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A Biographical Memoir by

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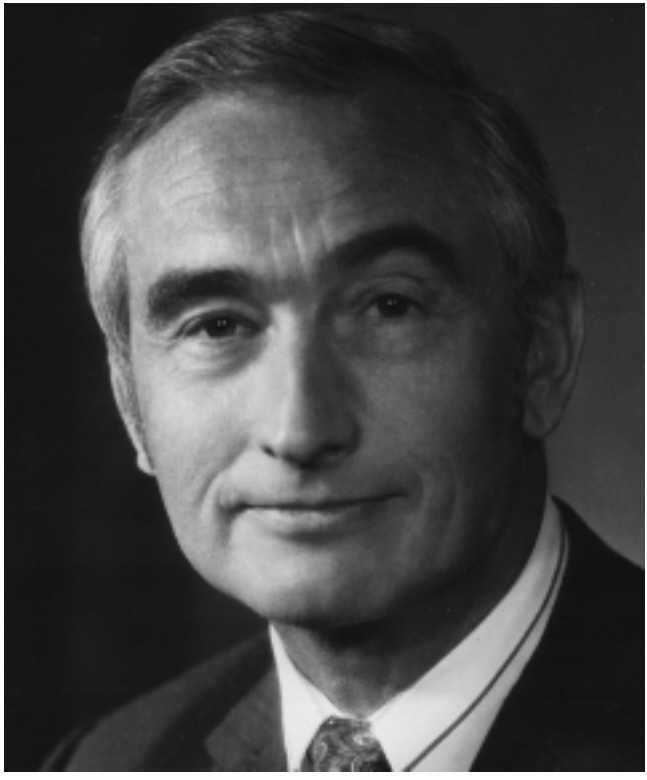

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Louis H Sarett

LEWIS HASTINGS SARETT

December 22, 1917–November 29, 1999

BY ARTHUR A. PATCHETT

LEWIS H. SARETT WAS the first chemist to synthesize cortisone. It was a feat of remarkable complexity involving nearly 40 chemical steps from desoxycholic acid and was achieved during World War II as a chemist in the Merck Research Laboratories. This synthesis and subsequent improvements of it ultimately led to cortisone's use in treating rheumatoid arthritis and was the first of Sarett's many contributions to medicine during a 40-year career at Merck. When he retired in 1982 he was senior vice-president for science and technology. He had been a key contributor to Merck's growth, and in later years Sarett was an influential industry spokesman for U.S. science policy.

Lew Sarett was born in Champaign, Illinois, on December 22, 1917. His father was a professor of speech at Northwestern University, a poet, and an outdoorsman. The latter interest led him to locate his family in Laona in northern Wisconsin while he lived in Evanston, Illinois, for one semester of the school year. Lew enjoyed rural life, but the commuting ultimately became too much for his father, and the family moved back to Illinois, where Sarett attended high school in Highland Park. A beginner's chemistry set introduced him to science, and with the encouragement of

one of his relatives, Charles Osgood, later to become a curator of the Peabody Museum at Yale, he acquired an interest in fossils. Apparently on his own, Lew became an avid chess player and even in retirement he continued to play chess using a computer as his opponent. One of his characteristics as a chemist and manager was his love of challenges and an ability to devise detailed strategies. These traits were evident in his lifelong enjoyment of chess.

In 1935 Lew enrolled in Northwestern University where he originally thought he might major in mathematics, but the chemistry department, which included Charles Hurd and Ward Evans, was a good one. Sarett had a natural talent for chemistry, more so than for advanced mathematics, so he became a chemistry major. He continued playing chess and, with the encouragement of his father who was an athlete in college, he also took up wrestling. He did well in his chemistry courses and graduated from Northwestern University in 1939 with Phi Beta Kappa honors.

To continue his studies after Northwestern Sarett applied to four graduate schools. Princeton offered him a teaching assistantship, which he accepted on the recommendation of Professor Hurd. Princeton's department was strong in physical chemistry (Henry Eyring, Hugh Taylor and John Turkevich), but Sarett wanted to do synthesis. The choices were Greg Dougherty and Everett Wallis, and the latter's work in steroid chemistry held great appeal. Some of the best chemists of the day were working on steroids. Sarett was caught up in that cutting-edge research, which intensified when the United States entered World War II in December 1941. Sarett's assignment with Wallis was to explore bromination reactions of steroidal ketones with the long-range objective of converting steroids like cholesterol into the female sex hormone estradiol.

