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IN MEMORIAM

Daniel Porte Jr, 13 August 1931–13 May 2023

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Daniel Porte Jr passed away peacefully at the age of 91, remaining until the very end interested in science and particularly the work of his former trainees. He was a gifted scientist, outstanding mentor and consummate human being.

Born in New York, the son of a cardiologist, his future in medicine may have been pre-ordained, but the trajectory it would take was beyond the imagination of most. Dan completed his undergraduate education at Brown University in Providence, Rhode Island; this was followed by medical school at the University of Chicago, where he graduated with his MD in 1957. He then moved to the west coast of the USA to undertake his internal medicine training at the University of California, San Francisco, and while there spent a block of time performing research in the institution's Cardiovascular Research Institute.

In 1963 he was recruited by Robert H. Williams to join the Division of Endocrinology at the medical school at the University of Washington in Seattle. Here he rapidly established himself as an outstanding physician-scientist and was promoted from an Assistant Professor, his initial faculty appointment, to Professor of Medicine in just 8 years. During his 34 years on the faculty, he also made major contributions to leadership at the University of Washington and its affiliated hospitals, including as Chief of the Division of Endocrinology and Metabolism and as Director of Research and Development at the Veterans Affairs Medical Center in Seattle. In 1977 he became Director of the National Institute of Diabetes, Digestive and Kidney Diseases (NIDDK)-funded Diabetes Endocrinology Research Center at the University of Washington and for 19 years guided its growth to become one of the preeminent diabetes research institutions in the country. In 1999, he retired from the University of Washington and relocated with his wife Eunice to San Diego, California, where he was appointed as Professor of Medicine at the University of California, San Diego, and continued to provide patient care at the VA San Diego Health Care System.

His research in Seattle evolved over many years, but a consistent theme was the brain–islet axis. In the early days he studied the role of the sympathetic nervous system in the control of islet function, and particularly insulin secretion. He showed in humans that the well-recognised increase in plasma glucose with adrenaline (epinephrine) was the result of decreased, rather than increased, insulin release as a result of activation of the alpha-adrenergic receptor [1, 2]. Then, he demonstrated that the neurotransmitter noradrenaline (norepinephrine) also inhibited insulin secretion in humans [3]. Based on oral glucose tolerance testing, he and his colleagues were subsequently the first to show that obesity is

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associated with enhanced insulin responses and that, in people with type 2 diabetes, such responses are diminished [4]. The concept that an early impairment in beta cell function is crucial to the pathogenesis of this disease proved to be correct but, like so many of his early findings, took a long time to be accepted, because many at the time viewed insulin resistance as the primary defect. The recognition of the critical role of the beta cell ultimately arose in part from work he participated in that established the importance of considering the prevailing insulin sensitivity when interpreting insulin responses [5]. Dan and his co-workers' studies of the beta cell also highlighted that the secretory capacity of the cell is reduced [6] and, using a 'home-grown' insulin antibody, that proinsulin processing is impaired [7] in people with type 2 diabetes.

While working on the beta cell, he also commenced studies on the role of insulin in body weight regulation. Given the finding of hyperinsulinaemia in obesity, he and Steve Woods developed the hypothesis that circulating insulin functions as an 'adiposity signal' that relays information to the brain regarding the status of body fat stores; the brain then uses this information to adjust food intake so as to promote homeostasis. Early support for this hypothesis was provided by Dan and his colleagues, who demonstrated in a primate model a dramatic reduction in food intake and body weight during an intracerebroventricular infusion of insulin [8]. Just as beta cell dysfunction in type 2 diabetes was originally seen as a heresy, the concept of insulin as an important neural signal was originally met with scepticism. Not to be deterred, he and his colleagues proceeded to make a series of seminal findings, including that insulin is transported across the blood–brain barrier via an active, receptor-mediated process [9], and that insulin inhibits a key subset of neurons in the hypothalamic arcuate nucleus that express both neuropeptide Y and agouti-related peptide [10]. Given the key role played by these neurons in the control of food intake, these findings helped set the stage for the ground-breaking identification of leptin as an adipose tissue hormone that acts on many of the same brain circuits to promote energy homeostasis.

For his scientific achievements he received numerous awards, including the two highest awards of the American Diabetes Association (ADA). In 1971 he was the recipient of the Eli Lilly Award for Outstanding Scientific Achievement, which in those days required the recipient to be under the age of 40. This was followed 19 years later by the Banting Medal for Scientific Achievement, a fitting tribute for all his scientific contributions. It is noteworthy that, in his 1990 Banting lecture, he gave tremendous credit to those he had trained and with whom he had collaborated, clearly recognising and honouring the importance of science as a team effort. The high regard in which his scientific contributions were held was also exemplified by his receiving in 1996 the US Department of Veterans Affairs Middleton Award for outstanding research accomplishments, an annual recognition conferred on a single investigator selected from across all medical disciplines throughout the Veterans Affairs system.

Dan always indicated that his scientific success was something constructed in large part from the interactions he had with others, be they junior or senior faculty, inside or outside his home institution, well recognised or less well known. But his true love was the opportunity to mentor so many young minds and witness them flourish in numerous ways, whether as scientists or clinicians. He also had a remarkable ability to recognise and pursue opportunities to assist others as they endeavoured to bring their ideas to the fore. This quality enabled many individuals to make contributions to the field of glucose metabolism who otherwise may never have had the opportunity to do so. Some of these aptitudes were taught and fostered by those who mentored him, and Dan spoke of how his approach had been moulded in part by the sabbatical he spent working with Albert Renold at the University of Geneva in Switzerland. It was therefore fitting that in 1995 he received the Albert Renold Award for outstanding mentorship from the ADA in recognition of his remarkable training legacy.

Outside his scientific contributions, Dan was an active citizen of our community. He served on a number of National Institutes of Health (NIH) committees, including the NIDDK Advisory Council, NIDDK's congressionally mandated Diabetes Research Working Group, and the Advisory Committee of the National Heart, Lung and Blood Institute (NHLBI) Program on the Etiology of Excess Cardiovascular Disease in Diabetes, and was a special advisor to the Director of NIH for Annual Scientific Review. At a difficult time for the ADA, he was called on to be part of its leadership and ultimately as President from 1986 to 1987. In those days the connection between the European Association for the Study of Diabetes (EASD) and the ADA was not as it is today, in part because communication and travel were so much more difficult. In fact, it was only during his tenure as President of the ADA that the fax machine become a feature in offices. Given his cooperative nature, which included in 1987 chairing the Joint Liaison Committee of the ADA and Endocrine Society, one is left to imagine what links he would have forged between the ADA and the EASD if his presidency had occurred sometime later. It was for his major scientific contributions along with his leadership that, in 2019, the membership of the EASD bestowed on him one of their highest honours: lifetime Honorary Membership.

Daniel Porte Jr left this world in the manner he wanted, at peace and surrounded by family. His legacy lives strong, not only through his science, but also through the scientists who he trained and the generations of their trainees. He will be sorely missed, but his spirit will live on through all of us forever.

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