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JOSEF FRIED
1914–2001

A Biographical Memoir by

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JOSEF FRIED

July 21, 1914–August 17, 2001

BY NELSON J. LEONARD AND ELKAN BLOUT

JOSEF FRIED WAS AN outstanding organic chemist who made very special contributions to the field of medicine. "Gus" Fried was one of the few scientists, but now increasing in number, who have had outstanding careers in both an industrial organization and an academic environment. In his graduate and postgraduate study at Columbia University he concentrated on methods of synthesis of cardiac aglycones. Following Columbia he had two industrial positions, the second one being at the Squibb Institute for Medical Research. In this friendly scientific setting he found, in his research on corticoids, that fluorine substitution at the 9 position of hydrocortisone increased its anti-inflammatory potency. This finding upset the belief that the activity of the natural material could not be enhanced. He also discovered that 16, 17-acetonide corticoids increased the potency while eliminating the salt-retaining effect. This discovery led to the commercialization of the first superpotent anti-inflammatory steroids. The fluorosteroids have revolutionized the treatment of many endocrine and skin disorders.

After 20 years at Squibb, Josef Fried moved to the University of Chicago as a professor in the Ben May Laboratory for Cancer Research and then in the departments of biochemistry and chemistry, where his research expanded

broadly in the area of natural products having biological activity. Within the class of human hormones known as the prostaglandins he devised new total syntheses of all the natural hormones and made analogs, some of them fluoro-substituted, that showed selective inhibitory action at specific prostaglandin receptors. He enjoyed close collaboration with professors in the medical school of the University of Chicago.

Josef Fried was born in the town of Przemsyl, Poland, on July 21, 1914, the first son of Abraham and Frieda Fried. The family moved to Leipzig, Germany, in 1919, where Josef received his education from elementary school through high school (1921-34). A second son, John, was born into the family in 1929. Josef developed an early interest in science, particularly chemistry. He also learned to play the violin, and he enjoyed listening to the classical church music that had abounded in Leipzig from the time of Bach. He received a thorough grounding in chemistry at the University of Leipzig during 1934-37, but he was in danger of not completing his bachelor's degree because of the 1935 Nuremberg Laws. By intrepidity and optimism he solved the problem. He went to the *Gauleiter* of the district, whom he convinced that the decree excluding German Jews from universities did not apply to Polish nationals. The combination of optimism with a willingness to confront and an ability to surmount difficulties was a special aspect of Josef Fried's character. In 1937 it enabled him to leave for Switzerland, where he spent a year at the University of Zürich with Professor Paul Karrer.

Professor Karrer, who was a sympathetic teacher, recommended, in the light of the political situation in Europe, that Josef should work toward his Ph.D. degree in the United States. Presumably he suggested Columbia University as one appropriate venue and Professor Robert C. Elderfield as a mentor. Josef entered Columbia as a graduate student in 1938, was awarded a Ph.D. in 1940 for his research on cardiac

glycosides with Elderfield, and stayed on as an Eli Lilly postdoctoral fellow until 1943.

Josef's parents and brother, John, left Germany for Switzerland one week before the Second World War began. It had been the family habit, after vacationing in Lugano each summer, to obtain re-entry visas to Switzerland before leaving. In August of 1939 this foresightedness saved their lives. While the three of them remained in Switzerland during 1939-41, through further foresightedness, Josef was able to help support them by the sale of his set of *Beilstein* and some Leica cameras that had accompanied him to America. Abraham, Frieda, and John Fried managed to come to the United States in 1942. Josef married Erna Werner in the United States in 1939. She had been a children's nurse, was well known to the family, and had reached the United States also by the Swiss route.

