PROFILES IN PROGRESS

# Daniel Porte Jr.: A Leader in Our Understanding of the Role of Defective Insulin Secretion and Action in Obesity and Type 2 Diabetes

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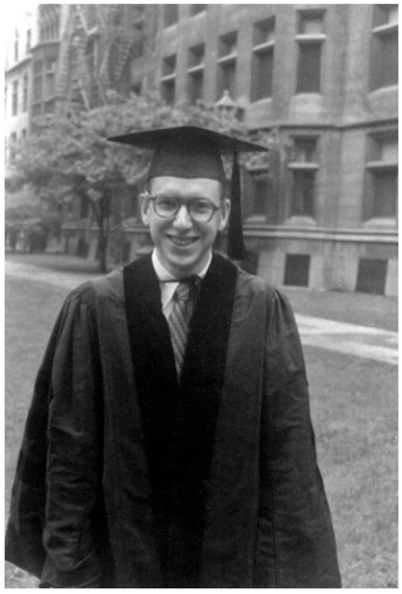
## The Early Years: From New York to Seattle

Daniel Porte Jr. was born in New York City in 1931, and with his father being a clinical cardiologist, medicine was part of his life from very early on. After completing his undergraduate studies at Brown University, he commenced his migration west by first attending medical school at the University of Chicago, where he graduated with honors in 1957. Completing his westward migration, Dan moved to San Francisco for his internship and residency training in medicine in the University of California system. During that time, he spent 2 years performing research with Richard Havel at the Cardiovascular Research Institute at the University of California, San Francisco. It was during this period that Dan published his first scientific article describing cholesterol-labeled lipoproteins as a tracer for examining the fate of plasma cholesterol (1), as well as a clinical research study of an unusual patient with McArdle syndrome causing defective muscle phosphorylase leading to defective exercise tolerance (2).

Based on this early experience, it became clear to Dan that his future lay in academia and clinical research, so he decided to travel north to the University of Washington (UW) in Seattle for fellowship training in endocrinology and metabolism. One of the academic attractants at the time was Robert H. Williams, who was a leading national force in endocrinology and Chairman of Medicine at UW. As lipids were an important area of investigation in Seattle as well as in San Francisco at the time, Dan continued to work in this area during his fellowship and early faculty years. Following the development of the insulin radioimmunoassay, however, a whole new field opened up and he moved his research in a completely new direction.



*Daniel Porte Jr. at medical school graduation, University of Chicago, 1957*

## Early Formative Studies: Regulation of Insulin Secretion

Dan commenced his research in glucose metabolism and diabetes with studies on the control of insulin secretion by the sympathetic nervous system. At this time glucose was widely viewed as the dominant, if not the sole, controller of insulin secretion. Dan's work started with a demonstration in humans, published in the *Journal of Clinical Investigation*, that the well-known hyperglycemic effect of epinephrine was accompanied not by the expected increase of insulin secretion but, in fact, by epinephrine's inhibition of insulin secretion (3), an observation which became a citation classic. Thus began Dan's view that sustained hyperglycemia, here mediated by epinephrine, required inhibition of insulin secretion. This concept was to reemerge later in his group's work demonstrating that β-cell dysfunction in type 2 diabetes was an early and primary cause of the sustained hyperglycemia that characterizes this disease (see β-CELL DYSFUNCTION IN TYPE 2 DIABETES). He went on to determine the mechanism whereby epinephrine impaired insulin secretion (4): epinephrine activated an α-adrenergic receptor later identified on the β-cell. This work was quickly followed by his demonstration, published in *Science*, that infusion of the sympathetic neurotransmitter norepinephrine also inhibited insulin secretion

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in humans (5). Thus, for the first time, the sympathetic nervous system emerged as an inhibitory controller of insulin secretion. This seminal work won him recognition in 1970 as a recipient of the Lilly Award for outstanding achievement by a young investigator (given to a scientist under the age of 40) from the American Diabetes Association.

