Homer Smith: His Contribution to the Practice of Nephrology

David S. Baldwin,¹ and Joel Neugarten

D.S. Baldwin, New York University School of Medicine and Renal Division, Tisch Hospital of New York University and Bellevue Hospital Center, New York, New York
J. Neugarten, Department of Medicine, Albert Einstein College of Medicine and Renal Division, Montefiore Medical Center, Bronx, New York

A generation of renal physiologists and clinical nephrologists owe their expertise to the direct influence of Homer W. Smith. Working with him in his laboratory, conforming with him personally, or corresponding through the mails, young would-be scientists worldwide were molded by him into investigators, teachers, and practitioners of renal medicine. A remarkable feature of Smith’s great influence on others was his extraordinary accessibility, which was coupled with an enthusiasm for discussion of any and all problems dealing with the function of the kidney. Since his death in 1962, a succeeding generation has inherited this legacy from Smith’s original disciples, who continue to disseminate the clarity of thinking and explicit articulation of this dean of all renal physiologists.

From the developmental and comparative physiology of the kidney, Smith went on to explore the fundamentals of mammalian renal function and ultimately human physiology and pathophysiology. His introduction of methodology for the precise measurement of renal function in humans lies at the basis of his many contributions to clinical medicine.

In the 1930s, as Chairman of the Department of Physiology at New York University, he created a precedent for collaboration between basic scientists and clinicians that has been followed worldwide.

Our daily thinking in terms of GFR, RBF, intrarenal resistances, tubular absorption and excretion, and body fluid homeostasis stems directly from his exposition of these fundamental concepts. An informed and logical approach to the many problems of renal dysfunction with which we must deal regularly would be inconceivable without Smith’s teaching, not the least of which is the language and mindset that we bring to the bedside.

His rigorous approach to experimental design and analysis of data was implanted into physician physiologists, who have carried over his incisive and skeptical attitude to the solution of clinical problems. Hemodynamic or “functional” disturbances as opposed to anatomic derangements, the concept of nephron loss, the significance of solute load, the mechanisms of acute and chronic renal failure, water conservation, edematous states, renal hemodynamics in hypertension and heart failure—all of these have been clarified for us by Smith’s explorations into their pathophysiology.

It may be said that the practice and exchange of ideas in clinical nephrology are based largely on a “kidney language” created by Homer Smith. In this essay, we present a brief summary of Smith’s most fundamental contributions and follow with examples of their clinical relevance. Although the landmark observations by Richards and coworkers on the composition of glomerular filtrate were achieved in the early 1930s, it should be borne in mind that Smith’s concepts evolved before the general use of the micropuncture technique.

MEASUREMENT OF FILTRATION RATE AND RENAL HEMODYNAMICS

Smith observed that the morphologic characteristics of the tubule in the aglomerular fish kidney resembled that of the proximal tubule of mammals (1). Because the “aglomerular tubule” is capable of excreting a wide variety of substances that appear in fish urine, he inferred by analogy that the human proximal tubule would behave similarly (1). Subsequently, his laboratory demonstrated the tubular secretion of phenol red, diodrast, and hippuril as well as creatinine (2). He realized that, in order to define the physiology of the filtering nephron, the use of a substance that is totally filtered with water and neither absorbed nor secreted by the tubules would be required (1,3). Such a marker could serve as well to estimate the quantity of water that is reabsorbed (or added) in the tubule and would allow the calculation of the tubular secretion of filterable substances contained in the plasma.

Smith was aware of data indicating that the aglomerular kidney could not excrete glucose (1). Because glucose is present in the glomerular filtrate but normally absent from the final urine, it obviously could not be used to measure filtration. However, the observation that glucose could not be secreted by the tubule directed Smith’s search to nonmetabolized carbohydrates as possible candidates for a marker of water filtration (3). Studies using a variety of different carbohydrates led to the demonstration that insulin is completely filtered from plasma, is metabolically inert, and is neither secreted nor reabsorbed by the tubules (3).
In addition, Smith and others showed that inulin and creatinine were concentrated in the urine to the same extent as in the dog, rabbit, seal, sheep, and frog (1). He reasoned that this observation could only be explained if both substances were excreted solely by glomerular filtration because it was inconceivable that two dissimilar substances would be secreted or reabsorbed to the same extent by the tubules of all of these different species (1). In contrast, the degree to which creatinine is concentrated in the urine is higher than that of inulin in humans, chicken, apes, and the dogfish (1). This observation suggested either that inulin was undergoing tubular reabsorption or that creatinine was secreted by tubules. He argued that the discrepancy between inulin and creatinine was the result of the tubular secretion of creatinine, because the extent to which inulin, sorbitol, mannitol, and sorbitan were concentrated in the urine was identical in the dog and in humans and it is improbable that all of these substances are reabsorbed to an identical degree in both species (1).