Princeton granted Sarett a Ph.D. degree after only two

and one-half years so he could begin working in early 1942 at Merck on the synthesis of cortisone. Syntheses of it and penicillin were given high priority in the war effort and consortiums of industrial and academic scientists were created to expedite their production. The cortisone consortium included a group at the Mayo Clinic under E. C. Kendall, and Sarett spent a short time there before working full-time at Merck. Great importance was attached to a cortisone synthesis since supplies from bovine adrenal glands were extremely limited and it was believed (although erroneously) that the hormone increased the endurance of German pilots at high altitudes.

Sarett's synthesis of cortisone from desoxycholic acid required moving the 12-ketone to the 11-position, introduction of an unsaturated ketone in the A-ring and replacement of the bile acid side chain by dihydroxyacetone functionality. Relocating the ketone was achieved using methodology pioneered by Tadeus Reichstein's group in Basel, Switzerland. Sarett degraded the bile acid side chain to a 17-ketone, from which he fashioned a protected dihydroxyacetone side chain in a multi-step process. Bromination and dehydrobromination afforded the unsaturated ketone functionality required in ring A. The Merck process research group led by Max Tishler supplied some of the intermediates required in this synthesis; however, without an assistant, Sarett had gone through nearly 40 steps to produce 18 milligrams of cortisone.

On March 1, 1944, Sarett married Mary Adams Barrie. They lived in Princeton and had two daughters: Mary Nicole Sarett of Skillman, New Jersey, and Katharine Wendy Young of Devon, Pennsylvania. Sarett frequently entertained Merck colleagues at his home and in later years he became a low-handicap golfer.

Shortly after the war ended, Merck management decided

to make cortisone available to clinical investigators to see if a use could be found for it. Sarett's partial synthesis had been improved and scaled up by Max Tishler's chemists and by April 1948 almost 100 grams of cortisone were on hand.

When later that year Philip Hench tried cortisone in a female patient with rheumatoid arthritis, her improvement was spectacular, and cortisone was hailed as a wonder drug. Knowledge of its efficacy led to urgent clinical requests for the compound. With justifiable confidence in Merck chemistry, George Merck convinced U.S. government officials that Merck could in reasonable time supply all that was needed. While Tishler's group improved the bile acid process still further and established its commercial viability, Lew Sarett and his group accomplished a total synthesis of cortisone, which he announced in 1952. Although it did not go into production, Sarett was very proud of that achievement, which the *Annual Reports of the Chemical Society* said was the best synthetic chemistry contribution of that year. Sarett's cortisone achievements brought him acclaim in the academic community. He was offered a faculty position at MIT, but he turned it down to accept expanded responsibilities at Merck as head of medicinal chemistry.

Cortisone's leadership position in the treatment of arthritis was overtaken by prednisolone following its discovery in 1955 by scientists at the Schering Corporation. They had been working on alternative methods of making cortisone; instead, they discovered that an additional double bond in the A-ring of cortisol modestly increased its potency, and more importantly, this change markedly reduced the sodium retention properties of cortisol. The realization that a natural hormone's efficacy and therapeutic index could be improved by chemical manipulation had profound consequences in the steroid field and in drug design more

generally. Josef Fried and his group at Squibb enhanced cortisone's potency by introducing a 9α-fluorine group. Sarett's group showed 16α-methyl steroids had advantages in both potency and sodium retention. Putting all of these structural features together, Sarett's group produced *Decadron*, which to this day is the high-potency clinical standard among anti-inflammatory steroids.

