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JOSEPH S. FRUTON
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A Biographical Memoir by
MAXINE SINGER

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JOSEPH S. FRUTON DIED ON July 29, 2007, in New Haven, Connecticut. He was Eugene Higgins Professor Emeritus of Biochemistry and professor emeritus of the history of medicine at Yale University. He had been at Yale since 1945 where he led the conversion of the historic Department of Physiological Chemistry into a modern Department of Biochemistry in the Yale Graduate School and School of Medicine. A gifted teacher in the lecture hall, he coauthored with his wife, Sofia Simmonds, *General Biochemistry,* the first comprehensive and rigorous textbook of biochemistry (1953). The book was translated into Japanese and various European languages. Several generations of biochemists in many countries were educated using this book, including many who steered the development of molecular biology by merging biochemistry with genetics. Fruton's primary research interests throughout his life were the specificity and mechanism of proteolytic enzymes. His historical research into the history of biochemistry was as distinguished as his laboratory work.

The first of Fruton's many honors was receipt of the Eli Lilly Award in Biological Chemistry from the American Chemical Society in 1944. He received the Pfizer Award of the History of Science Society in 1973, the Dexter Award in the history of chemistry from the American Chemical Society in

1993, and the John Frederick Lewis Award of the American Philosophical Society in 1990. He was elected to the National Academy of Sciences in 1952, the American Academy of Arts and Sciences in 1953, and the American Philosophical Society in 1967. Among the distinguished lectures Fruton gave was the Harvey Lecture (1957), the Dakin Lecture in 1962, and the Sarton Lecture in 1976.

Fruton was not an outgoing person and rarely talked informally with the faculty and students about his own history or nonscientific ideas. As his Ph.D. student from 1952 to 1956, I never had a conversation with him about personal matters or his strong political views. In later years he showed a sympathetic interest in at least this former student's work and family and talked about the achievements of his other students. Occasionally, he even shared his well-defined political views. Apparently, it was easier for him to write about such matters, which he did in his long autobiographical essay (1982) and book-length memoir (1994). The memoir reveals his strong philosophical and political views, his challenging and often difficult relations with some in the Yale faculty and administration, his personal codes for scientific and personal conduct, and his pride in his students' accomplishments. The self-revelations in the memoir help to understand some of these attitudes. For example, speaking of his father's influence he wrote, "If I acquired from him some less desirable qualities, among them an extreme sensitivity to personal slight he also introduced me to the value of books" (1994, p. 176).

Both of Fruton's parents were born to Jewish families of merchants in Poland and were married in 1911. Their only child was born the next year in Czestochowa, and in 1913 they moved to New York. The emigration was not successful and they returned to Poland in 1917 in the midst of the turmoil surrounding the Bolshevik revolution, World War I, and growing anti-Semitism. They moved about a good deal, and in 1922 Joseph was sent to distant relatives in Berlin, where he attended school. A year later he rejoined his parents to travel once again to the United States, this time permanently, as his father now had a secure position with the British-owned Cunard Line. In his memoir, *Eighty Years,* Fruton recognized that his parents' decision to move to the United States saved the three of them from the fate of his four grandparents, all of whom perished at Treblinka (1994).

By the time they returned to the United States, Joseph was fluent in Polish, English, German, and French. In the United States, too, the family moved about: from New York, to Philadelphia, to Chicago, and then finally to New York. Joseph began high school in Chicago and completed it at James Madison High School in Brooklyn. Through all of this peripatetic life, Joseph excelled in school wherever he was and when, in 1927, he graduated from high school *summa cum laude,* he was the youngest person in the class. One of the few diversions from his studies was the typical pastime of Brooklyn youth of limited means: watching the Brooklyn Dodgers play baseball from a rooftop close to Ebbets Field.