Dan's interest in neural control of the islet accelerated during his sabbatical in Geneva, Switzerland, at the laboratory of Albert Renold. In the Renold laboratory, he used a dog model to demonstrate that pancreatic nerve stimulation could inhibit insulin secretion (6). He extended those observations to include glucagon in collaboration with Errol Marliss and others by demonstrating that the same nerve stimulation increased glucagon secretion (7). These studies, together with his earlier work in humans, led to his landmark review with Steve Woods entitled "Neural Control of the Endocrine Pancreas" (8). This review legitimized the concept that the sympathetic nervous system was capable of modulating both insulin and glucagon secretion in directions that would stimulate hepatic glucose production and produce the hyperglycemia seen during stress.

Dan and his colleagues made another fundamental observation—that the insulin response to an oral glucose challenge is augmented in obese individuals (9). Combined with his findings on the inhibitory effect of norepinephrine, this work helped to establish that the amount of insulin secreted can be modulated up or down by a range of stimuli to accommodate changing physiological needs. This was a novel and paradigm-changing finding, because at the time neither the concept that insulin secretion is affected by body habitus nor the fact that it can be dynamically regulated by a large number of influences had been established. Today, these fundamental concepts are taught routinely in college physiology courses, but at the time this was completely uncharted territory.

In the same seminal study, Dan and colleagues also examined the insulin response to oral glucose in obese adults with diabetes (whom we would now consider to have type 2 diabetes), and they reported that the insulin response was markedly decreased, especially during an early time point after glucose administration. Further, in line with the now well-accepted idea that the degree of β-cell dysfunction is a determinant of the degree of hyperglycemia in these patients, they reported that the integrated insulin response over the course of the test was inversely related to the glucose excursion. Linking these findings back to his earlier work, he subsequently showed that sympathetic nervous system inhibition of insulin secretion is more pronounced in individuals with type 2 diabetes than in control individuals without diabetes, raising the possibility that increased sympathoadrenal tone contributes to β-cell dysfunction in this setting (10).

These observations—made more than 50 years ago—were not widely accepted for another 30 years or so, owing in part to important studies documenting the role of obesity-associated insulin resistance in diabetes pathogenesis. Work by many pioneering investigators at the time gave rise to the concept that insulin resistance (i.e., a reduced ability of insulin to promote glucose uptake and metabolism), rather than β-cell dysfunction, was the primary pathogenic mechanism in obesity-associated diabetes (11–13). Given the importance of insulin resistance in this disease process, the most parsimonious (and widely accepted) explanation for the hyperglycemia of type 2 diabetes was that β-cell dysfunction was a late event and secondary to insulin resistance, rather than playing a primary, causal role.

## β-Cell Dysfunction in Type 2 Diabetes

The controversy surrounding the relative contributions made by insulin resistance and β-cell dysfunction to the pathogenesis of type 2 diabetes set the stage for much of Dan's work over the next decade or more. Questions that Dan addressed included not only whether β-cell dysfunction is required for diabetes to occur, but whether it develops early in the disease, prior to hyperglycemia onset and, if so, what underlying mechanisms might be responsible. As part of this work, Dan felt it important to develop quantitative tools for in vivo measurement of β-cell function in humans. Early in the course of these studies, together with colleagues including John Brunzell, Paul Roberston, Roger Lerner, Bill Hazzard, John Ensinck, and Ed Bierman, he demonstrated that β-cell dysfunction in type 2 diabetes is characterized by loss of the first phase response to intravenous glucose and that this defect was detectable even at glucose levels well below the diagnostic criteria for diabetes (14), establishing that impaired β-cell function develops prior to hyperglycemia onset. This quantitative work culminated in the description of the maximal secretory capacity of the β-cell, which he and his trainee Ken Ward showed is also markedly impaired in type 2 diabetes (15).

Today, the causal link between impaired β-cell function and the pathogenesis of type 2 diabetes is fundamental to our understanding of the disease, having been buttressed by findings by many groups using wide-ranging experimental paradigms. As one example, multiple genome-wide association studies—a technology that could not have even been imagined 50 years ago—have established the pancreatic β-cell as a major target for type 2 diabetes–associated gene variants (16,17).