Thus, Smith concluded that the clearance of inulin, that is, the quantity of plasma water required to provide the amount of inulin appearing in the urine, was equivalent to the GFR (1–3). He was able to extend the use of the clearance concept to study a variety of renal physiologic processes. He reasoned that if the clearance of a freely filterable substance is less than that of inulin, then it must undergo reabsorption (1,2). Conversely, where the clearance of a substance exceeds that of inulin, it must be secreted by the tubules in addition to being filtered (1,2). The rate of absorption or secretion of these substances could be quantitated from knowledge of their rates of filtration and excretion. In the case of substances that are actively reabsorbed or secreted, their clearances approach that of inulin once the transport process is saturated (1,2). When the rate of filtration of glucose, for example, exceeds the maximum rate of tubular glucose reabsorption, excess glucose will appear in the urine and glucose clearance will rise to approach the inulin clearance as serum glucose levels are increased (4). In the case of creatinine, phenol red, diodrast, or other substances that are filtered by the glomerulus and later undergo tubular secretion, raising the plasma concentration above a critical saturating level will decrease their clearances toward the level of the filtration rate (4).

From this reasoning vis à vis filtration, reabsorption, and secretion, the logical progression for a man of Smith's intellect was to conclude that the clearance of a substance that is totally removed from plasma in a single pass through the kidney would provide a measurement of RPF (Fick principle) (5). Diodrast and later p-aminohippurate proved to satisfy these requirements and thus provided a tool for the investigation of renal hemodynamics under a variety of experimental conditions and in disease (5).

Smith was able to use this methodology to craft a series of studies evaluating renal function in the diseased kidney (6–8). He reasoned that the maximum rate of tubular reabsorption of glucose (Tm glucose) was a reflection of the number of intact functioning nephrons available for filtration and reabsorption (6–8). Similarly, the maximum rate of tubular secretion of diodrast could be used to estimate tubular excretory mass (6–8).

Smith used these new methods to examine renal hemodynamics in humans. In studies of the renal circulation in patients who had undergone spinal anesthesia, he found that renal hemodynamics remained unchanged (9). He concluded that, under physiologic conditions, the renal circulation was not under tonic sympathetic control. On the other hand, he used various maneuvers to provoke neurogenic vasoconstriction of the renal vasculature, leading to transient, reversible renal vasoconstriction and a decline in RBF (1,2,10). Stimulation of the sympathetic nervous system was achieved in these studies by subjecting patients to postural tilting or psychological stress (1,2,10).

Observations made in whole kidneys were used by Smith to evaluate the response of the renal microvasculature to various administered agents. Moderate doses of adrenalin increased the systemic blood pressure and filtration fraction, reducing RPF while leaving GFR unchanged (1,2,10). He concluded that the rise in filtration fraction after adrenalin resulted from predominant constriction of the efferent arteriole, which in concert with elevated systemic blood pressure, increased intraglomerular pressure and maintained GFR despite a reduction in RBF (1,2,10). Because Tm glucose was not reduced after adrenalin, he concluded that the maintenance of the filtration rate at normal levels was not associated with the closure of some glomeruli and compensatory hyperfiltration in others (1,2,10). During more intense vasoconstriction after larger doses of adrenalin, afferent constriction predominated and filtration rate fell. Conversely, Smith was able to induce renal hyperemia in the presence of constant or decreased systemic blood pressure by administering pyrogenic contaminants or triple typhoid vaccine (1,2,10,11). The increase in RBF was associated with renal vasodilation, decreased filtration fraction, and unchanged filtration rate (1,2,10,11). He interpreted these data to indicate that renal vasodilation was primarily occurring at the efferent arteriole with a concomitant decline in intraglomerular pressure, which offset any effect of elevated RBF on filtration rate (1,2,10,11).