Like many others in his generation, Fruton credited Sinclair Lewis's *Arrowsmith* as his inspiration for becoming a scientist. As an undergraduate at Columbia College he majored in chemistry and worked on the college newspaper. When he graduated from Columbia in 1931, he was already accepted as a graduate student by Hans Thacher Clarke, who was chair of the Columbia Department of Biological Chemistry. The laboratory community provided his first truly sympathetic environment and several of his colleagues there became his lifelong friends. His thesis research under Clarke concerned the chemical reactivity of cystine derivatives (1934), and he received the Ph.D. degree in 1934.

With Clarke's support Fruton was appointed a research assistant to Max Bergmann at the Rockefeller Institute for Medical Research (now Rockefeller University). Bergmann, a distinguished and accomplished peptide chemist, had recently arrived in the United States in one of the earliest waves of fine German scientists escaping from the Nazi regime. Leonidas Zervas, the gifted Greek peptide chemist, had joined Bergmann for a two-year stay. Earlier, Bergmann and Zervas had collaborated on the development of the seminal carbobenzoxy method for peptide synthesis and studied the dipeptidase of intestinal mucosa. Fruton was asked to continue this work, with special attention to the stereospecificity of the dipeptidase, a matter of great interest to Bergmann. Under the tutelage of Zervas, Fruton succeeded with the demanding chemical syntheses of various peptides. However, he became frustrated with the impure and uncharacterized enzyme preparations, a concern that was apparently not shared by Bergmann, who had Fruton and others embark on a series of studies of the specificity of papain. The key discoveries for Fruton during this time was Heinz Fraenkel-Conrat's demonstration that papain could catalyze the formation of a peptide bond[1] and confirmation of this with chymotrypsin by Bergmann and Fruton (1938). Fruton later called these reactions "transamidation"' or "transpeptidation." Fruton thought that Bergmann overinterpreted these findings as a path to investigating protein synthesis; he wrote in his memoir, "Bergmann's biological aspirations outstripped the chemical evidence" (1994, p. 46). Although Fruton was very interested in this work, Bergmann turned the topic over to another researcher. This was a common practice in Bergmann's laboratory and one that added to Fruton's growing frustrations. Later, Fruton would return to transpeptidation.

The crystallization of urease and pepsin by James Sumner in 1926 and John Northrop in 1930, respectively, resolved disputes over whether enzymes were protein molecules, but the basic primary structure of proteins remained controversial (1999). Fruton recognized two important issues concerning this dispute. First, that the analytical methods being used were insufficiently sensitive or quantitative to resolve fundamental questions about protein structure. Second, that studying the action of impure preparations of proteolytic enzymes on similarly impure protein substrates could not readily resolve the controversy because the chemistry of neither substrate nor enzyme was understood. Finally, in 1936 Bergmann agreed that Fruton could initiate studies with the crystalline proteinases. Fruton applied his new ability to synthesize peptides to the study of the specificity of proteolytic enzymes. Synthetic peptide substrates were used to demonstrate the demanding specificity of crystalline trypsin, and chymotrypsin (1938) and later of pepsin (1938). These elegant experiments established the specificities of the three enzymes as well as Fruton's place as an independent scientist. Efraim Racker's well-known admonition, "Don't waste clean thinking on dirty enzymes," was implicit to Fruton's thinking long before he met Racker.[2] Importantly, the work with synthetic substrates and crystalline enzymes strengthened the idea that proteins are polypeptides (1979).

Fruton's data strongly indicated that peptide bonds like those cleaved in the synthetic substrates must exist in the more complex protein substrates of the enzymes. However, neither his results nor improved analytical data for the amino acid constituents of proteins were conclusive in the minds of many protein chemists. The controversy over protein structure continued until well after the end of World War II when Frederick Sanger and his colleagues described the amino acid sequence of insulin. I was a graduate student in the Yale Department of Biochemistry in the 1950s when Sanger came to deliver a lecture on the structure of insulin, a discovery that ended the controversy by establishing that proteins are polypeptides. Fruton's enthusiasm for Sanger's work ensured that all the graduate students would listen carefully. The occasion is, even more than 50 years later, one that I remember well.

