NATIONAL ACADEMY OF SCIENCES

DONALD SHARP FREDRICKSON
1924–2002

A Biographical Memoir by

JAMES B. WYNGAARDEN

Any opinions expressed in this memoir are those of the author and do not necessarily reflect the views of the National Academy of Sciences.

Biographical Memoirs, VOLUME 87

PUBLISHED 2005 BY
THE NATIONAL ACADEMIES PRESS
WASHINGTON, D.C.

Photo by Fabian Bachrach

D S Fredrickson

DONALD SHARP FREDRICKSON

August 8, 1924–June 7, 2002

BY JAMES B. WYNGAARDEN

DONALD FREDRICKSON, eminent physician-scientist, former director of the National Institutes of Health, and first full-time president of the Howard Hughes Medical Institute, died suddenly on June 7, 2002, two months short of his seventy-eighth birthday. Fredrickson was semi-retired, living in Bethesda, Maryland, at his home of 50 years, where he swam in his back-yard pool every day. That morning his wife, Priscilla, found him floating in the pool. He could not be revived; the official cause of death was listed as drowning. Donald Fredrickson was buried in Rhijnhof, near Leyden, in the Netherlands on June 13, 2002.

Fredrickson was born and raised in Canon City, Colorado, where his father was a lawyer. He attended the University of Colorado for one year during World War II, before being transferred by the Army to the University of Michigan, where he earned a B.S. in 1946, and an M.D. with distinction in 1949.

An event in medical school profoundly changed his life. During a third-year elective he met a Dutch anesthesiologist

---

Reprinted from *Proceedings of the American Philosophical Society* (vol. 148, pt. 3, Sept. 2004) with minor additions. Courtesy of the American Philosophical Society.

who was spending a year in Ann Arbor. When Don mentioned that he was planning a summer bicycle tour with several classmates in Europe, the Dutch physician urged Don to visit his recently widowed sister in Holland. Don did so, intending to rejoin his classmates a few days later, but then he met the widow's daughter. The result was that Don canceled his bicycle tour and went to Scotland with his new friends. Two years later Don returned to Holland to marry Henriette Priscilla Dorothea Eekhof, to whom he remained devoted for the rest of his life. Don, a sparkling practitioner of the English language, in time became equally accomplished in Dutch.

Following graduation from medical school Fredrickson undertook residency and fellowship training in internal medicine under George Thorn at the Peter Bent Brigham Hospital in Boston, and then spent one year in the laboratory of Ivan Frantz, a cholesterol biochemist at the Massachusetts General Hospital. In July l953, Don moved to the National Heart Institute (NHI), a component of the rapidly expanding National Institutes of Health (NIH) in Bethesda, Maryland, which was to be his scientific home for much of his career. For several years he worked in the laboratory of Christian Anfinsen, a protein chemist and future Nobel laureate, under whom he acquired biochemical knowledge and laboratory skills while researching lipids and lipoproteins. Don concentrated initially on cholesterol metabolism, in collaboration with Daniel Steinberg. Later he focused on structure and metabolism of plasma lipoproteins and their role in lipid transport. He and his colleagues in the Molecular Disease Branch of NHI separated apolipoproteins A, B, and C into their component parts and sequenced and characterized apolipoproteins A-II, C-1, C-II, and C-III. In the early 1960s, Fredrickson and coworkers discovered two new genetic disorders of lipids. The first they named Tangier Disease,

after the island in the Chesapeake Bay where the first patient lived. This disease is characterized by lipid storage in various organs including tonsils and absence of high-density lipoproteins in plasma. Almost four decades later Tangier Disease was shown to result from a mutation in the gene for a protein that mediates cellular cholesterol efflux. The second disease they discovered was cholesteryl ester storage disease, a lysosomal enzyme disorder manifested clinically by hepatomegaly and hyperlipidemia in childhood and premature atherosclerosis.

The contribution that catapulted Fredrickson to worldwide prominence was his classification (with Levy and Lees) of lipid disorders into five categories based on their clinical characteristics and the patterns of array of plasma lipoproteins on paper electrophoresis, a relatively simple procedure widely available. This study eventually included data from over four hundred patients and their family members collected over about eight years at the Clinical Center of the NIH. The adoption of the Fredrickson Classification of the Hyperlipidemias (as it came to be known) as an international standard by the World Health Organization in l972 focused attention of physicians around the globe on these common abnormalities. In 1970 the NHI established a national Lipid Research Clinic Program headed by Robert Levy, one purpose of which was to evaluate the effect of lipid lowering on coronary heart disease. This became the first large study to show a beneficial relationship between cholesterol lowering and cardiovascular disease.

