Homer Smith: His Contribution to Physiology

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For three decades, from the mid-1930s until his death in 1962, Homer Smith was the preeminent figure among those interested in the physiology of the kidney. His leadership reflected not only the seminal research contributions of Smith and his colleagues and the conceptual framework that he developed, but also the extraordinary lucidity that he brought to the exposition of work in renal physiology—both his own and that of others. Not least, however, was the large number of younger people whose careers were launched in his laboratory and who went on to become leading contributors to the field.

Smith was appointed to the chairmanship of the Department of Physiology at New York University in 1928 (at the age of 33!), having already held the equivalent position at the University of Virginia for the previous 3 yr. Although before his appointment at N.Y.U., Smith had carried out studies on the composition of body fluids in several classes of vertebrates, he had not undertaken work directly related to the function of the kidney. He had, however, come close to kidney function when he did a study of nitrogen excretion in camels. It had been reported that the urine of the bactrian camel contained no urea or ammonia, an observation that surely required further investigation. The story (1) that Smith followed the camel of a visiting circus, put in hand, to collect the urine is almost surely apocryphal. Smith was certainly not averse to the expenditure of considerable effort to get the appropriate material for this study: for example, to Africa to collect lungfish and to Siam and Malaya to study freshwater elasmobranchs. In the case of the camels, however, the samples were collected for him by keepers at the New York Zoo. At least that is what Smith said in his article on the subject (2) and he was not likely to be hiding a rather unorthodox source of his material, because the study included not only the bactrian camel but the dromedary, llama, and alpaca as well, none of them likely to be found in a traveling circus. Of course, there was plenty of urea in the urine of all of them.

The channeling of Smith's efforts into renal physi-ology was probably the effect of a number of influences. He had a consuming interest in the constancy of the composition of the milieu intérieur as the environment in which higher organisms really live. This was the central theme of the book Smith later wrote, From Fish to Philosopher. As the keepers of that environment, the kidneys and their function demanded attention.

Smith also had a long association with E.K. Marshall, Jr., having originally been assigned to Marshall's unit in the chemical warfare service in World War I. It was through Marshall's influence that Smith had gone on to obtain his doctoral degree. They later had a continuing association at the Mt. Desert Island Biological Laboratory in Salsbury Cove, ME. Marshall was, of course, a key figure in renal physiology at that time, having been responsible for proving that the renal tubules have the capacity for secretory transport.

Finally, at N.Y.U., Smith was approached by two young physicians, William Goldring and Herbert Chasis, for help in trying to interpret some very confusing data dealing with urea excretion in febrile patients. It is not recorded as to just what kind of resolution of that problem was achieved at that time, but thus began a long, productive collaboration of the Departments of Physiology and Medicine that led to much of the work that established Homer Smith's laboratory as the germinal center of renal physiology.

CLEARANCE

During that period, which has been deservedly called the Smithian Era, the clearance technique was the major tool of the renal physiologist. Smith did not invent the clearance method or the term clearance, but it was he and his colleagues who gave it its real meaning and the far broader usefulness that was its potential.

The term clearance was first introduced by D.D. Van Slyke and his associates as it related to the excretion of urea (3). Van Slyke defined urea clearance as the volume of blood required to yield the amount of urea excreted in a minute's time and thus the virtual volume of blood completely "cleared" of urea. The urea clearance was conceived as an index of renal function, and no relationship to GFR was suggested.

The idea of a clearance as a measure of glomerular filtration was advanced by Rehberg (4). Proceeding from the assumption that urine formation involved only glomerular filtration and reabsorption (but no secretion) by the tubules, the clearance of the substance most highly concentrated in the urine relative to its concentration in plasma must be closest to being a measure of glomerular filtration. Of the known components of human urine, creatinine filled that bill, and Rehberg offered the clearance of exogenous cre-
atine as the GFR in humans. Unfortunately, the initial assumption that tubules do not engage in secretion was proved wrong, and again unfortunately, creatinine turned out to be secreted by the tubules of the human kidney (although not in the dog). As an index of overall renal function, the clearance of exogenous creatinine adequately served the purpose, but its usefulness was essentially limited to that application.

