at the University of Texas (24), the microbiologists at Merck were aware that Lactobacillus casei requires acetate in addition to the usual components of a basal medium, and that distiller solubles were provided this unknown "acetate replacing factor" (25). In 1956, Wright et al. at Merck (26) using an assay in Lactobacillus casei reported the isolation of acetate-replacing factor as a low-molecular-weight anionic colorless oil very soluble in water. Two months later, Wolf et al. (27) showed that the new factor was β-hydroxy-β-methyl-d-valerolactone and confirmed the structure by synthesis. They
named the new molecule mevalonic acid, labeled it with $^{14}$C and showed that the lactone was incorporated into cholesterol in rat liver homogenates more actively than acetate (28). In 1960, Bucher et al. (29) showed that $\beta$-hydroxy, $\beta$-methyl glutaryl-CoA (HMG-CoA) was the precursor of mevalonic acid in liver slices, and that its conversion to cholesterol was blocked by fasting, due to an inhibition of HMG-CoA-reductase.

In 1955, Festenstein et al. (30) in Morton’s laboratory in Liverpool isolated a nonsaponifiable lipid with a striking ultraviolet absorption at 272 nm from the intestinal mucosa of horses. Because the new substance was identified as a quinone and was found to be widely distributed in animal tissues, Morton named it ubiquinone. Two years later in David Green’s laboratory at the University of Wisconsin, Crane et al. (31) observed a novel quinone in lipid extracts of mitochondria and named it coenzyme Q because of its participation in the electron transport chain. Because of Folkers’ known prowess in the structural determination of natural products, Crane traveled to Rahway to seek help from the Merck group in solving the structure of this novel quinone. Within a year, Folkers’ group had determined the structure of coenzyme Q10 and other homologues isolated from different organisms (32).

A similar conclusion was reached by Isler at the Hoffman La Roche laboratories in Basel on samples supplied by Morton (33). The structure of human Q10 is 2,3-dimethoxy-5-methyl-6-decaprenyl benzoquinone.

I first met Karl Folkers in London at Ciba House in 1960 where he had organized a conference on Quinones in Electron Transport (34). When his paper on the structure of ubiquinone/coenzyme Q appeared in 1958, I was intrigued by its similarity to vitamin K and wondered whether coenzyme Q was an essential nutrient. We initiated studies to answer this question and found no evidence that restricting coenzyme Q in the diet had any effect upon hepatic levels of coenzyme Q in weanling rats over a 2-wk period. We concluded that coenzyme Q was not an essential nutrient and began studies to determine its biosynthesis. We reported our initial findings at the FASEB meeting in 1959, followed by a full paper in early 1960 (35) and others later (36). On the basis of these reports, Folkers invited me to attend the Ciba Foundation meeting in London in 1960. Beginning at that meeting and continuing thereafter, Folkers and I formed a friendship that lasted for years and eventually involved our wives during visits to New London, NH where we both had cottages on Lake Sunapee. Folkers bought his place in 1950 because of its proximity to Colby Junior College where Gordon Conferences were held annually.

Karl Folkers’ contributions to biological chemistry during his tenure at Merck were outstanding and revolutionized concepts in many areas of science. He was highly revered by his colleagues for his imaginative leadership. His monograph on Vitamins and Coenzymes with co-author Arthur Wagner published by Wiley and Sons in New York in 1964 is a classic that integrates knowledge of the chemistry of the vitamins with their biological action. In 1951, he received the Scientific Award of the Board of Directors at Merck “To honor his vision and research acumen, and to honor his many scientific contributions to mankind, especially his research on antibiotics and vitamins, culminating in the isolation and crystallization of vitamin B-12” and in 1956 he was promoted to Executive Director of Fundamental Research.

The move to the Stanford Research Institute

In 1963, Folkers resigned his position as Vice-President for Explorative Research to which he had been promoted in 1962 to accept a position as President and Chief Executive Officer of the Stanford Research Institute (SRI) with a courtesy appointment as Professor of Chemistry at Stanford University. It’s not clear why he did this, although at the time he told me that he wanted to expand Merck’s research program on coenzyme Q to involve applications to human disease, and that the top management did not agree with him. In any event, he assumed the job of running the Stanford Research Institute, a multidisciplinary contract research organization with 2000 employees and a budget of $35 million. The overall program of the Stanford Research Institute expanded under Folkers with an increase in building, land holdings, total personnel and budget. He continued some work on coenzyme Q dealing with new homologues and biosynthesis in bacteria.

The University of Texas and beyond

In 1968, he resigned from his appointments at the SRI to accept a position at the University of Texas as Professor of Chemistry and Director of a newly created Institute for Bio-medical Research. It seems that Folkers left SRI because of overtaxing administrative duties and a lack of time for personal research. He longed to be in a more academic environment where he could continue his crusade to make coenzyme Q a therapeutic force in clinical medicine. Unfortunately, many of his ventures in this area were with unsophisticated physicians who did not have a critical attitude toward clinical investigations; this work, comprising some 300 papers, has not in general been accepted by the medical profession. While at the University of Texas, he did work productively with Andrew Schally on the chemistry of the thyrotropin-releasing hormone (37).

Dr. Folkers received many honors and awards for his creative work in the isolation, structural determination and synthesis of compounds of biochemical interest. These include two Mead Johnson and Company awards for research on the vitamins of the B-complex, the American Chemical Society Award in Pure Chemistry, the Perkin Medal of the Society of Chemical Industry, the Nichols Medal from the New York Section of the American Chemical Society, the Spenser Award of the Kansas City Section of the American Chemical Society, the Van Meter Prize of the American Thyroid Association and the Priestly Medal of the Board of Directors of the American Chemical Society. He was elected to the National Academy of Sciences in 1948 and served as President of the American Chemical Society in 1962. He received five honorary degrees from the Philadelphia College of Pharmacy, the University of Uppsala, the University of Wisconsin, the University of Illinois and the University of Bologna. He received a Presidential Certificate of Merit from Harry S. Truman in 1950 and the President’s National Medal of Science from George Bush in 1990.

Dr. Folkers and his family used their summer home in New London as a vacation retreat even after they moved out of New Jersey. Folkers’ hobbies were photography and boating, which he enjoyed in New Hampshire. Mrs. Folkers used to move there on the first of June and stay until late September. Although Folkers was healthy during most of his long life, during his last years he developed some neurological changes in his legs and was forced to use a wheelchair at times. He died suddenly in New London on December 7, 1997 after returning from a trip to Sweden. He is buried in New London.

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