THE FLAME PHOTOMETER ENTERS MEDICINE

During World War II, several American academic physicians and physiologists interested in water and solute balance and in metabolism carried out studies for the Committee on Medical Research, a component of the Office of Scientific Research and Development. This work sought optimal care of downed flyers at sea and for similar misfortunes. Among the physicians was John P. Peters (1887-1956), also known to his trainees as “Whispering Jack Peters” or “the Boss.”1-3 As of 1945, Peters had been head of the Metabolic Division of the Department of Medicine at Yale University School of Medicine for 23 years; he practiced and taught at New Haven Hospital. Peters’ division trained many of the earliest leaders of nephrology in the United States. Peters was asked by the Committee on Medical Research to “look into” an instrument called the flame photometer, which was produced and made available by the American Cyanimid Company. The flame photometer uses a relatively simple principle. When heated, a solution containing a cation, such as sodium, emits light at a characteristic wavelength, or color. The intensity of the emission, which can be measured using a suitable filter and sensor, is proportional to the concentration of the specified ion. “The instrument looked interesting,” Peters wrote to a colleague.4 At that moment, he could not have guessed how critical the device would be in expanding research on the disorders of body fluids and in fostering growth of a new subspecialty called nephrology. The latter might not

In the 1940s, the flame photometer made possible for the first time relatively simple and quick measurements of sodium and potassium in serum and urine. During World War II, it unexpectedly fell into the hands of John P. Peters of Yale University, who sought to understand water and electrolyte physiology and apply such knowledge to patient problems. Pupils and young associates of Peters would seed the early nephrology divisions and training programs in the United States; the flame photometer was essential to their work and that of their trainees, both Americans and international visitors. Hyponatremia and the syndrome of inappropriate antidiuretic hormone secretion became the “attribute” disorders of nephrologists. Invention of a microflame photometer fostered the revival of micropuncture and transport studies. In the 1960s, the flame photometer was linked to Leonard Skeggs’ sequential automated analysis system, leading to enormous numbers of routine measurements of electrolytes. The growing number of nephrologists, then based mostly at teaching hospitals, thus found plentiful instances of sodium and potassium abnormalities to address. The autoanalyzer also catalyzed use of the anion gap, another emblem of nephrology in its early decades. Not only ideas and theories, but also the usually invisible machinery, enable the growth of a knowledge base and formation of a scientific discipline or medical specialty. Of course, the flame photometer did not itself shape the agenda of nephrology, but it allowed the most influential group of progenitors and their progeny to explore normal function and bring a strongly physiologic imperative to their daily work with patients.

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have pleased him: many senior figures in academic internal medicine in the 1940s and 1950s decréd its fragmentation into many subdivisions.

In the period between World Wars I and II, research within medicine departments of US medical schools generally fell into in two realms: infectious disease and metabolism. The latter term denoted virtually any work entailing the chemical measurement of something bodily. As written in a “Letter from the Editors” of the Journal of Clinical Investigation in 1949, for a time “clinical investigation was carried along in the expanding domain of the laboratory and to a degree was synonymous with chemical investigation.” John P. Peters exemplified this trend, although to it he added a capacity for astute synthesis. He and a few others active in the 1920s and 1930s studied the chemical content of the body fluid compartments and shifts of electrolytes and water. They were the new humoralists, or less fancifully, one can see them as continuing a lineage dating back to Claude Bernard and the milieu interieur. In 1935, Peters published a 400-page volume titled Body Water: The Exchange of Fluids in Man. Although Peters’ interests were broad, he became an authority on the kidney. Many of his “fellows” or trainees of the 1940s and 1950s chose to focus on renal physiology, renal disease, and particularly the related disorders of electrolytes and acid-base balance. These subjects promised abundant opportunity to apply quantitative chemical methods and physiologic analysis to the care of the sick.