These were exhilarating days in lipoprotein research as well as in the investigation of hereditary diseases in general, especially of the category of disorders characterized by Garrod in 1908 as *Inborn Errors of Metabolism*. The explosion of new knowledge in biochemistry and genetics led to the elucidation of the mechanisms of known hereditary diseases

and the discovery of many new ones. It soon became clear that what had been thought to be a single genetic disease entity often comprised multiple variants that represented different genetic mutations affecting a single protein. In addition, many common diseases were being recognized as having important hereditary determinants. In 1960 Donald Fredrickson joined John Stanbury and James Wyngaarden in creating *The Metabolic Basis of Inherited Disease*, a comprehensive, multi-authored compendium of hereditary disorders about which there was substantial biochemical and genetic knowledge. The original editors husbanded this influential reference work through five editions over 23 years. It has since been continued under other editors, as *The Metabolic and Molecular Bases of Inherited Disease* and is now a four-volume work in its eighth edition, a veritable encyclopedia of molecular medicine.

In addition to directing a vigorous laboratory program in which he trained a number of young physicians who later became prominent figures in lipoprotein research and academic medicine, Fredrickson served in several management positions within the NHI. In 1961 he became head of the Section on Molecular Disease and simultaneously clinical director of NHI. In 1966 he was elevated to chief of the Metabolic Disease Branch and also appointed director of the National Heart Institute, a virtually full-time position involving major interactions with the extramural research community and frequent appearances before Congress on policy and budget matters affecting NHI. He relinquished the institute directorship after two years in order to spend more time in research and to serve in a less demanding administrative position as director of intramural research in the recently renamed National Heart and Lung Institute. His research and administrative accomplishments earned

Fredrickson election to both the Institute of Medicine and the National Academy of Sciences in 1973 at the age of 48.

In 1974 Fredrickson left NHLI to accept the presidency of the Institute of Medicine of the National Academy of Sciences in Washington, D.C. Nine months later he was selected by President Gerald Ford to become director of the National Institutes of Health, a position he viewed as a "cause" he could not refuse. It was a role for which he was superbly prepared by virtue of his knowledge of the institution, his management experience at several levels, and his outstanding record as a research scientist and trainer of young investigators. He was also an exemplar of how human welfare could be advanced by medical science and a gifted communicator well qualified to become its ambassador at the highest levels of government.

Fredrickson assumed the directorship of the NIH on July 1, 1975, at a time of great apprehension on the part of a number of leading scientists over the safety of recombinant DNA research. At a Gordon Conference in the summer of 1973, several scientists had presented reports on the technical ability to join together covalently DNA molecules from diverse sources to create hybrid plasmids or viruses whose biological activity was unpredictable. Following this meeting a conference-approved letter was sent to the president of the National Academy of Sciences expressing great concern over potential risks of recombinant research. The letter was published in the September 13 issue of *Science* magazine. In response, the NAS appointed a high-level committee to consider the risks involved in this research, which in its report, released in a press conference at the NAS in July 1974, recommended a moratorium on certain kinds of experiments and asked the director of NIH (at that time Dr. Robert Stone) to establish a committee to develop guide-

lines for work with recombinant DNA that would minimize the risks. In February 1975, the National Academy of Sciences sponsored a meeting on these questions at the Asilomar Conference Center in Pacific Grove, California, involving 90 American scientists and another 60 from 12 other countries, as well as members of the press. On the final day of the conference, by coincidence, the new NIH Recombinant DNA Molecule Program Advisory Committee held its first meeting on the other side of the country in Bethesda, Maryland. This frenetic activity among scientists concerning a new technology with unknown risks—thought negligible by some, fearsome by others—was well publicized and created considerable public apprehension.

Few directors have taken office in such a highly charged atmosphere. In 1975, two great value systems were on a collision course: those of free scientific enquiry and of environmental protection. Scientists were deeply divided over the moratorium on recombinant DNA research and the entire Asilomar conference process. Many scientists felt they had made a serious mistake by airing technical concerns before a public ill-equipped to understand the complexities that science itself was only beginning to fathom. Fredrickson immediately found himself at the center of this controversy. In his new role as advocate for the life sciences, he sought and ultimately found a solution that enabled recombinant research to continue without compromising an NIH imperative of avoiding an overt regulatory role. But for the first two years of his tenure as director, the recombinant controversy consumed at least half of his time.

