Donald MacFarland Small, MD, MA (Oxon)

Donald M. Small passed away on Friday, Jan. 25, at his Southern California home at the age of 87. Don had a distinguished career over five decades, studying bile salts, lipids and atherosclerosis from a unique physical-chemical perspective, leading to seminal discoveries on the pathogenesis of gallstones, lipoprotein structure and atherosclerotic plaque formation and regression. With the support of his colleagues at Boston University, he served as the Editor-in-Chief of the Journal of Lipid Research from 1979 to 1982, helping to sustain and extend the quality of the journal. He also served as an Associate Editor of JLR from 2003-2006. He was a longstanding member of the Journal’s Advisory Board and Chair of the Board from 2015-2016.

Donald MacFarland Small was born in Newton, Massachusetts on September 15, 1931 to Willard and Grace Small but raised in Southern California. Don was a Phi Beta Kappa graduate of Occidental College (1950-54), and a Marshall Scholar to Magdalen College, Oxford (1956-58), receiving an MA (Oxon) degree in Animal Physiology. He received his MD from UCLA, School of Medicine, in 1960 and began his internship at Boston University Medical Center. He remained at Boston University for his whole career; he was Professor of Physiology & Biophysics, Biochemistry and Medicine. Stimulated by his mentor Franz Ingelfinger, who was chief of gastroenterology at BU and later the editor of the New England Journal of Medicine, Don travelled to France to carry out a fellowship in biophysics, under the guidance of Professor D.G. Dervichian at the Institut Pasteur in Paris. These studies involved physical-chemical analysis of the phase behavior of model lipid systems including those simulating the composition of human bile. This work led to several publications with Dervichian and Bourges, including a key contribution "Ternary and quaternary aqueous systems containing bile salts, lecithins and cholesterol" (Nature, 1966).

In 1968, Don returned to the United States and showed, with his colleague Dr. William H. Admirand, that bile samples from patients with gallstones contained an excessive amount of cholesterol compared to patients without gallstones. This work was published as "The physico-chemical basis of cholesterol gallstone formation in man" in the Journal of Clinical Investigation. In this work, Don plotted the composition of bile on triangular coordinates (which became known as Small’s Triangle, a modified version is shown to the right) and showed that gallstone patients had a composition that fell in the zone of cholesterol supersaturation and cholesterol crystal formation. Follow-up studies by Don, Martin Carey and others showed that in gallstone patients the liver is secreting either excessive amounts of cholesterol or insufficient amounts of the solubilizing factors lecithin and bile salts, leading to crystallization of cholesterol and the formation of gallstones. In essence, Don had discovered the cause of gallstones.

Don’s work represented a conceptual breakthrough that led to development of gallstone dissolution therapy, involving the administration of bile acids such as ursodeoxycholic acid to patients with gallstones, thus avoiding major surgery.
Subsequently, Don turned his research interests to studies of plasma lipoproteins and atherosclerotic plaques. In 1974, he published, together with his colleague Dr. G. Graham Shipley, a seminal paper in *Science* on the physical-chemical basis of lipid deposition in atherosclerosis. This paper showed that lipid phase diagrams could correctly predict the physical form of lipids in atherosclerotic plaques. With colleagues Graham Shipley, David Atkinson, Alan Tall, Richard Deckelbaum and James Hamilton, he published many studies on the structure of lipids and lipoproteins. In 1986, he published “The Physical Chemistry of Lipids, from Alkanes to Phospholipids,” a highly acclaimed 672-page resource. For more than 40 years, he and his colleagues studied the physical biochemistry of bile, lipoproteins and atherosclerotic lesions, and during this period, Don authored more than 300 publications.

Don assumed many important leadership roles at the School of Medicine and Boston University, local and national societies, and editorial boards, in addition to a variety of advisory board roles at the National Institutes of Health.

He founded the Biophysics Institute at Boston University School of Medicine that evolved into the Department of Biophysics and served as its Chair from 1988 to 2000. He guided its merger with the Department of Physiology in 2000, and served as Chair of Physiology & Biophysics until 2006 when he passed the role to David Atkinson. Don led an NIH-funded Program Project Grant “Structural and Cell Biology in Cardiovascular Systems” and together with his colleagues in the department received $51.7 million in grant funding during his career. He also served as Chairman of the Council on Atherosclerosis of the American Heart Association from 1992-1994 and Vice Chairman for several decades.

Among his many honors, he was selected by the American Heart Association in 1986 to deliver the George Lyman Duff Memorial Lecture on his extensive work on the physical-biochemistry of atherosclerotic lesions. He also received the first Distinguished Achievement Award of the Alumni of UCLA Medical School in 1988; the Eppinger Prize from the 4th International Congress on Liver Diseases in 1976; and the Annual Distinguished Achievement Award from the American Gastroenterological Association in 1972.

Don was committed to teaching and training the next generation of physician scientists, having mentored more than 45 MD and PhD postdoctoral fellows and served on greater than 40 PhD dissertation committees. His mentorship style was characterized by intensity, warmth and humor. Many of Don’s trainees have gone on to successful careers as scientists and leaders in lipid, gallstone, lipoprotein, atherosclerosis, and structural biology research.

Don’s curiosity and passion for science was boundless. Working right up until his retirement at the end of 2018, his final scientific paper in collaboration with Ajjaji et al, "Dual binding motifs underpin the hierarchical association of perilipins1-3 with lipid droplets" documented new work showing that perilipin proteins associate with lipid droplets in a hierarchical manner. The paper was published on January 16, 2019, in *Molecular Biology of the Cell*, just nine days before he died.

An avid sportsman and nature-lover, Don played many sports, enjoyed outdoor activities and traveled widely during his life. Don was a dedicated skier continuing in the sport up to
the age of 85. He navigated the Grand Canyon of the Colorado River several times including in a small kayak. A recognized gastronome and wine-connoisseur, he became a passionate cook in his later years and in 1991 published, with Cheryl Oliva and Anna M. Tercyak, "Chemistry in the kitchen: Making ground meat more healthful" in The New England Journal of Medicine. The paper outlined a technique that enabled saturated fats and cholesterol to be removed from meat without losing its flavor. This unique work led to a US patent award for the technology to Boston University. He had an insatiable curiosity in how everything in the world worked, a brilliant mind, and strong political views. While concern over the lack of adequate funding for pure scientific research was prominent throughout his entire career, in later years he grew extremely concerned about global warming, nuclear contamination and the increasing role of corporate influence on America's health care system, including medical research.

Don married his first wife Elisabeth (Betty) in 1957 while they were in Oxford, UK. Their first son Geoffrey was born in 1959 in Los Angeles and their second son Philip was born in 1964 while they were in Paris, France. Betty passed away in 2013. Don was married to his second wife Kathryn from 1986 to 2000 and they celebrated the birth of their son, Samuel, in 1991.

Don is survived by his former wife Kathryn Dame; sisters Jane, Mews, and Emilie; sons Geoffrey, Philip and Samuel; daughters-in-law Diana and Nina; grandchildren Hugo, Lily, Riley and Elmo; and niece Rebecca.

G. Graham Shipley
Alan R. Tall
David Atkinson