In 1936 Fruton married Sofia Simmonds, then an undergraduate at Barnard College. As one colleague observed, "They had a truly life-long love affair." Simmonds, known to all by her childhood nickname "Topsy," grew up in New York City. She graduated from Barnard College in 1938 and was awarded the Ph.D. degree in 1942 by Cornell University (in New York City) for work done in the laboratory of Vincent du Vigneaud. In 1969 the American Chemical Society awarded Simmonds the Garvan Medal, which recognizes the research accomplishments of outstanding women chemists.

In the late 1930s Fruton initiated work on intracellular proteolytic enzymes, the cathepsins (1941). But that effort and studies on the specificity of the crystalline proteolytic enzymes ceased after the United States entered World War II. The laboratory at Rockefeller, including Fruton, William Stein, and briefly Stanford Moore, turned to classified studies on the chemistry of agents such as nitrogen mustards. When the work was declassified after the war, Fruton and Stein described it in a series of papers published in *The Journal of Organic Chemistry*. For Fruton one of the more significant results of those years was the beginning of his long friendship with Stein.

Fruton began looking for an independent position soon after Max Bergmann became terminally ill in 1943. (He died in 1944.) When Fruton moved to Yale in 1945, he joined what was then called the Department of Physiological Chemistry as an associate professor in the graduate school; the department was located physically in the medical school. He believed that the Yale appointment reflected in part the influence of Abraham White, a member of the department who had been a friend for years. Another factor must have been his receipt of the Eli Lilly Award in Biological Chemistry in 1944, which recognized his central role in the recent experiments in Bergmann's laboratory. An essential consideration in Fruton's acceptance of Yale's offer was that Simmonds could also find a research position at the university. In those days discrimination against women made finding a university position that offered an opportunity for a wife who was also a scientist even more difficult than it is today. Eventually, Simmonds obtained a regular academic appointment and the professorial rank.

At Yale, Fruton became a dedicated teacher and chair of the renamed Department of Biochemistry. He and Simmonds gave clear and wonderfully organized lectures in the introductory course. Their lecture notes formed the basis of their textbook, *General Biochemistry* (1953). Students from several university departments took their course, among them Joshua Lederberg and Charles Yanofsky. The course was for me an extraordinary experience as it vindicated my decision to do graduate work in biochemistry against the advice of my undergraduate chemistry and biology professors who did not believe that biochemistry was a rigorous science worthy of attention. During my years as a graduate student, Fruton recruited an extraordinary group of faculty members, many of them still quite young. The group included Ephraim Racker, Frederic Richards, Irwin Rose, Harris Busch, Simmonds (who had been located in the Department of Microbiology), Melvin Simpson, Henry Harbury, Gerard Wyatt, and Thomas Bruice. Fruton was named Eugene Higgins Professor of Biochemistry in 1957. He worked hard to enhance the role of all the sciences at Yale; his experiences with this challenging task are recorded in *Eighty Years* (1994).

In New Haven, Fruton continued with the research problems that had engaged him during his last years at Rockefeller. He studied the specificity of the intestinal proteases and cathepsins. He branched out through collaborations with other faculty members. With Simmonds and Ed Tatum he worked on the utilization of amino acids and peptides by *Escherichia coli* (1947). With Julian Sturtevant he worked on the thermodynamics of peptide hydrolysis, a matter of significance to speculations about how peptide bonds were formed in cells (1952).

Fruton and Charles A. Dekker used the stereospecificity of papain in the condensation of methionine with aniline to resolve D,L-methionine, thereby permitting the synthesis of peptides of L-methionine (1948). Serine peptides were also synthesized in those early years at Yale. With several students he expanded the study of intracellular peptidases and proteases. Transpeptidation by papain and chymotrypsin was of continuing interest, especially when Mary Ellen Jones, an outstanding graduate student, discovered that cathepsin C could polymerize dipeptides to form long polypeptides (1952). Although he had rejected the idea when Bergmann espoused it 10 years earlier now, because the intracellular cathepsin C (and other cathepsins purified in his lab) catalyzed transpeptidation, Fruton hypothesized that such reactions might play a role in peptide bond formation in biological systems (1952, 1953).