As head of medicinal chemistry at Merck, Sarett became an industry leader in drug design. He evolved rules for the minimum systematic development of screening leads and elaborated receptor concepts to rationalize the anti-inflammatory activities of cortisone analogs. His department in Rahway, New Jersey, also had responsibility for Merck's animal health products. That business had begun several years earlier with Tishler's development of sulfaquinoxaline for coccidiosis. Sarett and his group led by Ed Rogers and Horace Brown produced the coccidiostats *Amprol* and *Nicarbazin* and the anthelmintic *Thibenzole*. They were market leaders for many years.

Most importantly, Sarett continued to innovate therapy for arthritis. When manipulations of the steroid nucleus failed to improve the therapeutic index of *Decadron*, he and Ralph Hirschmann devised steroidal conjugates that were selectively activated in the inflamed joint. These compounds unfortunately lacked oral activity and so were not developed, but this work was a dramatic early example of drug latentiation that is still a viable way to maximize safety.

Ultimately, addressing the shortcomings of steroids required a fundamental change in strategy. *Aspirin* had been in use for many years, so there was precedent for nonsteroidal arthritic drugs. The problem was how to discover new therapeutic mechanisms or improve the potency of aspirin. Under Sarett's leadership Merck scientists took up that challenge. A reliable animal assay for anti-inflammatory activity

was developed by Charles A. Winter, and T. Y. Shen headed the chemistry effort. Together with their colleagues this team and Sarett in a remarkable burst of creativity produced *Indocin*, *Clinoril*, and *Dolobid*. With *Decadron* these drugs became mainstays of therapy and have been used to alleviate the pain and disabilities of millions of rheumatoid and osteoarthritis patients.

In 1969 Sarett was made president of the Merck Sharp and Dohme Research Laboratories, a position that he held until 1976. During that time Merck became a leader in vaccine research. Maurice Hilleman's group in its West Point laboratories produced a triple vaccine for measles, mumps, and rubella, and *Pneumovax* was introduced, affording protection against 14 strains of pneumonia.

Sarett had a longstanding interest in natural products and one of his legacies was to strengthen Merck capabilities in fermentation product research. An early achievement was the identification of a methoxycephalosporin in 1972 from which Burton Christensen and his associates produced *Mefoxin*. This injectable antibiotic had excellent activity against a group of organisms resistant to existing antibiotics. For several years it became one of the leading antibiotics in hospital use.

Most importantly, in 1976, the year of his retirement as president of the Merck Research Laboratories, the broad-spectrum antibiotic thienamycin and the antiparasitic drug avermectin were discovered. Their development in subsequent years led to *Imipenem* and *Ivermectin*. The former is one of the antibiotics of last resort in hospital use today. The latter is widely used to treat roundworms in cattle and sheep and prevent heartworm infections in dogs and river blindness in humans.

Sarett also organized the New Lead Discovery Department first under Ralph Hirschmann and then under Arthur

Patchett in 1972. Sarett was ahead of his time in recognizing a need to generate compounds in large numbers for biological testing. That department, whose structure and mission were established by Sarett, produced several of Merck's biggest products in the 1980s and 1990s, including *Vasotec*, *Prinivil*, and *Mevacor*.

When Sarett was promoted to corporate management in 1976, he was the inventor or coinventor of 178 U.S. patents. His scientific honors were numerous and included:

1951	Northwestern Alumni Associate Award of Merit
	Merck Board of Directors Scientific Award
	Leo Hendrik Baekeland Award of the American Chemical Society (North Jersey Section)
1959	Julius W. Sturmer Memorial Lecture Award
1964	William Scheele Lecture Award, Stockholm, Sweden
	American Chemical Society Award for Creative Research in Synthetic Organic Chemistry
	Synthetic Organic Chemical Manufacturers Association Medal for Creative Research in Synthetic Organic Chemistry
1966	New Jersey Patent Award, New Jersey Council for Research and Development
1972	Chemical Pioneer Award of the American Institute of Chemists
1975	National Medal of Science
1976	Perkin Medal Award of the Society of Chemical Industry

From 1976 to 1982 Sarett was Merck senior vice-president for science and technology and directed the strategic planning activities of all the company's divisions worldwide.

