# *In Memoriam*: William E. Connor (1921-2009)

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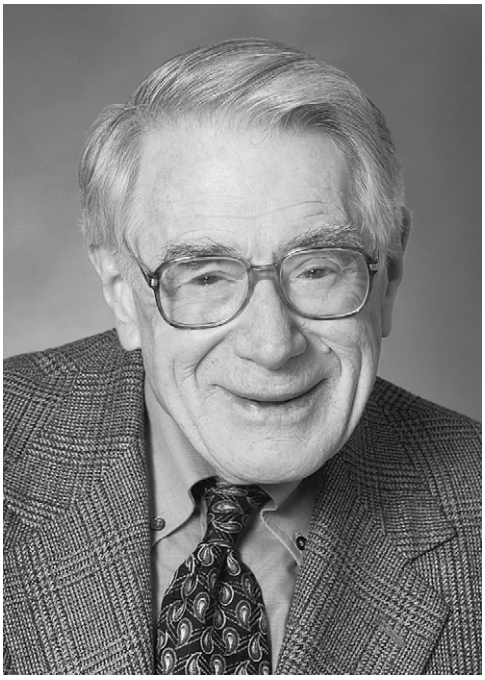
The fields of lipid, sterol, and nutrition research have lost a true pioneer, a physician-scientist who made highly significant contributions for over five decades. William E. Connor, MD, passed away in Portland, Oregon on October 25, 2009. Bill, as he was fondly known, enjoyed a career spanning two centuries and was very much active in patient care, research, and advocacy when he died at the age of 88 years. He was still transitioning and bringing to a close actively funded research projects he led when he died after a long battle with prostate cancer. Bill once mentioned the "R" word in a lab meeting, but the next week quickly put an end to further discussion of retirement. It seems he was happiest doing what he did every day: caring for patients and investigating ways to improve their lives. It is understandable, but regrettable (considering the lipid field has grown rapidly since Bill's career began) that the name of this pioneer, who had such a profound influence on this field, may not be readily recognized by some newcomers to the field. Bill Connor published 400 scientific articles, the most recent appearing this month, with more to follow posthumously.

Bill was born in Pittsburgh, Pennsylvania, spent his childhood in Iowa, and earned his BS and MD from the University of Iowa. After serving in the Army Signal Corp. in Hawaii during World War II, he completed a US Public Health Service Internship and residency and practiced for two years before completing an American Heart Association Research Fellowship at the University of Iowa, where he stayed on as faculty from 1958 to 1975, climbing the ranks to Professor of Medicine. He moved to Oregon Health Sciences University (now Oregon Health & Science University), in 1975, where he had a long and distinguished career until his death. As a Visiting Fellow, he spent time at the Sir William Dunn School of Pathology, Oxford, UK (1960), Indiana University and Karachi, Pakistan (1961–1962), Australia National University, Canberra (1970), and Baker Medical Institute, Melbourne, Australia (1982). Bill Connor belonged to a select set of pioneers one can best describe as 'cholesterol experts to the cholesterol experts'. It has been said that if all the experts and believers in the 'cholesterol hypothesis' in the world had been gathered in a medium-sized hotel in the 1950s, there would still be vacancies. In 1956, Bill published his first paper on the association of hyperlipidemia and coronary atherosclerosis. Thus began his odyssey of elucidating the role of lipids, but more specifically dietary cholesterol, on the pathogenesis of atherosclerosis. The body of his work has influenced so many aspects of our current knowledge in the field that documenting each significant contribution would require a separate treatise.



Bill Connor was a physician-scientist carrying out translational research long before either of these concepts had gained any traction. He was the true triple threat; his students and his trainees knew him as a respected teacher and mentor, his peers as a thoughtful scientist, and his patients as the best physician they could ever have. In collaboration with a variety of colleagues, Dr. Connor made a number of links between nutrition and disease that were at the time controversial, but which have since become

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*DOI 10.1194/jlr.E005900*

accepted as fact. He published a series of papers on the role of dietary cholesterol in regulating plasma cholesterol, followed by papers showing that diabetics could eat a low-fat, high fiber diet (instead of a high-fat, low fiber diet) and still control their blood sugar levels (1), elucidating the trafficking of cholesterol during fetal development [note his classical 1969 paper in the *Journal of Lipid Research* using a chick egg showing the brain needed to synthesize all its own cholesterol after the development of the blood-brain barrier (2)], describing secretion of cholesterol by the skin (3) and transfer of plasma cholesterol into semen (4), proving that altering diet could lead to regression of atherosclerosis (5), that use of omega-3 fatty acid rich foods lowers triglycerides (6), and on to the role of nutrition on plasma lipids in the Tarahumara Indians of Mexico (7) as well as in school-age children in Iowa [the Muscatine Study (8)], etc.