The precise measurement of glomerular filtration becomes important only when the values are to be used to measure other aspects of renal function, that is, reabsorption and secretion by the tubules. It was in recognizing the clearance of an appropriate marker substance as a measure of glomerular filtration, seeking out that marker substance, and thus providing the means to calculate the rate of filtration of the other solutes in the plasma that Smith and his colleagues made the measurement of clearances the valuable tool that it became.

GFR

Search for a substance the clearance of which would equal the rate of glomerular filtration started from another observation of Marshall, namely, that sugars do not enter the urine of aglomerular fish. Assuming that the tubules would not reabsorb nonmetabolizable sugars, Smith and his colleagues examined the clearances of several sugars foreign to the body and settled on xylose as the appropriate material because the clearances of sucrose, raffinose, and xylose were essentially the same as that of glucose after the administration of phlorizin. For several years, members of Smith’s laboratory used the xylose clearance as a measure of filtration rate in examining the excretion of various other substances in glomerular fish and dog and in human subjects. It is interesting as an example of the way preconceived notions affect the interpretation of data that a comparison of xylose and creatinine clearances in the dog led to the conclusion that creatinine must be secreted because its clearance exceeded that of xylose (5). The clearance of creatinine, however, was independent of its concentration in the plasma, thus fulfilling one of the criteria posited by Smith for a substance excreted only by glomerular filtration without reabsorption or secretion. All other substances thought to be reabsorbed or secreted had clearances that varied with plasma concentration because of the tendency of transport processes to become saturated. When, after the administration of phlorizin, the clearances became equal, it was assumed that the secretion of creatinine rather than the reabsorption of xylose had been inhibited. Changes in the absolute values of the clearances did not help to distinguish between the two possibilities because both clearances usually decreased.

A few years later, when inulin was introduced more or less simultaneously in Smith’s laboratory and that of A.N. Richards, it became clear that the problem had been the reabsorption of xylose. In the dog, creatinine and inulin had the same clearance, and in all of a wide series of studies in a variety of vertebrates, the xylose clearance was well below that of inulin. Inulin has been the standard for measuring glomerular filtration ever since and has made possible most of the studies that were to follow.

EFFECTIVE RBF

Elsom and his colleagues in Richards’ laboratory had found that the iodine-containing compounds diodrast and hippuran, used as urologic contrast media, had very high clearances (6). It is interesting to note that their use of these observations was limited to showing that the clearances were so great that they could not conceivably be produced by glomerular filtration alone and therefore must be secreted (a conclusion that had been reached in the case of phenol red some years earlier by most observers). Even though one of their studies (7) involved the direct measurement of RBF (thermostromuhr) for comparison with hippuran clearance, they did not suggest the possible use of diodrast or hippuran clearance as a way to measure RBF.

Again it was Smith and his colleagues who saw the potential value of the findings of others. The clearance of diodrast set a lower bound on the RPF, and at the same time, it yielded a value of RBF that was so large that the actual level of RBF could not be much greater. They therefore concluded that the diodrast clearance could be considered a measure of effective RPF. (It was only later than sampling of renal vein blood showed how close the RPF was to the diodrast clearance because roughly 90% of the diodrast was extracted in the passage of the blood through the kidney.) Some years later, after a study by Smith and his coworkers of the clearance of a number of derivatives of hippuric acid (8), p-aminohippurate (PAH) was selected to replace diodrast because the chemical determination of PAH was much simpler than that of diodrast.

TUBULAR TRANSPORT CAPACITY

Saturation of transport capacity had been recognized as responsible for the depression of clearance as the plasma concentration of secreted substances was raised. Smith undertook to take advantage of this phenomenon to analyze several additional aspects of renal function: the maximum transport rate and the relationship of load to transport capacity. The procedure was to increase progressively the plasma concentration of the substance under study to a level well beyond that at which transport capacity was saturated. In the case of a secreted substance (e.g., diodrast, PAH), the rate of excretion remained proportional to the plasma concentration until saturation of the transport capacity was approached, the excretion thereafter increasing more slowly and eventually only to the extent that the amount filtered increased. Conversely, in the case of a reabsorbed substance (e.g.,
glucose), the rate of reabsorption remains equal to the amount filtered until saturation is approached, at which point the material begins to appear in the urine and eventually increases in proportion to the amount filtered as the amount reabsorbed remains constant (9).

