BIOGRAPHICAL MEMOIRS

Ronald W. Estabrook

January 3, 1926–August 5, 2013
Elected to the NAS, 1979

A Biographical Memoir by Bettie Sue Masters

The life of Ronald Winfield Estabrook was full and productive, personally and professionally. His independent scientific career spanned fifty-four years, and his contributions to the field of cytochrome P450-mediated metabolism were seminal and prolific.

Estabrook was born in Albany, New York, on January 3, 1926, and he enlisted in the U.S. Navy in 1943 at the age of seventeen. Through the V-12 Navy College Training Program, which offered the opportunity for enlisted personnel to become commissioned officers, he was enrolled at Princeton University and subsequently served on a submarine chaser and minesweeper as a navigator in the minefields surrounding Japan and Okinawa. Upon his return from World War II, he enrolled in Rensselaer Polytechnic Institute, earning a bachelor's degree in biology, and then entered graduate training at the University of Rochester with Elmer Stotz. He earned his Ph.D. upon defense of his dissertation research entitled, "Studies on the Cytochromes in Heart Muscle Extracts." Because Stotz's research was well-recognized for its emphasis on hemoproteins, this phase of Estabrook's training established the mindset for his life's work. As a logical extension, his postdoctoral training period was with Britton Chance at the University of Pennsylvania, where he mastered the techniques of spectroscopy. He then took his family to Cambridge, where he worked with David Keilin at the University of Cambridge's Molteno Institute for Research in Parasitology. These outstanding and well-meshed training periods set the stage for his independent research career, which he began as an assistant professor in 1959 in the Eldridge Reeves Johnson Research Foundation, under Chance's direction, at the University of Pennsylvania.

Figure 1 Ronald Estabrook in his preferred attire — suspenders.

He was promoted to professor in 1965. During his affiliation with the foundation, Estabrook made seminal discoveries, using spectroscopic techniques, leading to the identification of a spectral species, to be known as cytochrome P450, that acts as the terminal oxidase for the metabolism of steroids and drugs. At the time of this writing, almost 90 percent of all therapeutic drugs are known to be metabolized by these hemoprotein enzymes of which there are fifty-seven isoforms in humans. Estabrook, David Cooper, and Otto Rosenthal[1] cleverly employed

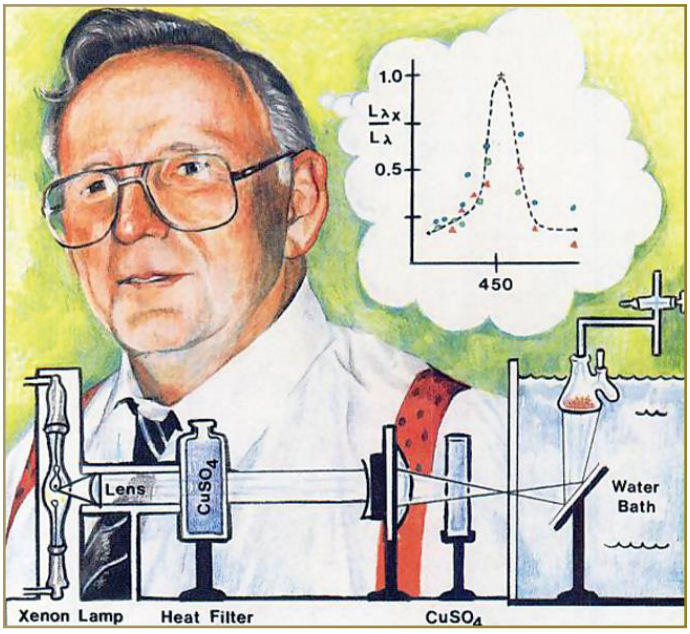

Figure 2 Caricature of Estabrook and the spectral technique used to dissociate carbon monoxide binding. *Artist: Dorothy Siler Roberson.*

a spectral technique that Otto Warburg had used to identify cytochrome oxidase as the terminal oxidase in the mitochondrial respiratory chain. This technique, depicted in Estabrook's caricature in the image in Figure 2, used light spectroscopy to dissociate the carbon monoxide binding at the peak wavelength of 450nm to reverse the inhibition of the metabolism of steroids in both liver and adrenal cortex microsomal and mitochondrial preparations, respectively. The reversal of carbon monoxide binding, which inhibited its metabolic activity, established the role of the pigment absorbing maximally at 450nm in the metabolism of these vital steroids.[2] Estabrook's studies continued using the sophisticated spectral techniques of the time, including dual-wavelength spectrophotometry, developed in the Chance laboratory for the study of turbid subcellular fractions.[3] These techniques were to become essential for spectral species in turbid suspensions of other tissue fractions, as had been effective in studying mitochondrial fractions. Later, the development of stopped-flow, rapid-reaction techniques permitted the measurement of rates in these turbid suspensions. Estabrook would use these techniques effectively in his further pursuits of cytochrome P450-mediated reactions in subcellular preparations of the endoplasmic reticulum, called microsomes.

