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JOHN CLARK SHEEHAN

1915—1992

A Biographical Memoir by

E.J. COREY AND JOHN D. ROBERTS

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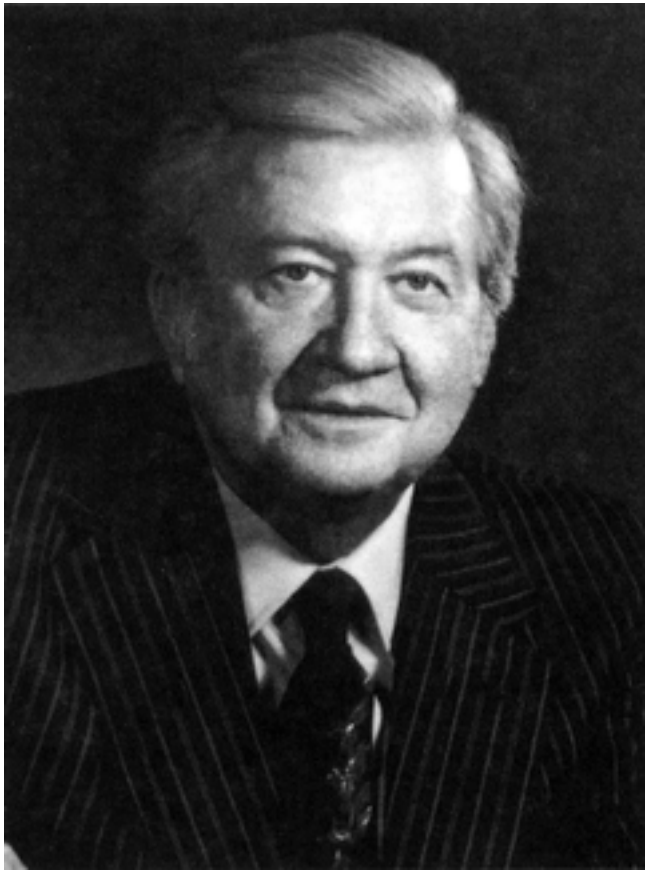

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John C. Sheehan

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September 23, 1915–March 21, 1992

BY E. J. COREY AND JOHN D. ROBERTS

JOHN C. SHEEHAN WILL long be remembered for having solved one of the most formidable and prominent problems in synthetic chemistry of the twentieth century, the chemical synthesis of the penicillins, and for helping to lead organic chemistry to new heights in the post-World War II era. He made major contributions to the Massachusetts Institute of Technology, his academic home for four decades. His teaching and research were instrumental in rejuvenating chemistry and maintaining its excellence at the institute, which also received enormous financial returns from his successful work on synthetic penicillins. His fundamental research provided the chemical base for the development of modern semisynthetic penicillins, which have saved countless human lives.

John C. Sheehan was born on September 23, 1915, in Battle Creek, Michigan. His father, Leo C. Sheehan, then sports editor and police reporter for *The Battle Creek Enquirer*, and his mother, Florence, were described in the news article marking the birth as "prominent in the younger society circles of Battle Creek." In addition to Irish forebears, the family had a substantial Yankee background; some sixteen known ancestors dated from revolutionary times. Florence Sheehan was a brilliant woman and skilled genealo-

gist who did professional work in the field and later became the Michigan registrar for the Daughters of the American Revolution. John's father left home at fifteen with only an eighth-grade education to "see the world" and found work as a reporter in San Francisco, where he witnessed the 1906 earthquake. Leo Sheehan was a skilled writer and progressed with *The Battle Creek Enquirer* to city editor and then to managing editor. He later functioned as a ghostwriter for Frank Murphy, once governor of Michigan and a Supreme Court justice.

John's grandfather, John W. Sheehan, was an outstanding lawyer who had business dealings with William Jennings Bryan, the famous political leader and orator. His maternal grandfather, Nathaniel Y. Green, was a bank manager and maintained an interest in nature and learning. A skilled amateur taxidermist, he had a large collection of birds. He greatly stimulated John's interest in science by giving him a Zeiss microscope with an oil-immersion lens and also introduced John to the curator of the local museum who helped him with several small science projects. John's grandfather had a telescope for astronomical observations and took John to meetings with the local group of astronomy buffs.