Dan's pioneering work in β-cell function and type 2 diabetes became a magnet for investigators from around the world who came to Seattle to work with Dan and pursue additional, fundamental questions relevant to glucose homeostasis and type 2 diabetes pathogenesis. Among these was Richard Bergman, who with his colleagues early in the 1980s developed a mathematical method for analysis of insulin sensitivity and glucose effectiveness from a frequently sampled intravenous glucose tolerance test. Richard had developed this "minimal model" method in dogs; it was validated in humans in collaboration with Dan's group in Seattle (18). Now a standard tool employed for studies of human metabolic physiology, the use of this form of modeling analysis in clinical investigation was revolutionary at the time. Another example of an international leader in type 2 diabetes research whose time in Seattle had a profound impact is C. Nick Hales from the U.K. His work with Dan Cook, who was among many young scientists recruited to UW by Dan, led to the discovery of the ATP-sensitive potassium channel, a breakthrough finding for understanding the mechanism underlying glucose-induced insulin secretion at the cellular level.

The antibody used by Dan and colleagues for measuring insulin concentrations had a somewhat unexpected but

highly informative additional benefit. This antiserum cross-reacted with other insulin-like molecules including proinsulin. By determining the relative concentrations of proinsulin and insulin, Dan and colleagues added to evidence that the amount of proinsulin (relative to insulin) that is secreted is abnormally elevated in type 2 diabetes across a range of human populations, including Pima Indians (19). The widespread use of this antisera expanded what we know about proinsulin secretion and its inefficient processing in relation to type 2 diabetes (20,21).

In recognition of his numerous contributions to our understanding of the importance of insulin secretion in the physiology and pathophysiology of glucose metabolism, Dan was awarded the American Diabetes Association's Banting Medal for Lifetime Scientific Achievement in 1990. His lecture "β-Cells in Type 2 Diabetes Mellitus" was a stunning recount of his contributions for which he subsequently received numerous other major awards (22).

## The Brain as a Target for the Action of Insulin

A remarkable aspect of Dan's career is that in parallel with his groundbreaking work on β-cell function and type 2 diabetes pathogenesis, Dan was also developing a program investigating brain mechanisms controlling body fat stores and the role of insulin in this process. Until fairly recently, obesity was not viewed as the result of an underlying homeostatic defect but as the consequence of environmental factors and lifestyle choices. Certainly, that was the prevailing attitude in the 1970s, when Dan began his collaboration with Steve Woods. Steve was a faculty member in the UW Department of Psychology and was interested in physiological mechanisms involved in control of food intake and body weight. Working with Steve, Dan became interested in the hypothesis, first articulated by Gordon Kennedy in the 1950s, that body fat stores are subject to homeostatic control. Specifically, he proposed that humoral signals are generated in proportion to body fat stores and that they enter the brain to provide an afferent signal to neurocircuits that control food intake and energy expenditure. Such "adiposity negative feedback signals" were viewed in this model as being paramount to the process of energy homeostasis, the process whereby energy intake and expenditure are matched over long time intervals to maintain stability in the amount of fuel stored as fat.

Such signals had yet to be identified at that time, but they struck Steve and Dan as a matter of considerable scientific interest. Building off of Dan's earlier demonstration that obesity is associated with hyperinsulinemia, Dan and Steve considered the possibility that circulating insulin might gain access to the brain and function there as an adiposity negative feedback signal. Consistent with this possibility was evidence that insulin receptors are present in brain parenchyma, including in hypothalamic areas known to be important for the control of food intake and body weight. The two of them then set about investigating the hypothesis that as body fat mass increases, a heightened insulin signal to the brain elicits a compensatory decrease of food intake that promotes the return of body fat stores to their baseline value. Conversely, knowing that weight loss induced by caloric restriction is associated with a fall in circulating insulin levels, they proposed that reduced insulin action in the brain in this setting activates hypothalamic neurocircuits so as to increase food intake and recover lost weight. As an initial test of this hypothesis, they performed a study in which insulin or vehicle was infused directly into the brain in a primate model. Their finding that food intake and body weight drop precipitously during an intracerebroventricular infusion of insulin was a paradigm-shifting observation, published in *Nature* in 1979 (23).

