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JOHN P. PETERS SYMPOSIUM

John P. Peters and Nephrology

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John Punnett Peters, M.D., (1887-1955) can be said to have established the solid foundations of modern nephrology in an understanding of the chemistry of the body.

The rebellious son of an Episcopal minister and noted Egyptologist, he was sent to a military preparatory school (Manlius) as a boy and then to Yale, where he majored in classics and won his varsity letter in diving. To earn money for his tuition at medical school, he taught English and classical languages at Manlius for a year. After graduating from Columbia's College of Physicians and Surgeons and its residency program in Internal Medicine, he worked first at Cornell Medical College and then at the Rockefeller University Hospital in New York with outstanding biochemists of that day, including D.D. Van Slyke, A.B. Hastings, and W.C. Stadie. In 1921, at the age of 34 years, he was recruited to the Yale School of Medicine and soon appointed to the John Slade Ely Professorship in Internal Medicine, where he was to remain a bulwark of the School of Medicine at Yale for the rest of his life (Figure 1).

In the early part of the 20th century, physicians were beginning to interpret patients' symptoms in terms of biochemical processes and apply quantitative methods of chemistry and physics to the problems of disease. At the end of World War I, venipuncture was becoming a common procedure, and such chemists as Van Slyke, Folin, Benedict, and Bang were developing practical methods for the analysis of blood. These were rapidly applied by a group of enlightened young clinicians that included James Gamble, Daniel Darrow, Fuller Albright, Allan Butler, and John P. Peters, who quickly established the basis of our present scientific understanding of body fluids. Peters was preeminent in this company, not only because of his mastery of both biochemistry and bedside medicine, but also because of his lucid and prolific writings.

An ardent social activist, Peters was the moving spirit behind *Principles and*

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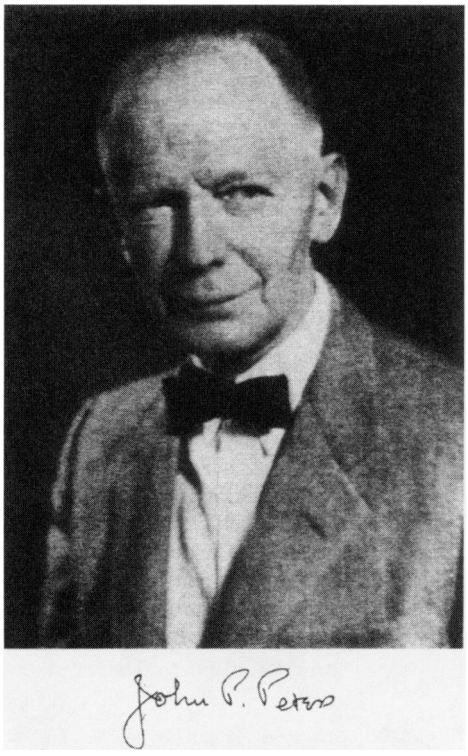

Figure 1. John P. Peters, circa 1947.

Proposals, published in 1937 by a committee of 400 physicians, urging that public funds support medical care for the indigent, medical research, and the improvement of medical education, and that federal health and medical activities be consolidated into a separate department. Although these proposals sound modest today, they were bitterly attacked at the time as radically dangerous and leading to "state medicine." In 1953, Peters was dismissed from his $50-per-year consultant position on a Public Health Service peer review panel because of an anonymous accusation of disloyalty. Dr. Peters fought the case to the United States Supreme Court, claiming the right to face his accusers, and was eventually exonerated.

It is appropriate, but in a sense paradoxical, to commemorate the contributions of John P. Peters to nephrology, because he never considered himself merely a nephrologist. He was a physician first and foremost, interested in the chemical derangements of disease. He called his domain the Chemical Division of the Department of Internal Medicine, and the interns and residents assigned to his service referred to it as "metabolism." Of course, metabolism included renal disease, which fascinated him from his early days in medicine, even before he performed cystoscopy on soldiers at the front who had trench nephritis in World War I and studied patients with glomerular nephritis on the research wards of the Rockefeller Hospital in New York. But metabolism also encompassed diabetes, endocrine diseases, lipid disorders, cirrhosis of the liver, toxemias of pregnancy, rheumatoid arthritis, gastrointestinal disorders, infections of the urinary tract, hypertension, and, frequently, heart failure — in short, anything that the boss happened to be interested in and that measurably altered the chemistry of body fluids.