The amount secreted or reabsorbed when saturation was achieved was designated as the Tm or transport maximum. The corresponding initial letters of "tubular mass" made it easy to consider the value a measure of the amount of functioning renal tissue, and indeed, Smith chose at first to call it that, although later that term was abandoned and the Tm was considered only a measure of transport capacity.

The other use to which Smith turned these "titration curves" was to estimate the extent of balance on one hand between the filtration in individual glomeruli and the reabsorptive capacity of the conjoined tubule and, on the other, the relationship between the perfusion of individual tubules and their capacity to secrete (10). As illustrated in Figure 1, the reabsorption of glucose becomes incomplete before reabsorptive capacity is fully saturated, and similarly, the extraction of dextran from the plasma begins to fall before the secretory capacity reaches its maximum. Thus, when transport, in either direction, is plotted as a function of plasma concentration (or load), the resulting figure is not two straight lines meeting at the point at which load is equal to transport capacity. Instead, in the region where that angle would occur, the straight lines are replaced by a curve (the "splay").

Smith had the ingenious idea that this splay could be used to yield an estimate of the extent to which the transport capacity of an individual tubule was matched to the load delivered to it. If each tubule removed all of the transported substance presented to it until its transport capacity was saturated, then the splay must be attributable to the fact that some tubules had a higher filtration rate relative to their reabsorptive capacity, whereas others had a higher ratio of transport capacity to GFR. In the case of secreted substances, the corresponding variable would be blood flow to individual tubules and their secretory capacity. The results suggested a fairly close match of those variables. When one takes into consideration the fact that it is quite unlikely that an individual tubule transports every molecule presented to it until its capacity is saturated, so that there must be some "splay" even in individual tubules, the match of transport capacity to load must be even better than the estimates Smith derived.

EXCRETION OF WATER AND ELECTROLYTES

After the conclusion of World War II, Smith and his coworkers turned their efforts to an examination of the process of urine dilution and concentration and the excretion of sodium. It must be kept in mind that, up to that time, the distribution of fluid reabsorption along the mammalian nephron was not nearly as well established as subsequent micropuncture studies in mammals have made it. The division of water reabsorption into a larger "obligatory" reabsorption and a smaller "facultative" reabsorption had been proposed some 10 yr earlier in Smith's 1937 book The Physiology of the Kidney (11). The studies of the late 1940s reemphasized that idea, attributed obligatory reabsorption to the proximal segment, and Smith inferred that it was, in all probability, a passive process secondary to the reabsorption of sodium with its balancing anions. The free water clearance was recognized as the volume equivalent to the sodium reabsorbed in the distal segment. The return to isotonicity and, beyond that, to hypertonic urine was to be attributed to pituitary antidiuretic hormone. In considering the final process, the production of concentrated urine, Smith might be said to have missed the boat. It is well known that Smith dismissed the idea that the concentrating process was attributable to the loop of Henle acting as a countercurrent multiplier—this despite the fact that Henry Wirz, the major physiologist proponent of the idea, had spent most of a year in Smith's laboratory. Of course, Smith was not alone in his skepticism; most of the rest of us were pretty slow to come around as well. Smith did concede formally some 10 or so years later in a very graceful and amusing admission of his error (11). As a matter of
fact, this reluctant acceptance of the Wirz-Kuhn model was rather out of character for Smith, who was generally quite ready to modify his views on the basis of new data. He did not even balk at accepting potassium secretion, despite the fact that this made it impossible to measure reabsorption or secretion as the difference between filtered and excreted—one of the fundamental assumptions of most of his earlier work.

