JOHN P. PETERS SYMPOSIUM

John P. Peters: His Role in Diabetes, Research, and Patient Care

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If one were to state a focus for Dr. Peters’ work it would be for fluid homeostasis. His work on body water, electrolytes, and acid-base balance are certainly the most important and the most enduring of his contributions to biomedical science. His contributions to the field of diabetes extended across the entire spectrum: carbohydrate metabolism and diabetes, lipid metabolism and diabetes, plasma proteins and diabetes, and perhaps most importantly, the management of diabetes.

At the heart of Dr. Peters’ work was his ability to make quantitative measurements and his ability to apply them to experimental evidence and patient care, which is noteworthy, especially considering the context in which he worked. His contributions to science and biomedicine extended from 1917 to 1955. Thus his work either pre-dated or was concurrent with some enormous contributions in the field of diabetes. First and foremost, he predated the introduction of insulin. From an experimental point of view and a patient care point of view, the treatment of diabetes without insulin is almost mind-boggling for those of us in the field today. In addition, Dr. Peters either pre-dated or spanned the antibiotic era, and it is unimaginable to think about managing diabetics prior to that time. He clearly pre-dated our ideological distinctions of the forms of diabetes but already had enormous insight into this important issue, and he clearly pre-dated the ability to measure polypeptide hormones in blood and to use these to characterize the etiologic distinctions. Yet again, he had enormous insight into what would later evolve as more specific classifications of the disease.

As reported in a paper that was published in 1917 in the Journal of Biological Chemistry, Dr. Peters injected adrenaline into two patients and observed their blood sugar going up and their carbon dioxide going down [1]. His focus is the mechanism of hyperglycemia, and he talked about the issue of whether vascular changes introduced by adrenaline or the acidosis or the loss of alkali, as he puts it, is in fact related. He concluded that this is basically due to
glycogen breakdown — and this was well before four Nobel Prizes were awarded for our understanding of how adrenaline raises the blood glucose concentration.

In 1931, he had already begun to talk about what would later become etiologic distinctions in diabetes. He had begun to discuss issues such as insulin resistance. He used this terminology in the context of other endocrinopathies, but he clearly understood the relationship of this to the more common forms of diabetes. He focused on protein and fat metabolism. He was particularly aware that diabetes was a starvation state, not in the sense of deprivation of nutrients, but in the inability to use those nutrients. He recognized that deprivation of those nutrients was not useful in the treatment of disease, a perspective that was not prevalent at the time. He was particularly concerned about the combustion of ketones and about ketoacidosis and about the nature of acidosis in diabetes. He pointed out that bicarbonate is seldom necessary when insulin is used. He described in great detail the relationship of electrolyte depletion to water balance. He was particularly concerned about the metabolism of ketacids and the necessity of administering carbohydrate in an attempt to accelerate their combustion, decrease the accelerated catabolic state in fatty acid oxidation, but the difficulty in doing so without creating a greater osmotic load and a greater fluid loss. He and his colleagues described in great detail a number of case reports of individual patients, and he appreciated the enormous heterogeneity that was present in each individual and each case of diabetic ketoacidosis. He also appreciated the fact that these people needed to be treated as individuals.

Every house officer at Yale knew about his attempt to use fructose-containing solutions in the treatment of diabetic ketoacidosis in an attempt to administer carbohydrate without increasing the osmotic load. It was something of a controversial concept as to whether or not this was possible. Years later, an article published in the June 1999 issue of Diabetes is titled "Small amounts of fructose markedly augment hepatic glucose uptake in the conscious dog" [2]. While Dr. Peters might not have favored the use of the conscious dog, the article clearly supports the notion that he held at that time and that has continued to merit study.

Dr. Peters introduced the intravenous glucose tolerance test, which is still used today to diagnose diabetes and in fact is used in a variety of other ways now to measure degrees of insulin resistance, to measure insulin secretion, and a number of other factors.

Dr. Peters used a very careful quantitative methodology. While he didn't believe patients should be statistics, he did believe that science should be statistically proven.

He had clear views about both the application of science and the management of patients with diabetes: "The common practice of speaking of spontaneous diabetes mellitus of man as a disease, is not yet, and may never be, justified. The term is applied to any condition in which the oxidation of carbohydrate is chronically impaired." It is a concept that we continue to struggle with today. We have at least made some progress in dividing diabetes into Type 1, a clear autoimmune disease, and Type 2, a disease of insulin resistance but undoubtedly a disease made up of multiple different etiologic categories. Dr. Peters understood this at a very early time.