The measurement of the chemical constituents of body fluids provided the first of three cornerstones of Peters' approach. He understood and appreciated the importance of accurate, impeccable measurement, collaborating first at the Rockefeller with expert professional chemists and then at Yale with three associates, all remarkably talented and dedicated women, each meticulous to a fault, whose systematic analyses set national standards. These were Anna Eisenman, Evelyn Man, and Pauline Hald. For many years, Hald was in charge of New Haven Hospital's Laboratory of Clinical Chemistry. During that time, all determinations met the highest research standards; all assays were performed in duplicate, and the first job of a research fellow in metabolism was to calibrate his or her own pipettes to the second decimal by repeatedly weighing their mercury content.

From the standpoint of nephrology, the single most influential technical accomplishment of Peters' metabolism division at Yale was the introduction into the clinic of the flame photometer. Dr. Peters first learned of the flame photometer as part of his work for the Office of Scientific Research and Development during World War II. He was asked to report on the applicability of the new device produced by American Cyanamid Company to the war effort. A later version manufactured by Perkin-Elmer Corporation (Norwalk, Connecticut) was modified for investigative use within Peters' division. The flame photometer made it possible to obtain accurate values for sodium and potassium concentrations in small samples of serum or urine within minutes. Previously, measuring sodium and potassium levels required laborious and time-consuming barometric techniques. Within a few years after Pauline Hald's first publication on Yale's flame photometer in 1947 [1], "the flame," as it came to be known by its friends, was exploring sodium and potassium disorders in clinics around the world. In its early years at Yale, to ensure its proper application, any patient who needed a serum sodium and potassium measurement automatically generated a metabolism consultation. This provided an enormous substrate of clinical material, wonderful experience for metabolism residents, and grist for the integrative and analytical mind of their boss.

The second great cornerstone of Peters' approach was the use of the balance technique as a tool for clinical investigation. Of course, he was not alone in this. Balances of nitrogen, inorganic salts, water, and calories were part of the armamentarium of the best clinical science in the first part of the 20th century, used by Donald Van Slyke, Robert Loeb, James Gamble, and David Barr, all contemporaries and friends of Peters. However, few had the temerity to apply the necessary exacting analyses of diet, urine, and feces to the range of sick patients that Peters attempted. Balance studies are difficult to perform under the best of circumstances in healthy volunteers. The task that Peters set for himself was particularly daunting because his patients were very sick, and there was no specialized research ward. Complete collections could be obtained only through a combination of luck and perseverance. In a report in the *Journal of Clinical Investigation* in 1929, he apologized:

> The most serious difficulties resulted from the physical and mental conditions of the patients under investigation. Base and chloride deficiencies are seldom encountered in advanced nephritis except when uremic symptoms have appeared. Even before stupor and coma develop to make all metabolism studies futile, minor, sometimes temporary mental disturbances appear to interfere with the proper cooperation between the patient and the metabolism staff. Seldom were complete collections obtained for long periods [2].

The third and most important element of Peters' contribution to nephrology was his remarkable ability to take raw data from his own and other laboratories and synthesize and integrate them into a logical framework possessing enormous intellectual and even esthetic appeal. As Gerald Klatskin once remarked, Peters seemed to have an extra integrator in his brain. He regarded the disorders encountered in disease as normal physiological responses to unusual conditions produced by pathological processes. This powerful insight pervaded his thinking. He believed strongly, as did Alexander Pope, that the proper study of mankind is man. His associates might experiment on animals, but he preferred to concentrate on examining disordered physiological processes at the bedside with accurate chemical techniques and the power of logical inference. (In his 34 years at Yale, his name appears on only one publication dealing with animal exper-

iments, with Lafayette Mendel, Professor of Physiological Chemistry at Yale, on the production of edema in rats by a low-protein diet in 1929 [3]).

Peters was a brilliant critic. He could usually remember who had published one's own experiments 20 years earlier, usually in German. His special forte was to examine an investigator's data more carefully than the investigator himself, often reaching an opposite but correct conclusion. When he was occasionally accused after such a tour de force of missing the forest for the trees, he retorted that those who refused to examine the trees were doomed to be lost in the woods.