The problem of how proteins are synthesized was, during the 1950s, a topic of widespread speculation and mainly inconclusive experimentation. Fruton's approach, although firmly grounded in elegant chemical and enzymatic experiments, did not address the question of how specific long sequences of amino acids could be constructed. It did not account for various hints that RNA and the microsomes being studied at the time might be important for protein synthesis. And it did not establish a mechanism for provision of the energy required to form large numbers of peptide bonds.

The second edition of *General Biochemistry* summarized the most recent experiments that demonstrated the rapid incorporation of radiolabeled amino acids into microsome fractions, the inhibition of protein synthesis by ribonuclease, and the evidence that DNA played an essential role in protein synthesis (1958). The text makes it clear that by this time Fruton recognized that transpeptidation by proteinases was unlikely to account for cellular protein synthesis. Yet, like many contemporary biochemists with strong roots in chemistry, he continued to be uncomfortable with experiments that used barely purified and poorly characterized cell extracts. By 1961 these issues were all resolved, at least in outline, and it was plain that proteinases were not involved in cellular protein synthesis.

The Frutons enjoyed their first sabbatical year in Cambridge, England, during 1962-1963. Fruton worked on peptide synthesis in the laboratory of Lord Todd. He was also able to make frequent visits to the recently established Laboratory of Molecular Biology, where he gained an appreciation of the developing work on protein structure and the fruitful combination of biochemistry and genetics. Perhaps it was this experience that many years later fostered his straightforward and fair description of the failure of his own ideas about how proteins are made (1999, pp. 454-459). During that year abroad, he decided that in the future he would "concentrate [his research] on the specificity and the mechanism of the action of pepsin" (1982).

From 1963 on, Fruton kept close to his resolve to concentrate on pepsin. With the collaboration of a series of gifted chemists, he used specifically designed peptide substrates to probe the detailed mechanism of pepsin action. Particularly important to this work were the efforts of Ken Inouye and Goverdhan P. Sachdev in Fruton's laboratory. Earlier conclusions indicating that pepsin had esterase activity and preferred cleaving the peptide bond between two aromatic amino acids were confirmed and extended (1967). Studies with peptides that were extended in length toward the amino and/or carboxy terminus from the two aromatic amino acids surrounding the susceptible bond turned out to be particularly informative because the catalytic rate of cleavage was greatly enhanced without affecting the affinity of the peptide for the enzyme (1969, 1970). The experiments led Fruton to conclude that pepsin interacted with the longer substrates at a site on the enzyme distant from the catalytic site and was sufficiently flexible in structure so that the secondary binding could increase catalysis (1970). This interpretation was one of the earliest recognitions that substrate binding to enzyme could have a significant effect on the structure of the interacting molecules. Stimulated by Lubert Stryer, then a Yale faculty member, Fruton adopted the use of fluorescent peptides to probe further the proposed flexibility (1975). The last of a series of papers using the fluorescent probes, and Fruton's last research paper, was published in 1983, 49 years after his first publication.

Fruton's thoughtful teaching was not restricted to formal lectures. Graduate students were given the opportunity to select their own research projects with his guidance. Consequently, they did not necessarily work on proteolytic enzymes. As a graduate student, while I worked on phosphamidase and phosphoprotein phosphatase, I shared a laboratory with George Taborsky who worked on nitrite reduction reactions; Taborsky's work was later extended by Christine Zioudrou, a postdoctoral associate who had been a student of Zervas in Greece. Occasionally, Fruton would continue such work after the student completed the Ph.D. degree but often the problem was left for the student or others to pursue. Similarly, he encouraged his students to obtain postdoctoral training in fields other than his own. Thus, I was surprised when he suggested in 1956 that I try to obtain a postdoctoral position with Leon A. Heppel, who was one of the few biochemists then working on nucleic acids; it was the best advice I ever received.