Peters noted, "Diabetes is one of the most common disorders, the incidence in the population is as high as 10 percent." That's very close to the statistics that we actually use today. He then goes on to point out the nightmare of determining the genetics of the disease, something we clearly do not understand even now, although we've made progress in our understanding. We can define autosomal dominant forms of diabetes known as
MODY diabetes. We can define syndromes of defective insulin receptors. We can find mitochondrial disorders in which the genetic disease is actually known. We can at least have a very early glimpse of the etiologic classifications of diabetes, something that Dr. Peters was greatly concerned about.

He also pointed out, "So great is the incidence of vascular disease that it is regarded by many as a consequence of diabetes. It is, however, a fallacy to presume that because two variables are correlated with one another they have the relation of cause and effect, or without other grounds to assign to one of them the role of cause." That could perhaps relate to many things, but it clearly relates to our understanding of macro-vascular disease. While we do not understand why that disease is so accelerated in diabetes, we can at least strip away the micro-vascular classification today and clearly attribute that to the metabolic disorder that is associated with diabetes. So, Dr. Peters would perhaps be pleased to know that at least a subset of this particular dilemma that concerned him can be answered today.

He stated, "On the other hand, some patients with clinical diabetes often require far larger doses of insulin to control glycosuria and hyperglycemia and can be withdrawn from insulin without a dramatic reaction." How could one describe what we call Type 2 diabetes any better today?

Peters wrote, "Since all of the activities and vicissitudes of life influence the course of diabetes, no satisfactory therapeutic regimen can be established or adjusted in a hospital. Hospitalization is necessary or desirable only for the management of complicating conditions or emergencies." Clearly Dr. Peters understood that diabetes is a disease in which the patient must participate, and that the interaction between the doctor and the patient can influence the disease.

The objective in the treatment of any chronic disease should be to enable the patient to enjoy as full and active a life as possible, according to Dr. Peters. "Medicine should not be entirely negative and restrictive. It should especially avoid emptying life of the features that give enjoyment and a sense of accomplishment." This is a very sensitive statement about the practice of medicine. "It is too early to congratulate ourselves and somewhat ridiculous to blame patients for the incidence of these associated, complicating conditions. Some of the most medically virtuous have succumbed early while rascals have escaped," he went on. "I would not say that only the good die young, but experience has convinced me that in this as in many another panels of life, virtue too often has to be its own and only reward."

Diabetes has an enormous effect with respect to kidney disease, amputations, and many other aspects. Cardiovascular disease is two times more common; stroke, two- to four-fold more common; and diabetes is the leading cause of new cases of blindness.

Now, what are we doing about this? The Captopril Study demonstrates that the administration of Captopril, an angiotensin converting enzyme inhibitor will ameliorate the course of end-stage renal disease by a factor of close to 50 percent at doses that do not effect blood pressure [3]. The Diabetes Control and Complication Trial, the largest clinical study of diabetes ever undertaken, is a study that has brought diabetes into the realm of what we now know is so important in cholesterol and hypertension control [4]. Because of this study, we can ascribe the same benefits to glycemic control.

Figure 1 shows glycosylated hemoglobin values on the vertical axis. There is a control group and an intensely treated group. There is only a 20 percent difference
in their glycosylated hemoglobin levels, and yet you see that all the intensively treated patients are still abnormal as shown by the shaded line. This study has proven that we can interdict the course of retinopathy by 27 to 76 percent, of nephropathy by 34 to 57 percent, and neuropathy by 60 percent. It is this kind of study that permitted me in my testimony to the Congress to defend an NIH budget of $14.6 billion for fiscal year 1999 and $944 million for my own institute. Figure 2 shows what I was able to present to the Congress. The vertical axis represents the percentage of the patients with end-stage renal disease, and the top line indicates what happens in the natural state, that is, under no particular therapy. The next line indicates what we can do with tertiary prevention, that is, the Captopril Trial. We can clearly reduce the magnitude of that effect by a significant amount. The next line shows what happens in the diabetes control and complication trial, with control of the metabolism and blood sugar. Note how markedly end-stage renal disease is reduced. The dashed line indicates what happens in a primary prevention trial. Now the first two are already done, we have results. The only thing we have to do there is to actually implement this. The last line is theoretical, it is a study that is ongoing, and the line is drawn to simulate the outcome of the study. Should we get a positive effect in the primary prevention study, we could reduce the course of end-stage renal disease to almost zero.

And now on a more personal note, as a full-time employee of the Federal Government, I think it would not be appropriate to simply reiterate or apologize for our government’s treatment of Dr. Peters. However, I think what is important is to see how he has thrown down the gauntlet for us. From the government’s perspective, there is enormous support for biomedical research, and the National Institutes of Health is attempting to fully respond to the challenge. To meet the challenge presented
by Dr. Peters, we must do everything possible to create healthy behaviors, such as smoking cessation. We must do everything possible to transmit this enormous energy of science into improving the health care of all people. That, I believe, would be an appropriate tribute to Dr. John Punnett Peters.

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