His most powerful contributions, and those for which he is deservedly most remembered, were his periodically revised syntheses encompassing his own work and ideas, as well as those of others, that created a framework of thought for clinical disorders of fluid, acid base, and electrolyte physiological processes. Many of these were published in the *Yale Journal of Biology and Medicine*, and others were published as chapters in books (particularly "Water Balance in Health and Disease," which appeared in updated form in three successive editions of Duncan's *Diseases of Metabolism*). Still others were prepared in response to invited lectureships. Two magnificent monographs stand out. One was *Body Water*, published in 1935. This was "prompted by...an attempt to construct a background for a more rational analysis of the functional pathology of renal disease...the initial stimulation came from a desire to elucidate the phenomena seen in nephritis" [6]. The second was *Quantitative Clinical Chemistry: Interpretations*, published first in 1932 and then with an entirely new 1,000-page second edition in 1946. In these remarkable volumes, not merely edited but entirely written by a single author, Peters integrated the knowledge of the day by using critical analysis of specific experiments and an organized personal clinical experience in a literary style that was elegant and forceful, a model of declarative prose.

It is clear from his writings that the kidney was his favorite organ. The descendant of a line of Episcopal ministers reaching back to Colonial days speaks of the other organs, the skin, lungs, and gastrointestinal tract, as "ruthless" in their disregard of the volume and composition of body fluids and so intent on their own highly specialized functions that their conduct is irresponsible. "The stomach continues unconcernedly to secrete hydrochloric acid long after the chloride of serum has fallen below the lowest normal limits" [4]. "The kidneys at times are compelled, in addition to their regular duties, to compensate for the mischievous irresponsibility of skin, lungs, and gastrointestinal tract towards their obligations to body water" [5].

The first half of *Body Water* is devoted to a detailed discussion, still remarkably instructive more than half a century later, of the Donnan effect, the meaning of osmotic pressure, and the implications of the experiments of Starling, Landis, and Krogh for the process of lymph formation and movement of interstitial fluids. The second half is a masterly analysis of the state of knowledge of kidney function in 1935, drawing heavily on the micropuncture experiments of A.N. Richards and the measurement of renal clearances by the great Danish physiologist Rehberg. It is here that the general principle that the kidney "responds to some function of the volume of the circulating blood but is indifferent to changes in the volume of the body fluids at large" [6] was stated firmly. This concept, later termed "effective blood volume," became enormously important for the understanding of disordered salt balance, edema formation, prerenal azotemia, and heart failure.

Peters preferred to regard the kidney not as an isolated organ, but as a conscien-

tious member of the community in which it lived, faithfully serving the needs of the body. He tended to regard all biological functions as connected. He writes:

> There is something a little absurd in discussing the pH or the acidity of urine and acid excretion as if either were an independent function. The acidity of urine, however it may be expressed or measured, is a heterogenous congeries of functions; it is, in the last analysis, determined by the mixture of acid and basic ions which results from the processes outlined above in which each of these ions is, within limits, separately controlled [6].

This view of urinary acidification expressed in 1935 formed the basis of the important contributions of William B. Schwartz four decades later to our understanding of the renal acidification process.

Peters' ideas on the importance of "effective blood volume" in controlling the kidney's excretion of salt are best expressed in an influential (and controversial) paper on "The Role of Sodium in the Production of Edema," published in the *New England Journal of Medicine* in 1948 [7]. This lecture was presented by invitation to a meeting of the Boston City House Officers Association (presided over by Dr George Schreiner, who later headed the famous renal unit at Georgetown University Hospital in Washington, D.C.). In the controversy raging then between the proponents of "backward failure" and "forward failure" in the pathogenesis of heart failure, Peters placed himself squarely in the backward-failure camp. If the effective blood volume was already low in heart failure, venesection was not likely to improve the situation. He could not resist remarking, "Stead and Ebert are so impressed with the importance of expanded volume that they have advocated venesection for the treatment of the shock syndrome of coronary occlusion. That their patients died seems not to have dismayed them" [7]. Eugene Stead, then Professor of Medicine at Duke, found it hard to forgive Dr Peters for that gratuitous comment.

