Dr Donald S. Fredrickson (Figure), who died on June 7, 2002, was an internationally recognized authority on disorders of lipid metabolism and, in the words of National Institutes of Health (NIH) director Elias Zerhouni, “a towering influence in the scientific community” (personal communication, NIH, July 23, 2002). In the past half century, Dr Fredrickson’s accomplishments in basic science, clinical investigation, and public service transformed the field of cardiovascular medicine and advanced the conduct of research. But Don Fredrickson is also the man who, in 1965, first invited me to work with him in Dr Robert I. Levy in the Molecular Disease Branch of the NIH. This marked the beginning of my research career. With the death of Don Fredrickson, an era has ended, and we who knew him have lost a friend and colleague.

Don’s accomplishments in science and medicine helped create the field of lipidology, an entirely new discipline. His earliest research interests focused on sterol metabolism. Subsequently, he concentrated on the structure and metabolism of the plasma lipoproteins, their role in transporting fats, and the genetic factors regulating their metabolism and concentration in the blood (personal communication, NIH, July 23, 2002). At the Molecular Disease Branch of the NIH, which he headed from 1966 to 1974, Don and his colleagues were involved in discoveries that included separating apolipoproteins A, B, and C into their component parts and characterizing and sequencing apolipoproteins A-II, C-I, C-II, and C-III. In addition, he discovered two genetic disorders: Tangier disease (TD), which is characterized by an absence of HDL, and cholesteryl ester storage disease, a lysosomal enzyme deficiency. The study of TD has since become a key to our understanding of lipoprotein metabolism.

Together with Bob Levy and Robert S. Lees, Don Fredrickson developed a typing system that describes five patterns of lipoprotein disorders and their clinical characteristics. First presented in the New England Journal of Medicine in 1967, this system of phenotyping includes type III and type V hyperlipoproteinemia and familial hypertriglyceridemia, which were previously unrecognized as discrete forms of dyslipidemia (personal communication, NIH, July 23, 2002). Known as the Fredrickson Classification of the Hyperlipidemias, the system was promptly accepted by the World Health Organization as an international standard, bringing lipoprotein and lipid disorders to the world’s attention.

Don described this period of his life as his “exhilarating days among the lipoproteins,” a phrase that indicates both his love of basic research and his gift for descriptive language. The numerous publications that bear Don’s name as author or editor are models of lucid scientific writing. Each one was a scholarly endeavor, and I recall sitting with him and carefully going over the articles on which we collaborated. In 1960, just seven years after the discovery of the double helix, Don joined with John Stanbury and James Wyngaarden, “with the bold intention to take up from where Garrod had left his descriptions of inherited metabolic disorders in 1908.” Together they created the first edition of The Metabolic Basis of Inherited Disease. Now titled The Metabolic and Molecular Bases of Inherited Disease, this bible of molecular medicine has just been issued in its eighth edition.

Don Fredrickson was a true physician-scientist. He understood that research must be unhurried and allowed to evolve in unpredicted directions, yet he believed that it should ultimately be applied to solving the problems of human disease. In introducing their system of classifying the hyperlipidemias, Don and his coauthors stated that their intent was not to discuss lipoproteins for their own sake, but to illuminate the clinical problem of hyperlipidemia and help the physician develop a rational approach to the hyperlipidemic patient. In 1970, the groundbreaking research by Don and his colleagues prompted the NIH’s National Heart and Lung Institute (subsequently renamed the National Heart, Lung, and Blood Institute) to develop the nationwide Lipid Research Clinics Program (LRCP), which was spearheaded by Bob Levy. One purpose of the LRCP was to conduct a randomized, prospective trial evaluating the effect of lipid lowering on coronary heart disease. The Lipid Research Clinics Coronary Primary-Prevention Trial (LRC-CPPT), a novel collaboration involving government, academic research centers, and the pharmaceutical industry, was the first large study to show a relation between cholesterol lowering and a reduced incidence of cardiovascular disease. It led to the
creation of the National Cholesterol Education Program, which has had a profound influence on the diagnosis and treatment of cholesterol and lipid disorders in the United States.

Beginning in 1953, Don held several important research and administrative positions at the NIH, including Director of the National Heart Institute (an early predecessor of the National Heart, Lung, and Blood Institute) from 1966 to 1968 (personal communication, NIH, July 23, 2002). His laboratory and clinic attracted worldwide attention, and patients with disorders of lipid metabolism were regularly referred to him. Don also promoted the international exchange of scientists from the United States, Europe, and elsewhere.