During this time, he and his wife, June, were raising their four children—daughters Linda, Laura, and Jill, and son David—as his career was blossoming. In 1968, Ron was named chair of the Department of Biochemistry at the developing University of Texas Southwestern Medical School, where Charles C. Sprague, M.D., had been recruited from Tulane University to become dean in 1967. Sprague and Donald W. Seldin, M.D., chair of the Department of Medicine, collaborated to build the basic science departments, with Ron Estabrook being the first successful recruit. Following his own instincts, Ron recruited four young investigators, including René Frenkel, Louis B. Hersh, Julian A. "Bill" Peterson, and Bettie Sue Masters, to jump start their careers and bring new blood into the medical school. Each young investigator was allotted space for a laboratory and set-up funds to purchase appropriate equipment to pursue their respective research programs. They were motivated and energetic, and the *esprit de corps* was infectious. It is not certain that the administration knew what had landed in their midst, but they continued the recruitment of new chairs of the basic science departments, which proved to be a key decision in the development of the University of Texas Health Science Center at Dallas, as it was known then. Peterson[4] and Masters[5] were to pursue their research programs complementary to the program in cytochrome P450-mediated metabolism and the enzymatic mechanisms involved in both hemoprotein- and flavoprotein-mediated processes, respectively. Frenkel and Hersh successfully pursued their separate research programs in metabolism and mechanistic enzymology.

The cytochrome P450 group, under Estabrook's leadership, was able to coalesce and build an NIH-funded program project supporting multiple investigators that was successfully renewed for several five-year cycles. During these very productive years, Estabrook was successful in attracting outstanding scientists from Europe and Asia for visiting professorships and fellowships and, as a result, creating a mecca for this area of research. His ideas flowed freely throughout the interacting laboratories and many publications emanated from the various international collaborations. The packets of publications assembled for renewal applications to the National Institute of General Medical Sciences constituted a very heavy mailing of the paper versions of grant applications required in those days.

When Estabrook arrived in Dallas, he was introduced to Virginia Lazenby O'Hara, whose father was the founder of the soft drink company that produced Dr. Pepper. She found Estabrook's enthusiasm for research and his ambitions for the Department of Biochemistry infectious. She endowed the Virginia Lazenby O'Hara Chair for his support and was very generous in purchasing state-of-the-art equipment, such as mass spectrometers, thus propelling the research efforts of departmental faculty. Estabrook served as department chair from 1968–82 and, in 1973, he was named to serve simultaneously as the first dean of the Graduate School of Biomedical Sciences at the University of Texas Health Science Center at Dallas, as the institution was named then. In 2007, the University of Texas Southwestern Medical Center named one of its six colleges for Estabrook to honor his contributions to the institution.

During these formative years and through numerous reciprocal international visits, new studies revealed the kinetics and mechanisms of various cytochrome P450-mediated activities catalyzed by microsomal and mitochondrial cell fractions, using static and kinetic spectroscopic techniques and isolation and purification of the components of the systems from various organs and bacterial sources. At the same time, although it was originally believed that only several cytochromes P450 existed in mammalian species from spectroscopic studies,[6] induction studies revealed that more species might exist, and later genetic techniques would demonstrate that there were many and they were ubiquitous.

Prior to the identification of cytochrome P450 as the terminal oxygenase in the endoplasmic reticulum, Estabrook's studies had centered on mitochondrial electron transport systems in various mammalian organs, as well as in bacteria and houseflies, whatever model seemed appropriate. These included studies on the antimycin A and oligomycin inhibition of mitochondrial electron transport.[7] His bibliography, last calculated by the Web of Science platform, featured more than 250 publications.[8-11]

Ronald Estabrook enjoyed several hobbies. When his children were younger, he built dollhouses that his wife, June, decorated and furnished. He was a consummate photographer and was always seen capturing the essence of scientific meetings and social activities with his colleagues and friends. Unfortunately, much of his photographic collection, saved on a university server, was lost when the server was upgraded, and many files were not saved. He was also a philatelist and numismatist—a collector par excellence. When he posted mail through the U.S. Postal Service, it always featured interesting and unique stamps.

Estabrook's mind was keen and tenacious. He would invariably ask questions at scientific sessions, preceding his query with a complimentary remark, followed by "but …". His questions were always to the point and elucidative. He was asked to summarize each specialty meeting at its end so that the attendees would grasp the essence of the science. He was a master at this!

Estabrook's influence in the molding of basic science in medical education was also significant. He served on many panels instituted by the National Academy of Sciences and the former Institute of Medicine (now the National Academy of Medicine) and summarized the Robert Wood Johnson report on recommended changes in medical education.[12]

It should be noted that Estabrook's influence in science was also expressed in his nurturing of aspiring scientists, who would become notable in their own chosen scientific endeavors. By giving members of his faculty at the University of Texas Southwestern Medical School the opportunity to develop their own programs, while providing some cushion of support, he helped launch the careers of six department chairs: Thomas Smith (Howard University), Bettie Sue Masters (Medical College of Wisconsin), Michael R. Waterman (Vanderbilt University), Louis B. Hersh (University of Kentucky), Russell A. Prough (University of Louisville), and Michael Douglas (University of North Carolina). These individuals would in turn influence the futures of many other young scientists through their positions as chairs of basic science departments, thereby producing a superfamily of biomedical scientists.

Ronald Winfield Estabrook's influence on the field of cellular electron transport and, in particular, cytochrome P450-mediated metabolism, as well as in the societal impact of medical education, is immeasurable.

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