The notion that insulin functions as an adiposity negative feedback signal was highly controversial at the time, for several reasons. First, the brain was widely viewed as "insulin insensitive" because it was known that glucose uptake by the brain is not stimulated by insulin, and the notion that insulin has cellular effects beyond those involved in nutrient metabolism had yet to emerge. Second, interest in the notion that insulin's lipogenic action causes obesity was gaining momentum, and the idea that hyperinsulinemia protects against obesity (via a heightened central action of insulin) is at odds with this concept. As is truly characteristic of Dan's approach to science, he was completely unperturbed by being viewed as outside the mainstream, so instead of backing down, he and Steve endeavored to build a program over many years that ultimately would include Denis Baskin, Dianne Latteman, Al Sipols, Michael Schwartz, and Randy Seeley, among others.

*Porte family at Banting Lecture, 1990. Left to right: Kenneth (son), Jeffrey (son), Eunice (wife), Dan, Michael (son)*

Work by this group produced a number of fundamental observations that serve as a legacy to Dan and Steve's early ideas about both insulin action in the brain and energy homeostasis more broadly. Among these is evidence that in a dog model, insulin enters the brain from plasma in proportion to its circulating level in a manner that is saturable, consistent with transport across the blood-brain barrier facilitated by insulin receptors (24). They also identified a key subset of hypothalamic neurons involved in energy homeostasis as being sensitive to input from insulin. These neurons, situated in the hypothalamic arcuate nucleus, express both neuropeptide Y and agouti-related peptide (AgRP); currently referred to as AgRP neurons, they are now known to be of unparalleled importance in the control of food intake, particularly in response to fasting. The Seattle group members were among those to suggest that these neurons are activated during fasting (circa 1991), and because *1*) fasting lowers plasma insulin levels and *2*) both insulin receptors and AgRP neurons are concentrated in the arcuate nucleus, they showed in 1992 that the fasting-induced fall of insulin levels is required for the effect of fasting to activate these cells (25). This work established AgRP neurons as targets for the central action of insulin, constituting the first clear demonstration of hormonal regulation of feeding-relevant hypothalamic neurons, and this finding has since been replicated and expanded upon by many others.

The trail blazed by this body of work helped to set the stage for the discovery of the adipocyte hormone leptin. Like insulin, plasma leptin circulates at concentrations proportionate to body fat mass, and the Seattle group showed that plasma leptin enters the brain in proportion to its circulating level. Similarly, leptin receptors are concentrated in the arcuate nucleus, leptin acts in the brain to suppress food intake, and this effect is mediated in part by inhibiting AgRP neurons. It is a testament to Steve and Dan's legacy that much of the work that led to these fundamental conclusions was performed by the group that they assembled, using metabolism-based paradigms analogous to those that Dan had developed in his pioneering work on insulin secretion. One long-lived and highly relevant legacy stemming from this work is that it helped to establish that body fat stores are subject to homeostatic regulation and that, as such, obesity is best viewed as a disorder of energy homeostasis, rather than the consequence of dietary indiscretion or other behavioral shortcomings.

## The Porte Legacy: Leading By Example

In addition to his scientific accomplishments, Dan has been a shining example as a mentor and leader in how to perform science. There are numerous examples of leading scientists who were trained by Dan, and their accomplishments are a monument to his legacy. Among his most compelling qualities as mentor was his unbridled enthusiasm for science and his desire to stimulate young investigators to think creatively, critically, and independently as they developed their scientific careers. Dan also made sure that every trainee got to attend and present at appropriate scientific meetings and was introduced to leaders in the field.

Noteworthy also is that Dan is among those rare investigators who performed and published research across species ranging from rats and mice to dogs, baboons, and humans. This track record reflects not only the breadth of his research but his philosophy that any one experimental approach or model was secondary in importance to the scientific question that needed to be answered—if the question was sufficiently important, he would develop and implement whatever approach he felt was best to answer it. To one extent or another, we all experienced and benefited from components of his approach, some of which are described below.