COLUMBIA UNIVERSITY

When we two authors were in our second year of Ph.D. study at Columbia University, Josef was in his final year of research for the degree. He had been renamed "Gus" because Elderfield, despite his minor in German at Williams College, did not like to pronounce "Josef." It was not quick enough! From that time onward he has been "Gus" to friends, colleagues, and even family. Gus was most generous with his practical chemical advice to fellow graduate students and also when he was a postdoctoral fellow. He taught us all how to do column chromatography, which had not yet been adopted broadly in U.S. universities; how to induce almost any solid to crystallize; how to recrystallize rapidly using centrifugation rather than filtration in sequential operations; and how to keep up with the literature. His enthusiasm for organic chemistry was unlimited and infectious. Where Elderfield lacked, or was too busy for, hands-on advice,

Gus supplied it. Outstanding among Gus's qualities was his ability to listen carefully and then to give cogent advice that was wide-ranging, whether about a particular laboratory technique or on a decision as to what courses we should take. If we required an answer as to method or conditions of organic synthesis, we went first of all to Gus Fried. Usually, the answer was so helpful and correct that he had solved our problem. We appreciated that Gus had an encyclopedic knowledge of organic chemistry and wanted to share it with students and colleagues. He made himself available to all of us, and he became a coauthor on the papers of six of Elderfield's Ph.D. students, including a 1942 publication with William S. Knowles, one of the three 2001 Nobel laureates in chemistry.

Gus and Erna were enthusiastic attendees at chamber music concerts in New York City. Regular Sunday afternoon visits to the Museum of Modern Art provided a balance for the week's chemical work in the laboratory. Erna's delicious dinners were frequently offered to those of us who were single graduate students. Strong and lasting friendships were established during those graduate years. Gus and we two authors have enjoyed steady contact with each other over a very long span of years, enthusiastic about each other's successes and supportive when there were difficulties—great, great friends.

One of the early difficulties that Gus Fried encountered was obtaining a suitable position to follow his postdoctoral fellowship at Columbia University. He was interested in teaching and had already shown himself to be effective in directing graduate research as Professor Elderfield's assistant. However, at that time no teaching position was available to him. He interviewed at several pharmaceutical companies but had no success there either. We have concluded that the anti-Semitism prevalent at the time in both academic

and industrial settings was to blame. Gus was aware of prejudices that existed, but he never seemed unduly bothered by them. He accepted life in a way that others would have found unacceptable then or now. He never allowed difficulties to dampen his optimism and enthusiasm. He settled for a job at the Givaudan Research Institute of Givaudan-Delawanna, guided in part by the Swiss connection. His hope for involvement in pharmaceutical research, however, was maintained. In 1944, when Oskar Wintersteiner, who had recently been appointed director of research at the Squibb Institute for Medical Research, offered Gus the position of head of the antibiotics and steroids department. Gus eagerly accepted.

SQUIBB INSTITUTE FOR MEDICAL RESEARCH

What attracted Gus was Wintersteiner's description of the long-range basic programs and his trust that these would prove highly profitable to Squibb in due course. No less attractive to Gus were Wintersteiner's personality and scientific accomplishments. The two had met briefly at Columbia University when Wintersteiner was on the staff of the College of Physicians and Surgeons, and both shared an interest in steroid hormones. A bond between them was established readily because of Wintersteiner's Austrian background, his culture, and his style of doing chemistry, in addition to their common interest in music. Wintersteiner played the piano and organ, and Gus the violin. Gus spoke of his new boss as "a highly civilized human being, a man of great modesty and integrity." Squibb research was concentrated initially on the isolation of new antibiotics. Fried and Wintersteiner collaborated on streptomycin and related compounds. A side effect of this research was their successful chromatographic technique for the crystallization of sugar components, which constituted a vast improvement over

