The development of clearance methods for measurement of glomerular filtration and tubular reabsorption

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This essay looks at the historical significance of four APS classic papers that are freely available online:


In 1932 when Jolliffe, Shannon (Fig. 1), and Smith published their studies on the renal handling of sugars, it had been 8 years since micropuncture experiments unequivocally proved filtration to be the first step in urine formation (1, 11). Their paper poses the problem in its first sentence. "No substance is known to be present normally in the plasma and urine of vertebrates which can be safely used to evaluate the quantity of glomerular filtrate under physiological conditions." They therefore set out to find a "foreign substance" useful for such a measurement.

The decision to search among sugars followed from several observations including those of Wearn and Richards (11), that glucose was present in the glomerular filtrate, and those of Marshall (3), that glucose was excreted by glomerular but not aglomerular fish. The Marshall results had special resonance for Smith, given his lifelong engagement with marine physiology, and suggested to him that sugars were not secreted, a necessary characteristic for a filtration marker. The hitch was that the tubule reabsorbed glucose. For measurement of glomerular filtration rate (GFR), he needed a sugar that was not reclaimed, a "foreign" sugar. Xylose, sucrose, and raffinose were chosen for study based at least in part on a characteristic, evolutionary-teleological bent in Smith’s thinking. He argued that being a fuel, glucose was conserved by reabsorption, from which one could infer that metabolically inert carbohydrates might go unreabsorbed, hence the three test sugars.

Although these sugars seemed to perform well, doubts lingered that they might be reabsorbed in small degree. At about the same time, Richards and colleagues in Philadelphia and Smith and Shannon in New York tested the larger fructose polymer, inulin (4). In papers submitted 2 weeks apart, one using dogs, the other humans, the New Yorkers reported that inulin clearance slightly exceeded that of xylose, implying some small reabsorption of the monosaccharide (5, 9). They again invoked the absence of inulin in the urine of the agglomerular fish as a point against its secretion. However, they...
wrote “...we hesitate to argue from the fish to the mammalian kidney...” (9). The hesitation seems a touch disingenuous for Smith, whose most famous book of popular science was to be titled From Fish to Philosopher. But they did adduce more direct evidence against secretion in that inulin clearance was independent of its plasma level, unlike the pattern of a secreted substance but like that expected of a filtration marker. The arguments against reabsorption were that inulin clearance exceeded those of other filtered substances, e.g., urea, glucose, and xylose, and was unaffected by the blocker of glucose transport, phlorizin. They concluded that inulin was a near perfect filtration marker, which was eventually verified conclusively by micropuncture and tracer studies. It remains the standard against which filtration markers are gauged.

Reabsorption of glucose precluded its use to measure filtration but this transport process constituted an important physiological problem of its own. With the measurement of GFR in hand, glucose transport could be quantified, and Shannon did so (7, 8). By the time of the first of his two studies on this topic and three years after the inulin papers, creatinine had been accepted as an alternative to inulin as a GFR marker, especially in the dog. Employing the simultaneous measurements of creatinine and glucose clearance, the latter over a wide range of plasma levels, he and Fisher (8) established the notion of a transport maximum (Tm) for glucose. In subsequent studies Shannon, Farber, and Troast probed the stability and reproducibility of the glucose Tm (7). Repeated experiments in awake trained dogs showed that Tm glucose was stable over months and was not influenced by glucose or insulin levels. The stability of Tm glucose led them to propose that it be used as a marker of reabsorptive capacity.

Smith, Shannon, and their colleagues worked in the Physiology Department of New York University (NYU) where Smith was the chair. One of the authors of these classic papers, Saul Farber, went on to become Chair of Medicine and Dean at NYU. He recently recalled his work in these laboratories on the fifth floor of a building, which still stands at 26th Street and First Avenue (personal communication, S. J. Farber. January 13, 2004). Farber began in Shannon’s lab through a family connection. His uncle Joseph Bunim had been working with Shannon, to measure the diffusion coefficients of various substances including inulin. Farber worked nights and vacations during his medical school career and developed a lasting devotion to Shannon.

Shannon had received his MD from NYU in 1929 and, following his residency in medicine, returned to get his PhD working with Smith. Although Shannon had decreasing clinical contact as his career proceeded, Farber remembers that Shannon’s clinical notes written during his residency at Bellevue Hospital were so good that they were distributed as models to incoming house officers. However, as a lecturer Shannon might not have survived the assessment of current medical students. During one lecture, Farber found himself progressively confused. He went to Shannon’s office and asked to look at the notes which Shannon routinely wrote out on yellow foolscap. Shannon refused saying that the confusion was entirely purposeful and designed to send the best students to the literature. It seems unlikely that he used this technique in dealing with the Congress during his later work as Director of the National Institutes of Health (NIH). Indeed, an associate at the NIH, Thomas Kennedy, wrote, “It is doubtful that any Federal official, before or since, has ever been as respected by the Congressional committee that held jurisdiction over a federal agency as was Shannon...” (2). One last difference from modern procedure can be gleaned from the paper on inulin clearance in man. The first human to receive inulin in a preliminary test of safety was a subject labeled “J.A.S.” (9). Of the 7 subjects in the subsequent studies, J.A.S. had the largest body surface area at 2.10 m2. The subject must have been the six-foot, two-inch James Augustine Shannon.

Smith, Shannon, Marshall, and their contemporaries measured not only glomerular filtration but also tubular reabsorption and secretion (then called “tubular excretion”) of organic molecules. They explicitly raised the potential value of measuring tubular transport maxima in assessing kidney function. In later years, glomerular filtration became the dominant measure of renal function, particularly in clinical medicine. The utility of creatinine as an endogenous filtration marker undoubtedly contributed to this development. Moreover, multiple functions of the kidney, including not only tubular transport but also endocrine synthesis, do tend to decline with the GFR as renal disease advances. But the focus on filtration, indeed its virtual identification with kidney function in practice, may have distracted physiologists from the study of tubular organic transport and in particular from the study of tubular secretion.

Many substances are cleared more rapidly by tubular secretion than by glomerular filtration. Some such substances are probably toxins whose levels are maintained low by normal kidney function. Shannon emphasized this possibility when reviewing tubular secretion in 1939: “...it would be possible in man, through the intervention of tubular excretion, to maintain at very low concentrations in the body substances, which being continuously formed, had a deleterious effect upon the organism. ...We have no knowledge of evidence favoring or opposing the existence of such mechanisms in the normal animal; if they be present, some of the symptomatology characteristic of impairment of renal function may arise from the absence of their normal operation. The answer to this question must await the further identification of those substances which make up the unknown portion of the urinary constituents” (6). A few years later Smith reported that the reduction of secretory Tm for the test substance diodrast was “...the earliest impairment in renal function so far observed in hypertensive renal disease” (10). Sixty years later, we still have not capitalized on these observations of Shannon and Smith. But recent advances in the study of tubular transport, including molecular characterization of organic transporters, may lead us to identify clinically important organic solutes and new clinical tests of renal function. If we do, as often has been the case, they will have been forecast by these pioneering physiologists.

REFERENCES