Fredrickson had recruited to his staff a young psychiatrist, Joseph Perpich, who was also an attorney and who had experience as a law clerk under Judge David Bazelon and as a congressional staffer under Senator Edward Kennedy. Perpich became Fredrickson's closest advisor and assistant in deal-

ing with the recombinant DNA controversy, a role in which he had many occasions to utilize both his legal and psychiatric training. These were tumultuous times. There were endless rounds of meetings within NIH, within the Department of Health, Education and Welfare (HEW), with other government agencies, with congressional members and staffs, with scientists from the U.S. and abroad, with concerned faculty from nonscientific disciplines, and with many alarmed citizen's groups. The Director's Advisory Committee, comprising outside academics, members from industry and the public, plus ad hoc participants including ethicists, lawyers, and university and academy officers, met to consider the panoply of issues and offer counsel on guidelines. This procedure set a model that would be repeated numerous times in succeeding years. Yet, in the end there was rarely a consensus on risk or procedure, rarely agreement between scientists and nonscientists. In this fractious setting, Fredrickson made decisions he then had to sell or defend to the secretary of HEW and the Congress. In June 1976, with the approval of the secretary, NIH released guidelines for recombinant DNA research designed to ensure that all NIH-supported recombinant research conformed to stringent safety rules and to prohibit deliberate release of organisms containing recombinant DNA into the environment. NIH also established a Recombinant DNA Advisory Committee, comprising scientists, lawyers, ethicists, and public members, whose review and approval were required before any grant application involving recombinant DNA research could be awarded. Applications were also required to have the approval of an institutional biosafety committee before submission to the NIH. Industry voluntarily pledged to observe NIH guidelines in its recombinant research. These processes succeeded in restoring public confidence in the award and oversight processes of NIH concerning recombinant DNA research.

Similar processes and review procedures were set up in other countries in which recombinant research was conducted.

Over succeeding years the guidelines have been revised toward less stringency as scientific progress and a spotless safety record warranted. The end result was that, despite the introduction of more than a dozen bills in the Congress designed to regulate recombinant DNA technology, no such law was ever passed. Fredrickson later commented, "No law, inspection force, or other external regulation can protect the public interest like responsible and responsive self governance."

A quarter century later, many critics now believe that scientists over-reacted to imagined risks of recombinant research and that, in response, so did the public. But Fredrickson had to work with the hand he was dealt, and to his great credit he reached his decisions without negating either the freedom of scientists or the democratic process. Furthermore, the procedures he set in place to examine potential risks in recombinant DNA research have stood the test of time and are today being emulated in addressing risks of bioterrorism.

While many observers regard Fredrickson's skillful handling of the recombinant DNA research safety controversy as his greatest contribution as director, at least one student of NIH (Bradie Metheny) considers Fredrickson's successful defense of the general authorization of the NIH, contained in the Public Health Service Act of 1944, against attempts by Congressman Waxman to abolish that provision in favor of mandatory annual congressional authorizations, as a triumph of even greater consequence for NIH and biomedical research. However, this enervating and divisive battle, which eventually also involved the secretary and the White House, may have hastened Fredrickson's resignation in 1981. These two controversies illustrate one of the greatest contribu-

tions an NIH director can make, namely, dissuading Congress from passing unwise legislation.

After leaving the directorship of NIH, Fredrickson became scholar-in-residence at the National Academy of Sciences. Two years later he was appointed vice president of the Howard Hughes Medical Institute (HHMI) under his early mentor George Thorn, who had been the institute's president since its formation in the 1950s. When Thorn retired from the presidency one year later, Fredrickson was elected to succeed him. He was immediately immersed in the sale of Hughes Aircraft, which the institute owned under the terms of the Hughes will. The huge proceeds of the sale of the aircraft company to General Motors provided a $5 billion endowment for the institute, and enabled the institute to relocate from Coral Gables, Florida, to Chevy Chase, Maryland (to a beautiful site suggested by Mrs. Fredrickson) and to expand its fields of research from three to five programs. Neurosciences and structural biology were added to the existing topics of genetics, immunology, and cell biology. Under Fredrickson's guidance the emphasis of research was shifted from clinical to basic investigation, and the length of support for an individual scientist was extended from several years to a potentially lifelong duration. The number of Hughes investigators was progressively expanded (and eventually grew to over three hundred, located at 70 different sites in the U.S.). A portion of Hughes resources was assigned to grants to small colleges for science teaching and research. Finally, Fredrickson negotiated a joint program with NIH, in which Hughes selected and supported 50 medical students from around the country for a year or more of full-time research in an intramural laboratory at the NIH. These sweeping changes in the character and portfolio of HHMI, which represented wise and bold uses of its new bounties, transformed the institute into a major force in world science.