Dan Steinberg (another pioneer) wrote recently, "Bill was a way ahead of (his) time. He tried to get the AHA to adopt the Step III diet, much like Pritikin's, in the 1960s." As Dr. Steinberg quotes in his book, 'The Cholesterol Wars' (9), "To be sure there may be additional factors that confer on the Japanese and the Chinese their wonderfully low heart attack rate, but it appears that diet is the main reason. If so, we could reduce heart attack rates in the United States by almost 90% by radically modifying our diet, "Nipponizing" it, if you will. Such a proposal would, understandably, be met with loud guffaws. Actually just such a proposal was made almost 40 years ago by a farsighted pioneer in nutrition, William E. Connor. He urged the American Heart Association to recommend what he called an "alternative diet", a diet that he had shown lowered blood cholesterol in hyperlipidemic subjects by 26%. However, he was overruled by more conservative voices." and "the cholesterol content of the diet also makes a difference. However, the effect of increasing cholesterol intake is generally much less impressive than the effects of increasing saturated fat intake. The reason for this, as first shown by Dr. William Connor and his colleagues, is that beyond a certain "threshold" level of cholesterol intake further increases have little additional effect on blood cholesterol level. Adding just 100–200 mg cholesterol per day to a previously cholesterol-free diet can raise the blood cholesterol level by as much as 20%. Once the total daily cholesterol intake has reached about 300 mg per day there is a "saturation phenomenon" such that further increases in cholesterol intake have very little effect on blood cholesterol levels. In a sense the damage has already been done when the cholesterol intake is at or above 300 mg. For most Americans, daily cholesterol intake is already at or above 500 mg/day on their usual diet." Many of these concepts form the basis of the nutrition books written by Bill and his wife Sonja (see below).

All of these contributions exemplified his physician-scientist approach and there is no better single example of this than his report of a new disease, β-sitosterolemia (phytosterolemia), which he published with his colleague Ashim Bhattacharyya (10). This publication, in the appropriately named journal, not only described an unusual case of a novel sterol disorder, but reported a very methodical clinical investigation that Bill and Ashim undertook in an attempt to understand the disease. When one considers the era in which this paper was written, their Discussion, which offered a hypothesis for the potential defects [now proven (11–13)], was remarkably prescient. Subsequent investigations of this disorder led to the fundamental discovery of a pathway that had eluded us for almost a century, the pathway by which dietary cholesterol traffics in the intestine and how it is excreted in the bile. It remains, in our opinion, one of the best examples of how to perform clinical investigative research and exemplifies the scientific abilities of Bill Connor and his team [life-long colleagues Don Lin and Sonja Connor (also his wife)]. More recently, in 1994, Bill was assigned to review a manuscript on Smith-Lemli-Opitz syndrome (SLOS) and became fascinated. With his strong interest in nutrition and sterol metabolism, he thought he might be able to help these children whose ability to synthesize cholesterol is impaired and inspired an entire team of clinician-researchers at OHSU to take up the study of SLOS. This led to series of clinical and laboratory studies undertaken with the goal of improving management of these children (14–18). This year the team inspired by Bill was awarded the National Institutes of Health Rare Disease Clinical Research Network (http://rarediseases.info.nih.gov/Wrapper.aspx?src=asp/resources/extr_res.asp) funding to expand their studies to several sites across North America.

Finally, at age 87, Bill published the results of some of his studies on another rare disease, Cerebrotendinous Xanthomatosis, in the *JLR* and showed that dietary sources of cholestanol may be an important contributor to the high levels seen in affected individuals (19). And while his patients and their families will fondly remember Dr. Connor, he also has a very appreciative following nationally, astute lipidologists and patients alike who have recommended or used the nutrition books he wrote with Sonja. The New American Diet Cookbook (Simon and Schuster, 1987, New York, NY) is still one of the best nutrition books available and remains one our patients tell us they still use in striving for a better lifestyle.

Although the tribute to Bill Connor could end with a list of his medical and scientific achievements, his awards and accolades, the tapestry of Bill's life is far richer and intricate. He belonged to a generation that believed deeply in social responsibility and social justice. Bill became a life-long Quaker while serving in Hawaii during World War II. During his time in Iowa, he campaigned for abolition of the death penalty, repealed in 1965, and continued to advocate for the same cause in Oregon (named Chair Emeritus for Oregonians for Alternatives to the Death Penalty). Bill was a passionate peace advocate and worked on this effort with many groups. He led peace demonstrations during the Vietnam War at the University of Iowa. Bill campaigned for civil rights and even helped wash dishes alongside Martin Luther King, Jr. at an American Friends Committee family camp. He regularly volunteered his time at local free health clinics and was an avid supporter of environmental conservation. Bill was involved locally with the Friends of Marquam

Nature Park, the Nature Conservancy, and had climbed Mt. Hood, Mt. Adams, and Mt. St. Helens. He was often seen biking to work, and did yoga daily. He was, importantly, a family man, thrilled to spend time with children and grandchildren and carry on family traditions.

We stand on the shoulders of giants; Bill Connor was one of those giants, a kind and gentle giant. He touched many lives, including his loving family, his community, his patients and their families (local and national), as well as academic colleagues and even politicians. Those touched by Bill Connor, MD, teacher, scientist, physician, family man, and champion of social causes, are indeed fortunate to have known him.

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