In Memoriam

David L. Williams
1946–2004

The community of lipid and atherosclerosis research scientists lost a valued member with the passing of Dr. David L. Williams on July 16, 2004. David died in Houston, Texas, during artery graft surgery necessitated by his long struggle with Marfan syndrome. Those familiar with Dave's research will be saddened by the loss of an accomplished scientist whose insights, careful research, and intellectual rigor enhanced our understanding of steroid hormone action, vitellogenesis, reverse cholesterol transport, and the biology of apolipoprotein E (apoE). For those fortunate enough to have experienced Dave's mentorship, friendship, courage, love of life, and wonderful sense of humor, we also mourn the loss of a unique and inspirational personality.

David was born and raised in Wilkesboro, Pennsylvania. He attended the University of California at Berkley, where he received his A.B. in Zoology in 1967. For his doctoral training, he went to the University of Illinois at Urbana, where he worked in the laboratory of Jack Gorski. This was soon after Toft and Gorski identified the estrogen receptor and therefore an exciting early period in the nuclear receptor field. In a distinguished graduate career that produced nine publications over a 5 year period, he detailed the impact of ligand binding on the relative distribution of the estrogen receptor in the cytosol and nucleus. After a short stint as a postdoctoral fellow in William Rutter's laboratory at the University of California, San Francisco (UCSF), Dave joined the faculty of the Department of Pharmacological Sciences at the State University of New York at Stony Brook in 1974, as one its founding members. He remained in his position at Stony Brook for the next 30 years, becoming a full professor in 1986 and serving at various times as his department's vice-chair and interim chair.

David's research as an independent investigator focused initially on avian yolk protein production and its regulation by estrogenic steroids. During this time, Dave made numerous contributions, including the purification of multiple avian vitellogenins, the characterization of avian apoB as a single high molecular weight apoprotein, the establishment of the role of secondary structure in steroid hormone-mediated regulation of mRNA stability, and the elucidation of the developmental regulation of hepatic estrogen responsiveness, work done collaboratively with Catherine Lazier of Dalhousie University. His advances in this area were recognized by the National Institutes of Health in the form of a MERIT Award granted in 1990. Although the major emphasis during Dave's early career was on the regulation of avian yolk protein biogenesis by steroid hormones, these studies soon brought him into the mainstream of lipoprotein and atherosclerosis research.

In the course of studying hepatic apoB secretion, Dave observed that the avian kidney also synthesized and secreted apoB. Extending these studies to other avian tissues and apolipoproteins revealed that apoA-I was widely expressed in extrahepatic tissues, including kidney, adrenal, adipose, testis, artery, and skeletal muscle. This was the first demonstration that "peripheral tissues" synthesize apolipoproteins and contradicted the existing dogma that the liver and intestine were the exclusive sites of synthesis. In 1983, Dave went on to show that human peripheral tissues also synthesize apolipoproteins; however, in the case of primates, the apolipoprotein was apoE and not apoA-I.

Thus began Dave's long quest to understand the many facets of apoE biology. With Larry Rudel of Wake Forest University, with whom he has collaborated for more than two decades, Dave showed that apoE is also widely expressed in nonhuman primate tissues, including the brain. Along with Nisson Schechter, also at Stony Brook, Dave went on to show that apoE synthesis was induced in rat optic nerve undergoing Wallerian degeneration, suggesting a new role for apoE as a carrier of cholesterol in the central nervous system. When combined with the pioneering work of Bob Mahley and colleagues of the Gladstone Foundation at UCSF, these early studies helped lay the foundation for the extensive ongoing exploration of the role of apoE in brain pathophysiology.

To quantify apolipoprotein mRNA in these pre-PCR-era studies, David designed an extremely sensitive and accurate solution hybridization assay, which Mike Brown at the University of Texas Southwestern Medical Center once referred to as the "Lowry of mRNA measurement." In 1985, Dave wrote a review article for *ATVB* (then called *Arteriosclerosis*) entitled "Molecular Biology in Arteriosclerosis Research." This was at a time when many in the lipid and atherosclerosis fields were embracing molecular techniques, and Dave's article was widely read and highly influential in encouraging the expanding use of these approaches.