When it came to the excretion of sodium, it quickly became clear that the approach that had been so successful in accounting for the renal handling of many other substances—glucose, creatinine, phosphate, amino acids, etc.—was not going to explain the rate of sodium excretion. Perhaps Smith had anticipated this when, in his 1937 book, he wrote: "The history of renal physiology has erred, more often than not, by attempts at oversimplification. The problems of water and salt excretion appear to be extremely complex, and especially liable to this danger" (11; p. 233). In any case, when he took up work on the problem a decade later, he similarly said "The task of describing electrolyte excretion quantitatively does not promise to be a simple one" (12). (Smith was not the first author of the article from which this quotation was drawn, but the style was clearly that of Smith.) It did not take long to learn that the rate of sodium excretion was not the difference between the amount filtered and a fixed reabsorptive capacity. For a time, it seemed possible that the distal segment did have that fixed reabsorptive capacity and that what varied was the salt delivered to that segment as the result of changes in the volume of glomerular filtrate, a nearly constant fraction of which was absorbed in the proximal tubule. Changes in glomerular filtration, which in theory could account for most changes in salt excretion, could have been well within the limits of error of the measurements and that idea was only put to rest some time later with the experiments of De Wardener et al. (13). Smith cannot be seriously criticized for not explaining sodium excretion; nearly half a century later, although we know of some more recently discovered factors, we still cannot provide a quantitative explanation, much less a prediction, for the rate of sodium excretion.

WRITINGS

Smith's contribution to the field of renal physiology greatly exceeded the experimental work that came from his laboratory, seminal as that work was. He was without a peer in his ability to organize the information in a field within a rational framework and to present it lucidly in a literary style with a flair rarely to be found in the scientific literature.

Smith's brief novel Kamongo, published in 1932, grew out of his experience in his trip to Africa to collect lungfish; the book became a best seller. This work revealed not only his philosophical bent and abiding concern for what he later called "man's place in nature," but also showed his very considerable literary gifts. A second novel, The End of Illusion, published in 1935, followed his expedition to Malaya to study the body fluids of fresh water elasmobranchs. These efforts, although not immediately relevant to Smith's role in renal physiology, must have served not only to polish his style but also to help relieve him of inhibitions that might have kept him from the easy style that characterized many of his later scientific publications and that certainly departed markedly and often from the usual stiff and stylized language of the scientific literature.

I have recounted, in a brief previous tribute to Homer Smith, my experience in first encountering his writing in his textbook of 1937 (14) and the influence it had on the direction of my research interests. I recalled how, having picked it up out of idle curiosity and read a few pages, I proceeded to read it from cover to cover. My memory did not deceive me; its unusual readability and the lucid style in which the field was presented were apparent to me when, in preparing for this effort, I returned to the 1937 book for the first time in many years.

Inasmuch as the 1937 text pretty well covered what was known of renal physiology, it is largely a reflection of the enormous growth of interest in the field, to a large extent as a consequence of the contributions of Smith's laboratory, that when Smith brought up to date the knowledge of renal function in his 1951 book The Kidney: Structure and Function in Health and Disease (15), it was very much larger. The text had grown from some 260 pages to close to 900, and the bibliographic references had increased from a little less than 500 to 2,300. For some years thereafter, the new book was the authoritative standard for the field.

I suspect that few of those who are currently associated with nephrology have ever read any of Homer Smith's work. I would urge them to do so simply for reading pleasure if not out of an interest in the history of the field. Herb Chasis and Bill Goldring put together a selection of Smith's writings, with very brief comments by the editors, in Homer William Smith, His Scientific and Literary Achievements (16). It might be a good place to start.

The final appendix of that book is entitled "associates" and lists the names and then-current (1965) positions of over 100 people who had some direct association with Smith as coworkers or collaborators or who were simply close enough to have been strongly influenced by him. I fall in the latter category, never having actually worked with Smith but certainly influenced by him indirectly through his writings and directly in many pleasant and enlightening discussions. There is little question that one of the most important and enduring contributions of Smith was the line of investigators that flowed from his mentorship.

ACKNOWLEDGMENTS

My apologies to all of those others whose work has been included in the term that I have used: "Smith's laboratory."
REFERENCES