Peters' very first major work in the 1920s concerned the clinical implications of the Henderson-Hasselbalch equilibrium in normal blood and disease states. Using the apparatus designed by Donald Van Slyke for the determination of carbon dioxide combining power in blood, he systematically delineated the changes occurring in peripheral blood in uremia [8], diabetic acidosis [9], and heart failure [10].

The early publications of Peters on the physiology of respiratory alkalosis, [11] in which he and other volunteers overbreathed to the point of faintness and tetany, make interesting reading. In reports now mostly forgotten, he described quite accurately the rapid decrease in serum inorganic phosphate level and the increase in the concentration of chloride and organic acids in serum that formed the basis of many a later career when they were rediscovered by others.

Among Peters' most important contributions was his analysis of the pathogenesis of edema. He emphasized and put into context the importance of Starling's law governing the passage of fluid across capillary walls. His cogent monograph "Malnutrition and Edema" [12] and his clearcut demonstration that infusions of concentrated albumin solutions produced profound diuresis in nephrotic patients, but were antidiuretic in healthy subjects, established the importance of hypoalbuminemia in the causation of nephrotic edema. (This is a lesson still being relearned by some modern, less physiologically minded nephrologists.) He coined the term "dehydration reaction" for the renal retention of sodium on behalf of "some function of the volume of the circulating blood."

With Elkinton, Danowski, and Winkler, he investigated key aspects of the physiological state and treatment of salt-depletion shock [13]. His associates made

the important (and still unexplained) observation that when hyponatremia accompanies circulatory shock, protein is lost from the circulating bloodstream much more rapidly than when the serum sodium level is normal, thus providing a rationale for the correction of hyponatremia with hypertonic saline in the presence of hypotension.

Using the flame photometer, he investigated all sorts of hyponatremic states in sick patients. He and his associates described the tendency for patients with renal disease to waste salt in the urine [2] and for those with pulmonary disease and certain kinds of cerebral disease to do the same [14, 15]. It remained for William B. Schwartz, Fred Bartter, and Alexander Leaf and his associates (although never part of Peters' division, they were greatly influenced by his writings and thoughts) to show the importance of the inappropriate secretion of antidiuretic hormone in the pathogenesis of these disorders.

Peters had definite ideas about the treatment of acute and chronic renal failure, based on long clinical experience and meticulous balance studies. He derided the prevailing practice of restricting protein intake to the point of malnutrition, emphasizing the importance of adequate protein and calorie intake to maintain the body's stores of protein [16]. This concept has been rediscovered by the nephrology community with the observation that mortality in end-stage renal disease correlates better with hypoalbuminemia than with any other single measurement. He also emphasized the importance of preventing dehydration and maintaining salt and water balance in acute renal failure, as well as in chronic forms of renal insufficiency [17].

Peters recognized early the tendency in acute illnesses of all sorts to increase protein catabolism, a process he termed "the injury reaction," and noted the futility of attempting to reverse this early catabolic reaction by artificially high intakes of protein, as was then (and still is in some quarters) the custom in patients with acute renal failure and after surgery [18].

Peters was greatly interested in the phenomena of toxemias of pregnancy [19-21]. He held a unified view, decrying the notion that eclampsia was a different disease from preeclampsia simply because it presented with seizures and emphasizing the predisposing nature of underlying renal and vascular disease. Pregnancy, he believed, lent "a peculiar and explosive coloration" to conditions affecting the kidneys and vascular system, a concept that is now generally accepted with the discovery of the pathogenetic role of platelet aggregation and fibrin thrombi in this condition.

In the pre-antibiotic era in which he practiced, he was continually impressed with the importance of infection in triggering diabetic acidosis and initiating deterioration of renal function in patients with kidney disease, as a possible cause in a minority of cases of toxemias of pregnancy, and especially as iatrogenic complications of invasive procedures. Well before the landmark reports of Paul Beeson and Edward Kass on the role of the urinary catheter as a cause of urinary infections, Peters inveighed against the wicked consequences of bladder catheterization for the convenience of the medical and nursing staff. "Murder is against the law in Connecticut," he told me once when I wanted to slip a catheter into an elderly oliguric patient, "and I don't think that doctors should be above the law." He continued, looking sadly out of the window, "I knew a Frank Epstein once who put his patients first, who was not consumed by simian curiosity." I was suitably chastened but also touched by his obvious sincerity and concern.