Hughes awards became among the most generous and most prestigious in the life sciences. Hughes investigators have since won many distinguished prizes, including seven Nobel Prizes.

In 1987 Fredrickson resigned the presidency of the Hughes Institute, under pressure from the trustees because of financial irregularities that occurred on his watch. These events were front page news in the *Washington Post* and widely reported in national scientific journals. Yet, throughout this painful ordeal, Fredrickson remained personally composed with an almost existential detachment from the swirl around him. He returned to NIH as a Scholar at the National Library of Medicine, where he began working on two books, one on the history of the Clinical Center at NIH (which was not completed at the time of his death) and another on the recombinant DNA controversy of the mid-1970s (which was published in 2001). He also resumed clinical and research work in his old unit in the National Heart, Lung and Blood Institute. Among his patients in the Lipid Clinic were some of his original study subjects with Tangier Disease. In the late 1990s Fredrickson coauthored three research publications in *The Proceedings of the National Academy of Sciences* in which the molecular basis of the genetic defect of Tangier Disease was at last defined, almost 40 years after he described the entity. This was not only deeply satisfying to Fredrickson for personal reasons, it was also a cogent illustration of a point often made in his addresses, that the best science takes time to evolve and often awaits developments in collateral fields.

One of Fredrickson's patients during his earlier days of research on lipid diseases at NIH was the crown prince of Morocco, later King Hassan II. The two men developed a friendship that lasted throughout their lifetimes. Fredrickson

served as the king's personal physician for more than 25 years, often arranging for American specialists to travel to Morocco to attend the Monarch or his family. In addition, Fredrickson gave an annual state-of-the-art address to the Moroccan Academy on research advances in the life sciences and medicine. He and Mrs. Fredrickson were also invited to the palace each year to attend the king's birthday party.

Fredrickson was an eloquent speaker and gifted writer. His sentences seemed to flow with an effortless grace, and both in casual conversation and lectern deliveries they were adorned with wit and often with sparkling allusions to classic literature and great writers. Among his favorite authors were W. H. Auden and Oscar Wilde, from whom I suspect he developed a keen appreciation of the importance of style in speech and writing. He was much sought after for keynote and commencement addresses and delivered at least 40 honorary lectureships. He received numerous professional recognitions, including 10 honorary degrees. A measure of his scientific standing is that in Garfield's "citation classics" he is recorded as the most cited physiologist in the world between 1961 and 1975. His collected writings have been deposited in the National Library of Medicine at the NIH. These include three volumes of speeches, articles and selected papers; twelve volumes of diaries relating to his years as physician to King Hassan II; other diaries kept for nine years as a director of Colange, Ltd., a private family-owned European company; twelve "Green Diaries" from the NIH directorship period; and travel summaries from 1960 onward. His was an extraordinary life of remarkable personal achievement and distinguished public service, a life lived with elan and lofty purpose. Don Fredrickson was a valued friend and colleague for 57 years. He is survived by his wife, Priscilla, and two sons, Eric and Ruric.

IN THE PREPARATION of this memoir, I was greatly aided by "In Memoriam, Donald S. Fredrickson, M.D., 1924-2002," by Antonio Gotto, Jr. (Arterioscler. Thromb. Vasc. Biol. 2002; 22:1506–08); "Genetic Engineering and Related Technologies: Scientific Progress and Public Policy," by Joseph G. Perpich (in *Biotechnology in Society, Private Initiatives and Public Oversight,* ed. Joseph G. Perpich, [New York: Pergamon Press, 1986], pp. 87–109); and *The Recombinant DNA Controversy: A Memoir. Science, Politics, and the Public Interest, 1974-1981,* by Donald S. Fredrickson (Washington, D.C.: ASM Press, 2001).

SELECTED BIBLIOGRAPHY

1957

With M. G. Horning and C. B. Anfinsen. Studies on enzymatic degradation of the cholesterol side chain. II. Requirements of the mitochondrial system. *Arch. Biochem. Biophys.* 71:266-273.

1958

With R. E. Peterson and D. Steinberg. Inhibition of adrenocortical steroid secretion by D^4-cholestenone. *Science* 127:704-705.

With D. L. McCollester and K. Ono. The role of unesterified fatty acid transport in chylomicron metabolism. *J. Clin. Invest.* 37:1333-1341.