But the study of body fluids in health and disease before 1945 suffered from a critical deficiency; neither sodium nor potassium could be measured easily. The existing gravimetric method for sodium required “two precipitations (the second preferably to stand overnight), centrifugations, washings of the precipitate, and all the paraphernalia of a complex chemical analysis. . . .”\(^{(p67)}\)

One measurement of sodium in serum could take 24-48 hours. The classic titration method for potassium also demanded much time and effort. Of limited value in research, both assays were virtually useless for the repeated measurements needed when treating a patient with the rapid changes of diabetic ketoacidosis or fulminant diarrhea. The clinical laboratory of one teaching hospital for which I have found records, Woman’s Medical College of Pennsylvania, listed among a surprising variety of tests no measurements of sodium or potassium in its annual reports as late as 1942-1943.\(^{(8)}\)

The flame photometer, adopted for such use, could in one hour make a dozen or more measurements of sodium or potassium in blood serum using clinically tolerable small samples. Donald W. Seldin credited the flame photometer with “launching the analysis of sodium and potassium in blood and urine as routine clinical determinations.”\(^{(9)}\)

Another who trained under Peters wrote that it “revolutionized the approach to studies of their abnormalities in experimental subjects and sick patients.”\(^{(10}(p115))\)

Peters himself recalled in a review that the old method (for sodium) “had no clinical utility because it has been so difficult and time-consuming. Results . . . were of value in retrospect only. . . . They could not be used as aids to diagnosis and the conduct of therapy. . . .”\(^{(10}(p751))\)

Gerhard Giebisch, the eminent authority on potassium, credited the device with “a profound impact on the direction of renal electrolyte transport because it provided a convenient method for the rapid, precise measurement of ions in plasma and urine.”\(^{(11}(p167))\)

Before the flame photometer, sodium in blood plasma often was estimated from the sum of the values for the corresponding anions, chloride and bicarbonate. This was known to be inexact in some circumstances and seemed a weak compromise. However, relatively rapid and simple methods for measuring chloride and bicarbonate (really total carbon dioxide) had been developed in the first two decades of the 20th century. In part owing to ease of assay, a great deal of study before 1945 centered on chloride, or “the chlorides,” as often phrased (this is revealed by scanning the index of prominent journals of the 1930s and early 1940s, such as the Journal of Clinical Investigation). Chloride was of course understood as the dominant anion of plasma and thus coresponsible for the osmotic defense of blood volume. Also, in the language of acids and bases of the time, anions such as chloride were the “acids,” and thus chloride was the main “acid” of the blood. With the advent of the flame photometer, chloride
soon came to be seen as something like a fellow traveler, which in some ways it turned out to be, although the recent identification of chloride channels has revived interest in the anion. Sodium won dominance beginning in the 1950s not only because it could now be easily measured, but also because it soon became clear that active sodium transport was a key element of cell function, and that sodium movement had a central role in proximal tubular function. In addition, the newly available diuretic or natriuretic drugs were for many years understood and discussed as blockers of sodium transport, although they inhibit reabsorption of both sodium and chloride.

The first report describing medical use of the flame photometer appeared in 1947 under the authorship of Pauline Hald, a superb chemist and long-time Research Assistant at Yale, mostly working for Peters. Many American medical school research laboratories of the 1920s-1950s employed one or more women technologists or research associates, some of whom had substantial training in science and degrees from the “Seven Sister” schools (Barnard College, Bryn Mawr College, Mount Holyoke College, Radcliffe College, Smith College, Vassar College, and Wellesley College), although few could attain faculty status in that period. However, Hald, a Wellesley graduate, would later serve as Director of Clinical Chemistry at Yale-New Haven Hospital for many years.

The flame photometer, although already being manufactured, was still not nearly in the “open the box and plug it in” stage when Pauline Hald first laid hands on the device. She recalled that “[I]t was very unstable and it was a long time before we recognized that the contaminations came from the surrounding room atmosphere which contained high concentrations of sodium and potassium….” (P. Hald, written communication, August 1993). Seldin remembered that the American Cyanamid prototype “was designed as an absolute standard, and was agonizing to use.” The subsequent production model sold by the Perkin-Elmer Corporation proved easier to run, but its users still found the need to tinker and make modifications. One of John P. Peters’ trainees, J. Russell Elkinton, took a flame photometer with him from Yale to the University of Pennsylvania School of Medicine in 1948 to set up the “chemical section” in the department of medicine. Donald Seldin left Yale to introduce renal physiology and electrolyte studies at the new University of Texas Southwestern Medical School in Dallas. Other students and young associates of Peters initiated or helped develop programs in nephrology and electrolyte disorders at the University of North Carolina (Louis Welt), Boston University (Arnold Relman), the National Institutes of Health (NIH; Jack Orloff [Fig 1]), and the University of California at Los Angeles (Charles Kleeman). Franklin Epstein continued work at Yale and later moved to Harvard Medical School and the Beth Israel Hospital. These men constituted much of the early leadership of American nephrology. Not all of them literally carried flame photometers from Yale to their new posts, but their laboratories used the instrument. It had moved from the stage of shaky prototype or