Unlike many academic institutions and even other departments at Yale, Fruton's Department of Biochemistry welcomed women as Ph.D. students. At the time, Yale's undergraduate college was still an all-male institution. In my entering graduate class in biochemistry, the majority of the students were female. I never faced the difficult challenges that my female undergraduate classmates experienced as doctoral students in science departments at other institutions. Throughout his tenure as professor and leader Fruton's efforts were consistently distinguished by his encouragement and fairness toward female students and colleagues. Mildred Cohn gave one of the most memorable lectures during my years as a graduate student. Notably, *Proteins, Enzymes, Genes* (1999) is dedicated to the memory of four outstanding deceased women biochemists. Perhaps it was Fruton's recognition that his wife, Sofia Simmonds, was a skilled and knowledgeable scientist that accounts for his unusually positive attitudes.

By 1983 Fruton's career as an historian of biochemistry had already been flourishing for years and he was well known as a preeminent historian. Consequently, he had been appointed professor of the history of medicine in 1980. As early as 1949 he began to review books about the history of science (1949). Throughout his life he collected pamphlets, rare reprints, and books that are important to the history of science; his collection was divided in donations to Yale and the Rockefeller University libraries. Throughout the years, he gave many lectures and published many reviews and commentaries about the history of the field and the lives of biochemists (a full bibliography of these writings as well as Fruton's research papers is included in the memoir, *Eighty Years* (1994). Fruton's interests outside of experimental science were recognized early in his time at Yale and he was invited to join the Dissenters, a 14-member exclusive and secretive faculty dining club. Even among these self-identified "dissenters," Fruton was "grateful for the tolerance of my friends in the face of my frequent dissent from their view of the world" (1984, p. 136).

His first book, *Molecules and Life*, appeared in 1972, and four years later he published a brief history of biochemistry (1976). By this time Fruton counted among his colleagues distinguished historians of science (and of other matters) on the Yale faculty. He particularly valued Frederic Lawrence ("Larry") Holmes, professor of the history of medicine as a colleague. In 1982 when Fruton was made professor emeritus, he was able to devote full time to his historical studies and writings. *Contrasts in Scientific Style* (1990) is a unique contribution to understanding the practices of leaders of large 19th-century research groups and how those practices influenced the careers and work of their students and research assistants; this book won the John Frederick Lewis Award from the American Philosophical Society. It is difficult to write a succinct summary of *A Skeptical Biochemist* (1992) except to say that it describes Fruton's views on the history and methodology of biochemistry within the context of his deep knowledge of the history and philosophy of science. His masterful book *Proteins, Enzymes, Genes* (1999) is, in more than 700 pages, an extraordinary, detailed account of the development of the concepts and methods that afforded the remarkable present understanding of biological processes.

Fruton and Simmonds shared many interests besides science in the more than 70 years of their marriage. They both loved fine food, and Simmonds was a marvelous cook. Chamber music and detective stories attracted both of them. And they loved to travel for both science and meeting with colleagues and for the museums and zoos in cities worldwide. Simmonds was also professor emeritus of biochemistry at Yale when she died on July 27, 2007, three days before Fruton's death. The couple provided a major gift to Yale to establish the Joseph S. and Sofia S. Fruton Teaching and Research Fund for the History of Science at Yale.

WRITING THIS MEMOIR HAS been a challenge. My own research and scientific interests veered sharply from Fruton's once he sent me to Heppel's laboratory, and I had much to learn in preparing this text. I am grateful for the important help provided by David R. Davies. Sidney Altman, who was a close friend and colleague of Joe Fruton for years, and Tom Bruice kindly reviewed this essay. The task was made easier for me by Fruton's memoir (1994) and autobiographical essay (1982). But the challenge increased when I read Fruton's comment concerning "the mediocre quality of many of the recent biographical memoirs for deceased members" (Fruton, 1994, p. 267).

NOTES

1. M. Bergmann and H. Fraenkel-Conrat. The role of specificity in the enzymatic synthesis of proteins. *J. Biol. Chem.* 119(1937):707-720.
2. Others, including Arthur Kornberg, have been credited with this dictum, and it is difficult if not impossible to uncover its earliest usage.

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