As with many future chemists in their early years, John progressed from a chemistry set to a basement laboratory and was fascinated by explosives and rocketry. He was a natural experimentalist with skillful hands. He also built model airplanes, and one with a delta wing won a first prize for longest flight time in the self-design class. He was also a zealous competitor in other activities. The Battle Creek newspaper reported him as the premier marble shooter of his grade school, representing the school in the city championships; as winner of the city yo-yo championship with a perfect score, as judged by the world's champion yo-yo player of the time; as a finalist in a Boy Scout election picking a mayor for a day; as having been injured in a high school

football game; and as Battle Creek College's No. 1 tennis player, as well as a participant with his brother Joseph in numerous tennis doubles tournaments. However, not all was rosy in John's younger years. His father had a long struggle with cancer and died at age fifty.

John's brother, Joseph, most often known as Joe, later had a distinguished career as a professor of psychology at the University of California. As an adolescent and young adult, Joe suffered intensely from stuttering and with his wife, Vivian, herself an eminent speech pathologist, devoted their lives to developing and implementing very successful training programs for relieving speech defects. John and Joe's younger brother, David, now retired, was engaged in manufacturing in Battle Creek.

John was raised as a Catholic and attended Catholic grade schools. However, in later life, both he and Joe were not particularly religious. John attended Battle Creek College with a double major in chemistry and political science. He graduated with honors as valedictorian of his class and won a state college scholarship for graduate work in any field of his choice. He elected to study chemistry at the University of Michigan.

John received the Ph.D. degree in 1941. His thesis supervisor was Werner E. Bachmann, then engaged in the historic first total syntheses of the steroid hormones equilenin and estrone. John's research, on the synthesis of phenanthrene derivatives, was in Bachmann's other major field of this period, the investigation of potential carcinogenic hydrocarbons following along the lines of J. W. Cook, with whom Bachmann had worked earlier. John became a superbly trained experimentalist in the grand tradition of Bachmann and Bachmann's illustrious teacher, Moses Gomberg, the founder of the field of stable carbon free radicals.

Shortly after receiving his Ph.D., John married Marion

Jennings, who had graduated with him from St. Philips High School in Battle Creek. Earlier in 1941, Bachmann asked John to work with him as a postdoctoral fellow but did not specify the area of research. After John finished writing his thesis, Bachmann informed him that it would be national defense research on the synthesis of cyclotrimethylenetrinitroamine, code named RDX. This substance was known to be a very brisant explosive, but no commercial or large-scale synthesis was available for its preparation. Bachmann and Sheehan developed a procedure for synthesis of RDX by nitration of hexamethylenetetramine that they ran in the Michigan laboratories on a scale of more than a kilogram. One wonders whether the university administrators were aware of the substantial hazard involved in this project. John displayed a mixture of courage and prudence, wearing not only the usual safety glasses and laboratory coat but also a heavy towel wrapped around his neck as protection from flying glass.

While purifying the reaction product, John isolated cyclotetramethylenetetranitroamine, an excellent explosive in its own right. The Bachmann-Sheehan process was scaled up by Tennessee Eastman, and the RDX so produced was used with great success by the United States for the remainder of the war (often in mixtures with TNT). The rapid completion of his part of the RDX project enabled Sheehan to accept a position as a research chemist at Merck and Co. in Rahway, New Jersey, starting in October 1941 under the direction of Max Tishler. John participated in several key synthetic projects, where research was needed for scale-up to the pilot plant and beyond. One was a new preparation of calcium pantothenate; another was removal of immunogenic materials formed as by-products in fermentation broths for the production of streptomycin; and a third was isolation and purification of penicillin. Out of the latter came

processes for the separation of penicillin G from other penicillins by formation of a crystalline salt with *N*-ethylpiperidine and subsequent exchange to the sodium salt with sodium 2-ethylhexanoate. One of his laboratory associates at Merck was Donald J. Cram, who later shared with C. J. Pedersen and Jean-Marie Lehn a Nobel Prize in chemistry for work on inclusion compounds.