Dave revisited his interest in steroid hormone biology and his newfound focus on mammalian lipoprotein metabolism by studying the mechanisms by which the adrenal gland acquires and stores cholesterol for steroid hormone biosynthesis. Studies using adrenal cell lines, as well rat and mouse models, provided support for the hypothesis that apoE acts to enhance adrenocortical esterified cholesterol accumulation and diminish corticosterone production. Then, in collaboration with Jan Breslow at Rockefeller University, Dave ultimately discovered that genetic disruption of the apoA-I gene (and not apoE) causes a gross reduction in cholesterol delivery to the adrenal gland, proving that HDL serves as the predominant carrier of cholesterol to this tissue in rodents.

At about the time that Dave was demonstrating that sterol delivery to the adrenal is mediated by HDL, scavenger receptor class B type I (SR-BI) was identified as an HDL receptor by Monty Krieger at the Massachusetts Institute of Technology. Dave and Monty then collaborated to establish the role of SR-BI in adrenal cholesterol delivery. This was followed up by a series of in-depth studies on the molecular mechanisms responsible for SR-BI-mediated cholesteryl ester uptake and cholesterol efflux, many of which were performed collaboratively with George Rothblat and Mike Phillips, now at Children's Hospital of Philadelphia, as well as Robert Hamilton at UCSF. Among the many important advancements to emerge from these studies was the discovery that SR-BI, and the process of HDL selective uptake, was confined to biochemically and morphologically distinct microvillar structures specifically adapted to favor rapid cholesterol flux between HDL and the plasma membrane.

Among Dave's more recent discoveries was that apoE could achieve protection from atherosclerosis in mice independently of its role as a ligand for lipoprotein receptors. Indeed, when apoE expression was limited to the adrenals, a robust protection against atherosclerosis was observed with virtually no effect on plasma lipids. Although the basis for the non-lipoprotein-mediated effects of low-level apoE expression is not yet known, these studies have created a bridge between lipoprotein metabolism and vascular wall biology that continues to be the subject of broad inquiry.

Dave spent considerable time and effort training the next generation of scientists, and he excelled in this category. All told, 29 of his trainees have gone on to productive careers in academia and industry. These include 13 faculty members at 10 different academic institutions in the United States and abroad. Dave was also a dedicated and outstanding educator who consistently involved himself in the development and implementation of curricula and training programs. His annual series of lectures on "Principles of Medical Pharmacology" have been noted by three decades of Stony Brook medical and graduate students as educational highlights. In appreciation of his engaging and effective teaching style, Dave was awarded the Aesculapius Award for Outstanding Teaching by the Stony Brook University School of Medicine in 1997.

In addition to his research and teaching accomplishments, Dave provided extensive service to the scientific community. He was a member of the editorial boards of *Molecular Endocrinology* and the *Journal of Lipid Research* and also provided ad hoc reviews for more than a dozen scientific journals. He was an active member of the American Heart Association and served as a spokesperson for the National Marfan Foundation. Dave served on numerous review committees for the National Science Foundation and the National Institutes of Health and was a standing member of the National Institutes of Health Metabolism Study Section from 1991 to 1995. He was a frequent session chair and moderator and chaired the Gordon Conference on Lipoprotein Metabolism in 1998. Dave's many contributions will be commemorated annually at the Kern Aspen Lipid Conference by the David L. Williams Lectureship for Young Investigators.

Dave leaves behind many friends and colleagues who will miss him in so many different ways. His warmth, his affable style, his wry sense of humor, his love of baseball, fine dining, family, and friends, his selfless service to his department, university, and personal and professional communities are all parts of Dave's remarkable legacy. But perhaps more than anything, Dave will be missed for his ability to light up a room and to make us laugh. His advice and perspectives and his positive outlook on life, even in the face of his own formidable obstacles, were an inspiration to so many. Dave is survived by his wife, Mena Ostapchuk, and sons Matthew and Spenser Williams. He will be greatly missed.

Gregory S. Shelness
Paul A. Dawson
Wake Forest University School of Medicine