### Research Training Conference

One of the weekly features of the Porte training program was a work-in-progress seminar series known as the Research Training Conference. This was not the traditional seminar series or conference. Rather, it was an opportunity for research fellows to present their work at an early stage of development for critical input that was usually constructive, although at times it could feel "destructive" to those on the receiving end. Dan was a major force at these meetings, asking perceptive and penetrating questions that would get to the heart of what was missing or needed. By the time trainees graduated, they had been through this gauntlet of critical assessment so many times that they would be completely ready to face and defend scientific questions from anyone in the outside world, no matter the venue.

One of the saving graces for the presenter at these meetings was that there was no need to prepare a full 90-min presentation, since at least half that time would be spent in discussion, typically led by Dan. The nature of the discussion was such that while the presenter may at times have felt a bit intimidated, there was no shortage of learning how to describe and defend one's findings. This had the effect not only of building the trainees' confidence in their ability to present in front of virtually any audience, they also came away from the experience feeling that their work and ideas were valued by scientific minds that they respected. And outside visitors saw this, too. A number of visiting faculty attending this conference over the years took the concept home to incorporate it into their respective training programs.

### Grants Versus Contracts

In Dan's view, a research grant that was funded to you was for the purpose of enabling you to do the best science you could, and to this end the conceptual underpinnings of the grant must evolve over time. Thus, to Dan, a grant proposal was an opportunity to synthesize new ideas and to then develop and test them during the funding period. We were in this manner encouraged to chase the ideas that seemed most interesting and compelling as the data began to appear, rather than remaining wedded to what was in the original proposal. A frequent refrain from him was "This is a grant, not a contract!" It was this nimbleness that, in retrospect, made it possible for Dan's academic offspring to take science in new and interesting directions.

### Late Afternoon Meetings: The Good and the Bad

Dan's unbridled enthusiasm for science was perhaps best portrayed in small group or one-on-one meetings with trainees and junior faculty to discuss their ongoing research. In these meetings, usually held in the late afternoon, you were encouraged to express your own opinions about the data and their interpretation, whether you liked them or not. Dan was always optimistic and enthusiastic regardless of the data, and he remained 100% focused on the trainee and the conversation, typically in an open-ended manner with no prespecified stopping point. It was in these meetings that some of the most exciting ideas were born. And he would give credit where credit was due if an idea that he was initially less enthusiastic about came to fruition. Of course, these meetings also came with some provisos. It was not advisable to start one of these meetings if you had another appointment or, more importantly, if your family was expecting you for dinner in the next 2 hours!

### From Skepticism to Enthusiasm

What Dan might initially treat with an element of skepticism could, with the correct approach, eventually gain his enthusiasm. When a trainee would bring a new set of data for his review, for example, the most critical starting point from Dan's perspective was that the data were well founded, regardless of what they might imply. In his view, rather small numbers of observations could not be interpreted without supplemental testing to ensure their validity. Stated differently, Dan was skeptical of new observations—even if they might be consistent with his preconceived notions—until they had been properly vetted. He also strongly believed that prior to publication of any set of observations, the performance of a second series of studies using an alternative method was required to ensure their veracity. In this way, while Dan encouraged free thinking and enthusiasm in the conduct of their

research, at the same time he taught his trainees to ensure that the underpinnings for their enthusiasm were solid. Today, we consider it rigor and reproducibility. In the Porte lab, it was just good science.

## The Porte Legacy: Diabetes and Veterans Affairs Research

Aside from the impact Dan has had on individuals who were part of his own research group, he contributed to diabetes through his leadership roles both in Seattle and at the national and international level.