John's work at Merck drew very favorable attention from Homer Adkins, a consultant to the company and renowned professor of chemistry at the University of Wisconsin. Adkins recommended John to Arthur C. Cope, who had been appointed head of the Department of Chemistry in 1945 by the president of MIT, Karl T. Compton, on the advice of a friend and wartime associate, Roger Adams of the University of Illinois. John joined the MIT faculty as an assistant professor in 1946, at a salary he said was half his compensation at Merck. At the same time, John D. Roberts and C. Gardner Swain were brought on board by Cope, and in the next few years MIT under Cope's vigorous leadership was propelled into the front ranks of U.S. chemistry.[1]

Within just four years at MIT John Sheehan became known as one of the most creative and dynamic synthetic organic chemists in the world by his development of new methods of synthesis of peptides (carbodiimide coupling and phthaloyl *N*-protection), three new syntheses of ß-lactams, the first synthesis of the penicillin ring system, and isolation and identification of a number of important new natural products.

His research on penicillins, initiated in 1948, was remarkable for several reasons. It came on the heels of the large wartime U.S.-British project of research on penicillins (involving more than a thousand chemists), which failed to develop a chemical synthesis and produced instead an ominous summary of a great many failed attempts. By 1948

penicillin G was produced in abundance commercially by fermentation, and no other leading chemist saw any reason to take on the apparently hopeless task of synthesizing such an unstable molecule. In John's own colorful language, the chemical synthesis of penicillin was like "placing an anvil on top of a house of cards." Years of determined and skillful effort were rewarded by success in 1957 when John and his group completed the first synthesis of penicillin V. One of the intermediates in the synthesis was 6-aminopenicillanic acid, a substance that Sheehan recognized could be used to prepare a variety of penicillins other than naturally occurring ones. This prescient conception turned out to have great medical value because it made possible variations in the penicillin structure that could be used to combat the tolerance developed by bacteria to particular forms of the antibiotic. The Sheehan synthesis of 6-aminopenicillanic acid is impractical for making these superpenicillins, but the amino acid is available in quantity by fermentation. John later told of his involvement with penicillins in his book, *The Enchanted Ring—The Untold Story of Penicillin*,[2] which also includes an account of the complex legal skirmish over the Sheehan-MIT patents on penicillin synthesis. Although the legal battle was protracted MIT eventually received almost $30 million in royalties from the Sheehan patent. MIT established the John C. Sheehan Professorship of Chemistry in October 1992.

Sheehan retired in 1977 and was named professor of chemistry emeritus and senior lecturer.

John Sheehan's major research achievements are described in some 150 synthetic papers and forty patents that cover not only penicillin but also peptides, antibiotics, alkaloids, and steroids. For his scientific contributions, John received several high honors, including the American Chemical Society Award in Pure Chemistry (1951), election to the Na-

tional Academy of Sciences (1957), the American Chemical Society Award for Creative Work in Synthetic Organic Chemistry (1959), the John Scott Award for inventors benefiting mankind (1964), the Outstanding Achievement Award of the University of Michigan (1971), and honorary doctorates from Notre Dame (1953) and the Stevens Institute of Technology (1980).

Sheehan spent 1953-54 in London as scientific liaison officer for the Office of Naval Research. From 1961 to 1965, he served the President's Science Advisory Committee as consultant, member of the limited war panel, and chairman of the committee on chemistry and biology. In the latter capacity he was involved in technology transfer negotiations with the Japanese government. He later had a close association with H. Umezawa, director of the Institute of Microbial Chemistry, and made many trips to Japan in connection with his interests in antibiotics and other pharmaceuticals. Sheehan played an active role in Organic Syntheses, Inc., by serving as editor-in-chief of volume 38 and then for many years as a member of the Advisory Board and Board of Directors. He was also engaged in the affairs of the American Chemical Society and, among other activities, served on its Board of Directors for eight years. Sheehan was a member of the National Research Council's Committee on Protection Against Mycotoxins (1982-84) and the Committee on Commercial Airport Security (1988-92). Ironically, in the latter activity he was concerned with the detection of explosives, such as RDX, on airplanes and in luggage and shipments.