earlier methodology that included a long residence time of a saturated carbohydrate solution in the refrigerator or the mythical "seeding" process of stroking one's beard or mustache above the solution containing the sugar. Another research project was centered on the active compounds responsible for the powerful hypotensive effects of the roots and rhizomes of *Veratrum viride*, a chemical investigation carried out in close association with biological and clinical assays. The dramatic results of the published clinical trial of cortisone in rheumatoid arthritis at the Mayo Clinic guided the Squibb research in the direction of fermentation of natural steroidal products that would provide the necessary ring substitution in a readily available intermediate for the economical synthesis of cortisone and cortisol. Indeed, Gus was tremendously successful in this project. The discovery of the effect of 9α-fluoro substitution (for hydrogen) was the fortuitous result of his adjusting the stereochemistry at the 11-position of the steroid ring system. He produced 9α-fluorohydrocortisone that showed a 10-fold increase in potency due to the fluoro substituent. Gus Fried's patent application of 1954 survived all interferences and was issued in 1958 (U.S. Patent 2,852,511) with all generic claims intact. It was one of several hundred patents that he would author or coauthor in his lifetime of research. Ironically Squibb management dissuaded Gus from spending time making materials for clinical studies; nevertheless, Gus and his capable assistant Emily Sabo quietly continued to do just that, with very good effect.

By further modification of the steroid nucleus with a 16, 17-acetonide grouping and a 1,2-double bond, Gus synthesized Squibb's Kenalog AE, the first of the superpotent anti-inflammatory steroids, with 100 times the activity of cortisol. It was the prototype of some of the most potent and effective corticoids used in dermatology today. During the years

1959-63 Gus was director of the Division of Organic Chemistry at Squibb. During the Squibb years Gus and Erna lived in Princeton, New Jersey, and vacationed on Nantucket. There were regular weekly sessions of string quartet playing at their Princeton home, and there was sailing in Nantucket waters. Daughter Carol, born in 1946, attended Barnard College and became a teacher in a private school. Gus's brother, John, 15 years his junior, says that Gus's excitement and enthusiasm for chemical research and his invention of important hormonal therapeutics led John to shift from engineering to a career in medicinal chemistry. When they were both working for pharmaceutical companies in New Jersey, they finally had the opportunity to come together for family visiting and the discussion of new developments in medical science.

UNIVERSITY OF CHICAGO

During his time at Squibb Gus never lost interest in academic work. When Charles B. Huggins, who liked Gus and appreciated his accomplishments, invited Gus to become a professor in the Ben May Laboratory for Cancer Research in 1963, he was willing to switch from an industrial to an academic position. Professorial appointments followed in the Department of Biochemistry and the Department of Chemistry of the University of Chicago, the Louis Block professorship in the biological sciences division in 1973, and service as chairman of the Department of Chemistry during 1977-79. The Chicago situation was ideal because of Gus's concentration on natural products having biological activities. The medical applications were now expedited and complemented by his direction of young research colleagues in whom he showed great personal interest. Moreover, he could participate actively in collaboration with colleagues in the medical school of the University.

He concluded his studies of steroids, especially their chemical and enzymatic interconversions, with a novel and rapid procedure, by the use of the steroid dehydrogenase enzyme from *Arthrobacter simplex*, for indicating relative and absolute configurations at a newly generated center during a total synthesis. This method, coupled with ORD or CD measurements, accomplished what had been possible only by X-ray crystallography prior to 1970. His seminal patent on fluorocorticoids in 1958 received recognition 10 years later with an Outstanding Patent Award from the New Jersey Council of Research and Development.

In an expansion of research interests Gus Fried and Dorothy Schumm penetrated the question of the cause of the carcinogenic activity of polycyclic aromatic hydrocarbons as due to one electron transfer oxidation, using the potent carcinogen 7,12-dimetylbenz[α]antracene (DMBA) as a model, with one electron oxidizing agents. Prior studies had focused on the intervention of metabolites, all of which had lower carcinogenic activity than the original hydrocarbon. In collaboration with colleagues Bruce H. Wainer and Frank W. Fitch in the Department of Pathology and Richard M. Rothberg in the Department of Pediatrics, Gus Fried made and studied morphine antagonists. The immunological studies were extended to antibodies against the opioids codeine and hydromorphone and further to antibodies against the narcotic drug meperidine. The antiserum for the latter could be used in a radioimmunoassay for meperidine that was 100 times more sensitive than assay techniques employed before 1976. It could be employed in clinical practice to measure the clearance from serum and placental transfer of meperidine administered to women in labor.