A great teacher's legacy includes his students; some of these students who gravitated to the study of the kidney are listed in Table 1 . All these students have had students of their own, and through the com-

Table 1. Students of John P. Peters who made significant contributions to nephrology.

- J. Russell Elkinton
- Robert Petersdorf
- T.S. Danowski
- Lawrence R. Freedman
- Alexander Winkler
- Jack Orloff
- Ethan A.H. Sims
- Arnold S. Relman
- Louis G. Welt
- Franklin H. Epstein
- Donald Seldin
- Charles Kleeman

plex laws of heredity that transmit information from mentor to protege, Peters' contributions continue their proliferation so that his passionately skeptical intellectual DNA continues to thrive, although perhaps diluted.

Some of these fragments of genetic material were never the subject of scientific papers, but are nonetheless influential (Table 2).

"The proper study of mankind is man."

"If you don't examine the trees, you may get lost in the woods." In this, Peters practiced what he preached, and his notions of the natural history of disease were formed by the most meticulous review of large numbers of his own patients, personally annotated and filed. One of them, picked at random, fills three closely written pages: "Salvatore Cozzolino, married, liquor dealer, born 5/10/1903, died 11/5 to 6/1939. Chronic glomerular nephritis. In 1916, scarlet fever, followed by edema of the ankles and urinary trouble. Nine years later, headaches, hypertension, heart failure." (The patient had experienced malaria as a child, treated with quinine; it was endemic in New Haven at the turn of the century.) A large cardboard box labeled "Nephritis" contains a thousand case summaries like this, each painstakingly inscribed in Peters' own lapidary script, with every last detail noted.

"A patient needs a doctor, not a committee."

"Doctors treat individuals, not statistical averages."

"A scientific investigation must be more than a catalog of ships." Peters, who had majored in the classics as an undergraduate at Yale and read Homer in the original Greek, was referring to what he called the most boring book in Homer's Iliad, in which the ships carrying the Greeks to the shores of Troy were catalogued, together with their cargo, in an unending list. When George Thorn came to Yale in 1954 to deliver the annual Alpha Omega Alpha lecture on "The Uses of Cortisone" and enumerated the results in a few cases of 10 different diseases, Peters was the first to comment. He announced, "What we have heard is nothing more than a catalog of ships..."

Table 2. Favorite aphorisms of John P. Peters.

- The proper study of mankind is man.
- If you don't examine the trees, you may get lost in the woods.
- A patient needs a doctor, not a committee.
- Doctors treated individuals, not statistical averages.
- A scientific investigation must be more than a catalogue of ships.
- But do you know?
- Abjure noun-adjectives!
- Give the analgesic before opening your eyes, for morning nausea.
- Contrast baths, properly administered, for peripheral vascular disease.

His interns and residents were expected to know every detail about all his patients. When an unlucky intern tried to fudge an answer by saying, "As far as I know, Dr. Peters, she had a bowel movement yesterday." He was cut off with "But do you know?" Most of them never tried that ploy again.

He believed religiously that good English usage involved the avoidance of noun-adjectives wherever possible. Hence, it was "the volume of the circulating blood," not "blood volume," and "the size of the kidneys," not "kidney size." After a while, he accepted "serum sodium" as a workable substitute for "the concentration of sodium in the serum."

His interns were asked to determine the pattern of pain and administer the analgesic before the pain occurred. Nausea was best aborted and prevented, rather than treated after the fact, by giving black coffee in the morning before the eyes were open. Contrast baths, prepared according to a formula that only he remembered, administered for exactly the right number of seconds in hot water and exactly another number of seconds in cold water, were very good for peripheral vascular disease.

There is a message that transcends these. We are not used to thinking of the U.S. End-Stage Renal Disease program that provides dialysis and transplant care for all regardless of ability to pay, a community obligation, and a commitment of our government, as a contribution of John Peters to nephrology. However, I believe he would have regarded it as a logical extension of his *Principles and Proposals* of the 1930s. His students and his students' students can still hear the words of the red-haired rebellious son of an Episcopal cleric who believed in science rather than God, who taught Greek and Latin and English before he entered medical school, and who urged a rational and scientific program for the improvement of medical care in this country 65 years ago. He reassured us and reassures us still, in the cadences of Pericles, "The public will welcome and support such a program. For life and health are held dear by all men" [22].

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