Figure 1. Jack Orloff, MD, posed with an early flame photometer at New Haven Hospital, where it was first used in the clinical setting. Reproduced from Epstein with permission of Elsevier.
homemade contrivance to become an essential tool.

EXPANDING USE IN BOOM TIMES

MEDLINE shows 118 articles with flame photometer (or photometry) in their title between 1949 and 1959. Most describe home-built machines or modifications or report early results. Many research units fabricated their own, including several in Great Britain.\(^{15,16}\)

Perhaps it spread quickly and widely not only because of what it could do, but also because it was sufficiently simple that a laboratory could build one if it chose not to purchase. Flame photometry made its debut in *The Lancet* in November 1950 by way of a handsomely illustrated review from A.G. Spencer of the University College Hospital Medical School in London.\(^{15}\) Into the later 1950s, reports appeared in French, Spanish, and Japanese. Its early use outside North America ranged from aiding the study of renal cation transport in Prague to assessing the cochlear action of acetazolamide in Budapest.\(^{17,18}\) An indicator of the flame photometer’s acceptance was its increasing invisibility as researchers came to merely mention it in passing in the “Methods” section of their articles, simply a given for determining concentrations of cations. Largely invisible as well were the technicians who ran the instrument.

In 1960, biochemist Phyllis Bott\(^ {19}\) at the Woman’s Medical College of Pennsylvania in Philadelphia reported her design of a flame photometer adapted for measuring concentrations of sodium and potassium in ultrasmall samples. Bott alone had kept alive during the World War II years the technique of renal micropuncture first used in the 1920s by Joseph Wearn and A. Newton Richards at the University of Pennsylvania. Bott acquired full competence with micropuncture during her years with Richards. Transport studies using micropuncture and related methods became the most esteemed form of investigation within medical school nephrology divisions during the 1970s and 1980s. For most of these groups, elucidating normal physiology seemed the highest good, a preamble to understanding deviations caused by disease. Microflame photometry and related techniques advanced work in the laboratories of Erich Windhager and Gerhard Giebisch at Cornell University Medical College, Fred Wright at Yale, Carl Gottschalk at the University of North Carolina, Robert Berliner at the Laboratory of Kidney and Electrolyte Metabolism at the NIH, and others. Renal micropuncture exemplified the increasingly international flavor evident in nephrology.

The years after World War II marked the first time that medical scientists and students flowed from Europe to the United States to gain experience, reversing the direction going back to the 18th century. The scientific boom times of the 1950s and 1960s afforded plentiful opportunity in America. The first generations of American nephrologists (and their visitors) could do the work that interested them, seeking and finding the problems they wanted to explore, owing to the favorable environment of post-World War II America.

Nothing summarizes this more than the words of NIH director James Shannon (himself a renal physiologist), writing in 1967 of the “decision made early in the development of N.I.H. programs . . . that the Congress, in view of the state of knowledge concerning health and disease, must be persuaded to lend broad support to the sciences fundamental to medicine. Acceptance of this vitally important concept has been reflected in N.I.H. appropriations over the years.”\(^ {20(p100)}\) Another NIH official lauded the extramural program, which supported medical school researchers, as from its inception “a medical research program of scientists by scientists” with the basic tenet being “the integrity and independence of the research worker and his freedom from control, direction, regimentation, and outside interference.”\(^ {21(p559)}\) That is, biomedical scientists funded by the NIH—and in the United States, most of the best have been—would choose what to study, free from demands for practical outcomes or immedi-
ate relevance to disease. This founding notion has seen considerable alteration, of course.