He had corporate responsibility for licensing new products and technologies and built relationships with companies and academic groups. He also became a leading spokesman for Merck and the industry on national science policy, including service on the General Accounting Office's advisory group regarding the Food and Drug Administration (1978), a Commerce Department subcommittee on research support and industrial innovation (1978-79), and a U.N. advisory group on science and technology development (1978-82). He was also a member of the Task Force on Science and Technology for President-elect Reagan and served on the Science and Technology Panel of the Reagan transition team. Sarett testified seven times during 1980-82 before committees of the U.S. Senate and House of Representatives about the interrelationships of governmental policy and innovation in the pharmaceutical industry.

During his tenure as senior vice-president for science and technology, Sarett was asked if he would like to be director of the National Institutes of Health, but Merck President Henry Gadsden asked him to remain at Merck, and somewhat reluctantly Sarett turned down the NIH possibility.

He became a member of the National Academy of Sciences in 1977 and a member of the Institute of Medicine in 1978. Other honors included:

1977	Honorary doctor of science, Bucknell University
1980	Election to the National Inventors Hall of Fame Industrial Research Institute Medal
1981	Gold Medal Award of the American Institute of Chemists
1982	Proctor Medal of the Philadelphia Drug Exchange

Throughout his career Sarett was an active participant and advisor to numerous professional organizations. Among these activities were the following:

1966-69	Chair, Basic Science Advisory Committee, National Cystic Fibrosis Research Foundation
1967-68	Consultant, Department of Defense, Chemotherapy of Malaria and Schistosomiasis
1968-70	Member, Board of Trustees, Cold Spring Harbor Laboratory for Quantitative Biology
1969-71	Member, Advisory Council, Department of Chemistry, Princeton University Member, Editorial Advisory Board, *Chemical and Engineering News*
1969-82	Representative, Pharmaceutical Manufacturers Association
1971-75	Member, Governing Board, Association of Princeton Graduate Alumni
1972-73	Chair, Directors of Industrial Research

He also became a member of the Industrial Advisory Committee of the University of California, San Diego, in 1971; a member of the Center for Public Resources Task Force on Developing Countries' Health in 1979; and a member of the Pharmaceutical Manufacturers Association's Commission on Drugs for Rare Diseases in 1981.

Sarett retired from Merck in 1982 several months ahead of his sixty-fifth birthday and mandatory retirement as a corporate officer. An overflow crowd of admirers packed the Baltusrol Country Club in Springfield, New Jersey, on July 23, 1982, to express their gratitude and to wish him well. Among the speakers was his long-time mentor and colleague Max Tishler. With great pride he described Sarett's contributions to chemistry, to the growth and welfare of

Merck, and to the shaping of public science policy. It was a memorable night and a breadth of achievements unequaled in Merck chemistry was honored.

Sarett's first marriage ended in divorce and he remarried on June 28, 1969. His second wife was Merck microbiologist Pamela Thorp, and they were together for the remaining 30 years of his life. They had two children: Will H. Sarett of Bonney Lake, Washington, and Renee M. Sarett of Norwich, Vermont. Like Sarett, Pamela Thorp had grown up in Wisconsin and when he retired from Merck, they decided to relocate from Skillman, New Jersey, to a rural area. Their choice was to build a home in Viola, Idaho, where they could have fruit trees, tend garden, and Sarett would be well located for occasional hunting trips. The surrounding countryside was beautiful and the University of Idaho was nearby. He was offered a position in its chemistry department, but he declined feeling that he had been away from the laboratory for too many years. Instead, he joined the advisory committee of a venture capital company, New Enterprise Associates, and became active in the West Coast biotech industry. With years of experience he knew how to develop drugs and this knowledge was an important asset for biotech companies to draw upon; following his retirement from Merck he served on the boards of directors of more than 15 of them, including *Affymax*, *Amylin*, *Immunex*, and *Genentech* Development Corporation. He enjoyed working with innovators, and the entrepreneurial spirit of these smaller organizations brought back pleasant memories of his early days at Merck.

Lew Sarett died in Viola at age 81 of complications from advanced colitis. In addition to his wife and four children he was survived by five grandchildren. As Max Tishler said of him at his retirement dinner "both by words and by his

accomplishments he added a sense of excitement to invention in industrial laboratories."

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