In 1975, Don Fredrickson was appointed Director of the NIH, a position in which he “was viewed as the ambassador of the life sciences to the highest levels of the federal government.”21 Don was an outstanding choice to head the agency during a crucial time in its history. At the start of his tenure, recombinant DNA technology had just been developed. Apprehension regarding the social and ethical implications of this discovery prompted some influential scientists to call for self-imposed research restrictions. In response, the NIH formed the Recombinant DNA Advisory Committee (RAC).21,22 Don Fredrickson realized that this controversy signified the birth of a new era.23 As “a true statesman of science” (personal communication, NIH, July 23, 2002), he helped shape public policy on recombinant DNA research, achieving a balance between scientific freedom and responsibility. He resisted ill-advised legislation and regulation, actively sought public participation in the debate, and helped members of the scientific community recognize their accountability to society. One of his victories was the expansion of the RAC to include nonscientist members.1,21,22,24

Just five years later, Don’s political skills helped preserve the law that grants perpetual funding to the NIH. At the time, a proposed piece of legislation would have eliminated perpetual authorization, thereby subjecting the NIH to a political process at the end of each funding cycle. Some regard this victory as Don’s greatest contribution to the future of science.21

After retiring from the NIH in 1981, Don became a visiting scholar at the National Academy of Sciences, where he had been President of the Institute of Medicine for one year before becoming NIH Director (personal communication, NIH, July 23, 2002). From 1984 to 1987, he served as President of the Howard Hughes Medical Institute (HHMI), one of the largest private medical research and funding organizations in the world.25,26 Discussing the grant-giving principles that he advocated at the HHMI, Don explained in a 1987 interview that each award should represent a long-term commitment to the recipient.26 In the 1990s, almost 40 years after the discovery of TD, investigators in the field of lipidology identified its cause: a mutation in the gene for the adenosine triphosphate binding cassette (ABC)-A1 transporter, which is responsible for cellular cholesterol efflux.27–32 To Don, this represented a victory for the scientific principles that he espoused: the best research must be given the time and the freedom to evolve.

During the 1990s and up until his death, Don was a Scholar-in-Residence at the National Library of Medicine (NLM). In addition to engaging in research and other scholarly activities, Don was always available to provide advice and support (personal communication, NLM Executive Officer, August 7, 2002). From 1996 to 1997, he chaired the Long-Range Planning Panel on International Programs, an endeavor that reflected his lifelong commitment to worldwide scientific exchange. He was also instrumental in developing Profiles in Science, an Internet site containing the archival collections of prominent 20th century biomedical scientists who donate their collections to the NLM. As one of the first scientists to contribute his papers, Don encouraged others to do the same (personal communication, NLM Executive Officer, August 7, 2002). While at the NLM, Don also did the background research for his memoir of the recombinant DNA controversy, which he so effectively mediated during his tenure as NIH director (personal communication, NLM Executive Officer, August 7, 2002). Published in 2001, the book is a lucid and fascinating account of the scientific, social, political, and entrepreneurial forces underlying the controversy and of the delicate balance that was achieved between public welfare and scientific freedom.24

Despite his abiding faith in science, Don felt ambivalent about some of the medical inventions made possible by research. Addressing medical school graduates of the Mayo Clinic in 1983, he declared that “for most of us who come to offer advice, it is far easier to speak of molecules or genes than to talk of virtue.” Don’s concept of virtue was based on “a determination of the proper mean between excess and deficiency of action.”33 Never forgetting the importance of character in medical and scientific decision making, he described modern medicine as a fusion of experience, art, and science.33

Donald Fredrickson was a pioneer in the study of lipid metabolism and in establishing a link between lipid disorders and coronary heart disease, Western society’s number one killer. He trained a generation of basic and clinical researchers, contributing in immeasurable ways to their careers and creating a new type of specialist known as a lipidologist. These specialists are now national and international leaders in the study and treatment of cardiovascular disease.

On a personal note, I recall the day in 1965 when Don interviewed me for a research position in the Molecular Disease Branch of the NIH. With characteristic hospitality, he invited me to share a sandwich lunch in his office. Just five years earlier, Don had formed the Section on Molecular Disease, which he believed was the first use of this term in the organizational chart of the NIH.9 Happily, I was offered the opportunity to work with Don, Bob Levy, and the other extraordinary investigators on their team. In their laboratory, we found an atmosphere of great intellectual excitement and uncompromising scientific integrity.

Don was also a compassionate physician and clinical investigator whose patients ranged from everyday citizens to the King of Morocco. He moved easily from hospital room to the halls of power, treating each patient and colleague with kindness and attention. As a scientist, clinician, administrator, and public servant, Don Fredrickson adhered to the highest
standards of performance and integrity. His standards of writing and speaking were equally demanding, and he was eloquent in both forms of expression. Don was an absolutely honest, trustworthy, and candid individual. He was devoted to his family, his friends, and his profession. His legacy will be long lasting as we continue to discover how his contributions have benefited science and humankind.

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