To summarize to this point: whether doing clinical studies, ingenious clearance experiments, or the most exquisite and reductionist micropuncture investigations using single nephrons, for research involving sodium and potassium, the flame photometer enabled the research agenda and achievement of early nephrology. Of course, the use of isotopes and other methods eventually supplemented or supplanted the flame, but it remained fundamental, sometimes serving as a reference standard for newer techniques.

Although a modest device, the flame photometer to some extent symbolized postwar science more broadly, at least as of the 1950s. Relying on photoelectric cells and electronic circuitry, it replaced the weighing of precipitates and titration for color change, methods virtually as old as chemistry itself. When properly adjusted, it could make many measurements quickly, enabling research with a large “n” of patients or animals. I do not suggest that its early medical users themselves perceived the flame photometer as symbolic of anything. However, as the quotations show, they recognized its novelty and centrality to their work and to some extent spoke or wrote about it later almost nostalgically.

HYPONATREMIA, AUTOMATION, AND THE ANION GAP

In 1955 another former student of John P. Peters, Thaddeus S. Danowski (then at the University of Pittsburgh) with colleagues published a review titled “The Low Salt Syndromes,” meaning the various forms of hyponatremia. Danowski’s review classified hyponatremia into three forms based on the particular relationship of total-body sodium and total-body water, a formulation still used and taught today. In 1957, William B. Schwartz, Warren Bennett, and Sidney Curelop of Tufts University School of Medicine and Frederic C. Bartter of the NIH reported two cases of persons with “renal sodium loss” and hyponatremia “probably resulting from inappropriate secretion of antidiuretic hormone,” or what would soon become known as the syndrome of inappropriate antidiuretic hormone secretion (SIADH). SIADH might qualify as an endocrine disorder (ie, relating to a hormonal dysfunction). Its symptoms are largely neurologic. However from the 1960s on it became a hallmark disorder for the nephrologist, the new specialist fascinated by complex problems of electrolytes. Nephrologists won SIADH, hyponatremia, and also potassium derangements in part because they introduced the flame photometer into medicine and for a time held onto it. Disorders such as SIADH represented exactly the sort of chemical or physiologic puzzles that the students of Jack Peters and their students wished to discover in patients and solve. These men and eventually women exemplified perhaps more than any other segment of internal medicine the conviction that quantitative science can find application in the daily care of the sick. This is not quite the same as believing that the care of the sick demands the application of quantitative science.

The flame photometer would further assist the nephrologist as it moved from the research bench to the hospital laboratory, which by the mid-1950s began to make sodium and potassium measurements available to any clinician who requested one or both. Then, in 1957, an ingenious biochemist and inventor named Leonard Skeggs described his automated continuous-stream method for measuring the concentration of urea in blood. His apparatus allowed for the batching of many samples from different patients, followed by rapid automated assay and readout. Skeggs believed that automation could reduce error caused by variation in technique intrinsic to manual assays; this, not speed, first motivated his innovation. By 1960, the flame photometer was coupled to the automated system by Technicon Instruments Corporation, with which Skeggs worked. Skeggs and Technicon next produced the multichannel “AutoAnalyzer,” which could determine values for multiple blood chemistries in the same automated manner. Anyone who did hospital training in the late 1960s and 1970s remembers the commercial versions, the Technicon SMA-6 and SMA-12 (SMA stood for sequential multichannel autoanalyzer; Fig 2). These were remarkable machines that changed how medicine was practiced, especially in hospitals. An outcome of their use was the perplexity of discovering an abnormal value for a blood substance that had not
been of interest for the particular patient, but came along as part of the panel—that is, the answer to a question that had not been asked. The SMA process did not even allow for deletion of one of the measurements in the panel. The manufacturer asserted that the chemical panel could serve a screening function similar to the detailed history and physical examination carried out for every hospital admission. The incorporation of the flame photometer into the popular multichannel autoanalyzer uncovered numerous abnormal values, most of course not extreme, for blood sodium and potassium. By 1970, sodium and potassium topped the list of laboratory tests obtained for hospital patients, although it was usually the SMA that was ordered, not always the specific ion.\textsuperscript{28,29} This trend seems to have spread worldwide: a journal article from 1982 documents excessive ordering of electrolytes and urea at a university hospital in Zaria, Nigeria.\textsuperscript{30} The numerous abnormal values for sodium and, to a lesser extent, potassium spewed forth by the automated laboratory raised awareness of the disorders of their regulation and provided an enlarged clinical and research substrate for the nephrologist. That is, opportunities increased for consultation, teaching, case reports, and sophisticated elaboration of pathophysiology. Just as the flame photometer appeared at the right time to aid the genesis of a definable specialty of nephrology (at least in the United States), the autoanalyzer with its proliferation of chemical results came along at the time when the discipline was itself multiplying, with divisions, training programs, board certification, and societies.\textsuperscript{14}