### Diabetes Research Center

This center, funded by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), has been a focus of diabetes investigation in Seattle for over 40 years, and Dan led it for 19 years. Aside from the biomedical cores that provided cutting-edge services to members of the center, thereby offering new approaches for many to use in their research, the associated enrichment program brought a variety of knowledgeable and talented scientists to town and helped attract local faculty into diabetes who may not otherwise have become interested. The pilot and feasibility program of the Diabetes Research Center supported numerous young investigators, providing them with their first independent grant. UW's reputation in diabetes research was strongly enhanced by the existence of the Center, and it provided the basis for the endowment of one of the first chairs in diabetes research in the world. This led to Åke Lernmark's move to Seattle as the first holder of the Robert H. Williams Endowed Chair in diabetes research, and he spent more than a decade broadening the scope of type 1 diabetes research in the region.

### VA Puget Sound Health Care System

For 28 years, Dan also led the research program at the Seattle Veterans Affairs (VA) Medical Center as the Associate Chief of Staff for Research. He advocated vigorously for both protected time and for resources that would help local investigators to be successful. By the end of his tenure, the research program in Seattle had become a jewel in the crown of both the VA and the UW Department of Medicine. Reflecting this success both as an investigator and as an administrator, Dan was selected to serve as a member of the VA's National Medical Research Advisory Group in Endocrinology and Metabolism and as the VA representative to the NIDDK Advisory Council, a role he played for 6 years. He also received the Middleton Award from the VA in 1996.

*First Neuropancreatic Interactions Meeting, Kroc Foundation, 1976. Left to right, back row: Joe Goodner, Albert Renold, Harold Lebovitz, Norbert Freinkel, Yutaka Oomura; middle row, standing: Larry Frohman, Steve Bloom, Ralph Miller, Steve Woods, Tony Pearse, Terry Powley, Gerry Grodsky, Anton Steffens, Don McMillin, Ingmar Lunquist, Bart Hoebel, Philip Smith; middle row, sitting: Franz Matchinsky, Jacqueline Renold, Dan Porte, Eunice Porte, Mrs. Robert Kroc; front row: Neils Christensen, Ian Burr, Peter Amacher*

### American Diabetes Association

Dan's talents as a leader and innovator were also sought out by many professional organizations. He was happy to serve the scientific community and throughout his career contributed locally, nationally, and internationally. Perhaps the most noteworthy of these numerous roles was that of President, Medicine and Science, of the American Diabetes Association, a position that he held from 1986 to 1987.

## The Porte Legacy: The Trainees

No account of Dan's legacy would be complete without highlighting at least some of his many trainees. Among those not mentioned already are Jeff Halter, Chief, Division of Geriatric Medicine, University of Michigan, 1984–2011; Stu Metz, Chief, Division of Endocrinology and Metabolism, and Head of the Diabetes Program, University of Wisconsin–Madison; Yutaka Seino, Director General, Kansai Electric Power Medical Research Institutes; Mike Pfeiffer, Senior Director for U.S. Medical Affairs at Janssen, Pharmaceutical Companies of Johnson and Johnson; John Brunzell, Professor of Medicine, University of Washington; Jim Best, Dean, Lee Kong Chian School of Medicine, Singapore; Ken Ward, Cofounder, Pacific Diabetes Technologies; and many, many more.

## The Porte Legacy: Life Outside of Science

Dan was much more than a scientific leader, clinician, administrator, and mentor. Everyone who worked with him was embraced as a friend socially. Much of this attitude was the result of the personality of his wife Eunice, who he met while a student at Brown and who spent the next 56 years involved in all aspects of his life. They had three sons: Jeffrey, an obstetrician/gynecologist in New York; Michael, who is in media and also living in New York; and Kenneth, who has followed somewhat in the medical tradition, being a veterinarian in San Diego.

The Portes held numerous casual dinners and other events at their house and would always step up to help anyone with a personal issue. The Porte home always had a welcome mat out for anyone in need. As but one example, after Steve Woods had major surgery and was in and out of the hospital for several months, Dan and Eunice took him in, took care of him, prepared his meds every day,

fed him, and so forth until he was ready to return to independent life some months later.

It was Dan and Eunice's partnership and their relationship with all of us, as well as others they touched, that has made all our lives better for the time we spent with them.

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