Guided likewise by biological activity and clinical potentiality Gus turned his attention to the maytansinoids, a group of structurally related ansa macrolides with reported high

antileukemic potency and cytotoxicity. He contributed importantly to all phases of our knowledge about these compounds. It was during this investigation that William Elliott, an M.D. Ph.D. student in Gus's laboratory, recognized he had an entrance from the maytansine research into another field of natural products, namely, insect pheromones. While Gus was off on a scientific visit to mainland China, Bill Ellliott performed the two synthetic steps that would lead him from one field to the other in a stereocontrolled, efficient synthesis of α-multistriatin, one of the essential components of the aggregation pheromone of the European elm bark beetle. The success of the synthesis was evident when the windows of the laboratory became black with beetles, as Bill relates, and he could greet Gus with the important though diverted research results. Gus was intrigued with the results, and because the racemate had first been synthesized, it remained only to sort out which of the enantiomers was the active one. The diseased elms to which beetle attractant was supplied in a receptacle at the base are still standing on the Chicago campus. Ironically, it was deemed less labor intensive and costly to cut down diseased trees than to service them individually with the synthetic pheromone and then destroy the congregated beetles.

The determination of structure and the total synthesis of the prostaglandins, a class of human hormones with a wide range of biological activity, had been pioneered by Professor E. J. Corey of Harvard University. At the University of Chicago Gus Fried added research on the synthesis of analogs and their chemical and enzymatic conversions, and on the synthesis of prostaglandin antagonists containing a CF_2 group in place of a CH_2 group within their structures. This was an analogical extension of Gus's research in the fluorocorticoid series. Increased stabilization and greater hormonal activity were twin goals achieved in the prostaglan-

din series as well. He found both agonists and antagonists of the natural prostaglandins and thromboxanes. These derivatives have helped to clarify the biological function of both classes, members of the arachidonic acid cascade in human metabolism.

Gus Fried was elected a member of the National Academy of Sciences in 1971 and a fellow of the American Academy of Arts and Sciences in 1981. The American Chemical Society selected him for the Medicinal Chemistry Award in 1974 and the Alfred Burger Award in Medicinal Chemistry in 1996. In 1994 he received the Gregory Pincus Medal from the Worcester Foundation for Experimental Biology and the Roussel Prize from the Roussel Scientific Institute in Paris. As an executive member of the Council of the International Organization for Chemical Development, he was an active researcher on the development of the elusive male contraceptive.

To honor Josef Fried for his major contributions to the pharmaceutical industry and to the development of fundamental organic chemistry, Bristol-Myers Squibb and the University of Chicago launched in 1990 the first of a series of annual Josef Fried Symposia of Bioorganic Chemistry.

Recently many colleagues and friends spoke with admiration and warmth about Gus. Some of their statements follow.

•I recall the twinkle in his eyes and the valuable administrative advice that he provided.

•He was a skilled mentor.

•The Frieds' hospitality in the Chicago apartment and at their summer and weekend cottage on Lake Michigan was greatly appreciated.

•He had a major effect in changing the University of Chicago's patent policy.

•He never lost his enthusiasm for science and was always interested in national and international events, focusing on causes of social fairness and justice.

•His advice on chemical and biochemical problems was given in a spirited way that betrayed an excess of enthusiasm for the science.

•He was a warm and generous gentleman in the best sense of that word.

•He had an inveterate optimism about all things scientific and a pervasive understanding of chemistry.

Professor E. J. Corey (Nobel laureate, 1990) says of Gus: "He was an outstanding, highly creative scientist who straddled both the worlds of pharmaceutical research and academic science. He was one of my heroes, and I've always thought of him as a model scientist of great character and great human warmth."

We are most grateful to John Fried and Bill Elliott for the information they provided. We were also guided by the material that Gus himself placed on file in the Office of the Home Secretary of the National Academy of Sciences and for his personal account of the discovery of the fluorosteroids at Squibb that appeared in *Steroids* (1992).

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