1960-1983

With J. B. Stanbury and J. B. Wyngaarden, eds. *Metabolic Basis of Inherited Disease.* Editions 1-5. New York: McGraw-Hill.

1961

With P. H. Altrocchi, L. V. Avioli, D. S. Goodman, and H. C. Goodman. Tangier disease. *Ann. Int. Med.* 55:1016-1031.

1963

With K. Ono and L. L. Davis. Lipolytic activity of post-heparin plasma in hyperglyceridemia. *J. Lipid Res.* 4:24-33.

1964

With O. Young, T. Shiratori, and N. Briggs. The inheritance of high density lipoprotein deficiency (Tangier Disease). *J. Clin. Invest.* 43:228-236.

1965

With R. S. Lees. A system for phenotyping hyperlipoproteinemia. Circulation 31:321-327.

1966

With R. I. Levy and R. S. Lee. The nature of pre-beta (very low density) lipoproteins. *J. Clin. Invest.* 45:63-77.

With R. O. Brady, J. N. Kanfer, and M. B. Mock. The metabolism of sphingomyelin. II. Evidence of an enzymatic deficiency in Niemann-Pick disease. *Proc. Natl. Acad. Sci. U. S. A.* 55:366-369.

1967

With D. S. Waldorf and R. I. Levy. Cutaneous cholesterol ester deposition in Tangier disease. *Arch. Dermatol.* 95:161-169.

With W. K. Engel, J. D. Dorman, and R. I. Levy. Neuropathy in Tangier disease: a-lipoprotein deficiency manifesting as familial recurrent neuropathy and intestinal lipid storage. *Arch. Neurol.* 17:1-9.

1968

With A. M. Gotto, R. I. Levy, and A. S. Rosenthal. Human serum beta-lipoprotein. *Nature* 219: 1157-1159.

1969

With R. A. Heinle, R. I. Levy and R. Gorlin. Lipid and carbohydrate abnormalities in patients with angiographically documented coronary artery disease. *Am. J. Cardiol.* 24:178-186.

The regulation of plasma lipoprotein concentrations as affected in human mutants. *Proc. Natl. Acad. Sci. U. S. A.* 64:1138-1146.

With W. V. Brown and R. I. Levy. Studies of the proteins in human plasma very low density lipoproteins. *J. Biol. Chem.* 244:5687-5694.

1970

With J. L. Beaumont, L. A. Carlson, G. R. Cooper, Z. Fejfar, and T. Strasser. Classification of hyperlipidemias and hyperlipoproteinemias. *Bull. World Health Organ.* 43:891-915.

1971

With A. M. Gotto, R. I. Levy, and K. John. On the protein defect in a beta lipoproteinemia. *New Eng. J. Med.* 284:813-818.

With S. Quarfordt and R. I. Levy. On the lipoprotein abnormality in Type III hyperlipoproteinemia. *J. Clin. Invest.* 50:754-766.

1972

With H. R. Sloan. Enzyme deficiency in cholesteryl ester storage disease. *J. Clin. Invest.* 51:1023-1026.

1973

With J. L. Breslow. Primary hyperlipoproteinemia in infants. *Annu. Rev. Med.* 24:315-324.

1974

With N. J. Stone, R. I. Levy, and J. Verter. Coronary artery disease in 116 kindred with familial Type II hyperlipoproteinemia. *Circulation* 49:476-488.

1976

With R. S. Shulman, A. K. Bhattacharyya, and W. E. Conner. B-sitosterolemia and xanthomatosis. *New Eng. J. Med.* 294:481-482

1979

A scientist's view of priorities and control in the organization of research. In *Nobel Symposium Proceedings*, ed. T. Segerstedt, pp. 81-87. Stockholm: Pergamon Press.

1999

With A. T. Remalay, R. Rust, M. Rosier, C. Knapper, L. Naudin, C. Broccardo, K. M. Peterson, C. Koch, I. Arnould, C. Prades, D. Duverger, H. Funke, G. Assmann, M. Dinger, M. Dean, S. Santamarina-Fojo, P. Denefle, and H. B. Brewer Jr. Human ATP-binding cassette transporter (ABC 1); ZZ genomic organization and identification of the genetic defect in the original Tangier disease kindred. *Proc. Natl. Acad. Sci. U. S. A.* 96:12685-12690.

2001

The Recombinant DNA Controversy: A Memoir. Science, Politics, and the Public Interest, 1974-1981. Washington, D.C.: ASM Press.