Besides his work at MIT, Sheehan was involved in two rather unusual research activities of possible interest to those seeking alternative research support mechanisms. Thus, in 1958, the Schering Corporation set up the Research Institute for Medicine and Chemistry in Cambridge close to

MIT in appreciation of the contributions of M. M. Pechet to the company's clinical work. As director, Pechet invited D. H. R. Barton, then at Imperial College, London, to supervise a small research group. At Barton's suggestion, Sheehan also spent several years in a similar capacity. The first project of the institute was to achieve a synthesis of aldosterone, a goal that Sheehan hoped to reach by degradation of a steroidal alkaloid, but was better prepared by a nitrite-photolysis procedure developed by Barton. Subsequently, Sheehan extended his research on water-soluble carbodiimides at the institute for several years. Later in 1970 he was able to build on the results of a government-supported research program at Arthur D. Little Co. on cannabinoid derivatives as potential chemical warfare agents to set up a program aimed at the use of such derivatives in the treatment of nausea resulting from cancer chemotherapy. This work was carried out at a for-profit company called SHARPS Associates and the nonprofit John C. Sheehan Research Institute. The former was supported by contracts with pharmaceutical companies and the latter by research grants, as from the National Institutes of Health. The combined operation got off to an excellent start, but Sheehan was later greatly disappointed by subsequent management problems.

The present authors, one as a graduate student in the Sheehan research group and the other a professorial colleague, were greatly impressed by John's ingrained cheerfulness, optimism, and humor, as well as his broad chemical expertise. His 1948-50 research group included Gerald D. Laubach (later president of Pfizer, Inc.), Robert T. O'Neill (later a successful research chemist at Merck and a private businessman), Barry M. Bloom (president of Pfizer Research), Ajay K. Bose (professor of chemistry at Stevens Institute of Technology), David Johnson (research director at Bristol

Myers), E. J. Corey (later professor of chemistry at Harvard), and Kenneth Henery-Logan (who later participated in the successful synthesis of penicillin). This was no collection of shrinking violets, and they all found as much enjoyment in exchanges with John as in the research adventure itself.

John Sheehan was a man who made friends easily and had many close friends at home as well as abroad—the results of his extensive international travels. He was an avid competitor in all things, a trait that was particularly evident to those who played tennis with him. He enjoyed boating, was a close follower of politics and sports, a marvelous raconteur, and a lover of good stories told by others, as well as an entertaining dinner companion. John is survived by Marion, his lovely and devoted wife of more than fifty years; a brother, David Sheehan of Battle Creek, Michigan; three children, John C., Jr., of Denver, David E. of Key Biscayne, and Elizabeth (Betsy) S. Watkins of Sauderstown, Rhode Island; and six grandchildren.

Sheehan's career was multifaceted, with achievements that demonstrated an unusual ability to focus on chemical problems of great practical importance, the courage to pioneer against strong odds, and an unflagging determination to succeed.

THE AUTHORS ARE VERY GRATEFUL to Marion Sheehan; her sister-in-law, Vivian; Professor Ajay K. Bose; and Sir Derek Barton for providing valuable background material for this biography.

NOTES

1. For more on the Cope era at MIT, see J. D. Roberts, *The Right Place at the Right Time*, pp. 53-59. (Washington, D.C.: American Chemical Society, 1990), and J. D. Roberts and J. C. Sheehan, "Arthur C. Cope," *Biographical Memoirs*, vol. 60, pp. 17-30 (Washington, D.C.: National Academy Press, 1991).

2. J. C. Sheehan, *The Enchanted Ring—The Untold Story of Penicillin* (Cambridge, Mass.: MIT Press, 1982).

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