Because SMA instruments usually were set up to measure serum sodium, potassium, chloride, and total carbon dioxide in the same panel, they nurtured another segment of nephrology’s expertise: acid-base disorders and particularly
That virtual emblem of the specialty, the anion gap, or “delta.” It had long been understood that an increased difference between serum sodium and the sum of chloride and bicarbonate usually tagged metabolic acidosis. Pediatrician and scientist James L. Gamble of Children’s Hospital in Boston and Harvard Medical School taught this clearly with his famous “Gamblegrams,” as presented in the various editions of his classic Chemical Anatomy Physiology and Pathology of Extracellular Fluid, available from Harvard University Press from 1945 until 1982. With the advent of the AutoAnalyzer in the 1960s and 1970s, the “measured” extracellular electrolytes could be measured with ease and the numbers promptly reported; and this probably was done for most patients admitted to teaching hospitals. Through touring grand rounds lectures and plentifully copied reviews, nephrologists codified and disseminated a comprehensive approach to acid-base disorders based on serum electrolyte levels and of course blood gas analyses.31 Within American nephrology, there flourished for a time something like a cult of the anion gap.

CONCLUSIONS

That an instrument can shape or open a field of science is a commonplace idea in the history of science—one thinks of Galileo’s telescope, the microscope, Boyle’s vacuum pump, the chemist’s balance, and of course many more recent examples, such as several “blots” or the polymerase chain reaction. Still, we tend to associate the advance of science almost entirely with ideas and theory and ignore its material underpinning (although as noted, the early renal experts would recall the indispensability of the flame photometer). I am not arguing that the flame photometer alone made the specialty of nephrology. Rather, I suggest that early nephrologists, particularly those going forth from Peters’ division at Yale, already knew what sort of questions attracted their interest and energy. The flame photometer came to them out of nowhere and served as a vigorous catalyst. Its relative simplicity compared with the methods it replaced made their investigative work much easier; thus, more could be done. The speed with which the instrument could produce results ensured its clinical utility: its early owners could leave the laboratory to consult on actual patients with interesting electrolyte problems and bring those problems back to the bench. (The research-clinic dichotomy was not entirely sharp for the persons and period I have been discussing.) The hospital laboratory’s automated multichannel analyzer, which for a time incorporated the flame photometer, helped uncover disturbances of electrolyte levels and acid-base chemistry on a daily basis.

The ability to talk about and treat—but more so talk about—such complex disorders as SIADH and acid-base problems won prestige for nephrology, even a sort of mystique, although occasionally also some bemused derision for our sometimes rarified concepts (reset osmostats, “triple” disturbances, the “delta-delta,” and “incomplete” renal tubular acidosis). In addition, the renal people also had adduced the daunting array of glomerular disorders, another body of arcane knowledge owing its existence in good part to a device, the biopsy needle (and one might add the electron microscope). The nephrologist could apply and discuss physiology and pathology at the bedside, and for a long time internal medicine honored this more than procedures.32 The generations of nephrologists I discuss here produced many department chairs and deans, editors of the New England Journal of Medicine and Annals of Internal Medicine, a president of the Institute of Medicine, and a president of the American Association of Medical Colleges. Eventually, the nephrologist as chemical numerologist was largely supplanted by nephrologist as practical manager of a different sort of machine, the artificial kidney. This transformative invention reshaped nephrology—to some extent against its will—because it would extend, but transform, the lives of countless individuals with kidney disease.

ACKNOWLEDGEMENTS

Support: Research in part leading to this article had support from the National Library of Medicine and the National Endowment for the Humanities.

Financial Disclosure: The author declares that he has no relevant financial interests.

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