**URINARY DILUTION**

Smith made a detailed study of the ability of humans to excrete a dilute urine. He observed that the urine formed during water diuresis could be divided into two components: (1) osmotically obligated water equal to the osmolar clearance (C_{osm}), the volume required to restore urinary solutes to an osmolality identical to that of plasma; and (2) solute-free urine
(2,4,12). He defined free water clearance, $C_{H_2O}$, as the quantity of excreted water that exceeds the osmotically obligated fraction (12). Thus, the total urine volume represents the sum of the osmolar clearance plus the free water clearance (2,4,12).

Smith used several experimental observations to develop a model of urinary dilution by the mammalian kidney. Because the glomerular filtrate is an ultrafiltrate of plasma and is devoid of osmotically free water, the glomerulus could not contribute to the formation of a dilute urine (2,4). He rejected the possibility that dilute urine was formed by the addition of free water to the tubular urine (2,4). He argued that the dilution of the urine was accomplished by the active reabsorption of sodium and chloride in a tubular segment that was highly impermeable to water, leaving behind osmotically free water (2,4,12).

Smith concluded that the proximal tubule did not play a role in the dilution of the urine because it was permeable to water, and the reabsorption of solute in this segment is accompanied by the passive reabsorption of an osmotically equivalent amount of water (2,4,12). He arrived at these conclusions on the basis of observations in amphibians and mammals indicating that proximal tubular urine remained isosmotic (2,4). In addition, observations made in his laboratory after the intravenous administration of an osmotically active, nonreabsorbable solute to well-hydrated humans supported this hypothesis (12). The infusion of hypertonic mannitol resulted in increased urinary excretion of both the added solute and water in a proportion that was isosmotic with plasma. He interpreted these data to indicate that the proximal tubule is freely permeable to the passive movement of water and that the presence of a nonreabsorbable solute in the tubular lumen prevents the reabsorption of an osmotically equivalent amount of water (12). The descending thin limb of the loop of Henle is also relatively permeable to water. Tubular fluid becomes progressively concentrated at the hairpin turn as a result of the hypertonic medullary environment. According to Smith's ultimate scheme, the thin segment of the ascending limb was virtually impermeable to water and the urine entering the distal tubule was hypoosmotic to plasma (12). Further dilution of tubular fluid was accomplished in the distal tubule and collecting duct by the ongoing reabsorption of osmotically active solute (Na⁺, Cl⁻) in the face of a tubular membrane that is essentially impermeable to water in the absence of antidiuretic hormone (12). This process would generate free water. The construct predicts that maximum water diuresis could not be achieved in disorders characterized by the enhanced proximal reabsorption of sodium, which would decrease the availability of sodium for reabsorption in the distal diluting segments. Indeed, Smith noted that clinical situations in which urine sodium is low are characterized by impaired ability to form a dilute urine (2).

**URINARY CONCENTRATION**

Smith envisioned that in the hydropenic state, the elaboration of a urine with a higher osmotic concentration than the plasma is achieved by the reabsorption of water without an osmotically equivalent quantity of solute (2,4,12). This volume of water was originally designated negative $C_{H_2O}$ by Smith and later $T_{H_2O}^c$, defining the quantity of water required to restore hypertonic urine to an osmolality identical to that of plasma (2,4,12). $T_{H_2O}^c$ can be calculated as the difference between the urine flow rate and the osmolar clearance (Figure 1) (2,4,12).

Smith reasoned that, because the glomerular filtrate is an ultrafiltrate of plasma and proximal tubular fluid remains isosmotic with plasma even during antidiuresis, the urine must be concentrated at a more distal site in the nephron (2,4,12). He believed that an osmotically concentrated urine was formed by the removal of water from the glomerular filtrate rather than by the addition of solute (2,4,12). He arrived at this conclusion on the basis of studies he performed in which a mannitol-induced osmotic diuresis was produced in hydropenic subjects (13,14). Mannitol and sodium were the predominant urinary solutes in the hypertonic urine formed under hydropenic conditions (13,14). Because mannitol was known to be excreted solely by glomerular filtration and Smith thought it improbable that sodium could be secreted by tubules, he concluded that the elaboration of a hypertonic urine must be achieved by the reabsorption of water (13,14).

Smith developed a model of the urinary concentrating mechanism based on these and other observations he made during osmotic diuresis in the antidiuretic state (13–15). It was readily apparent to him that the rate of solute-free water reabsorption would determine the final urine concentration (2,13,14). It follows that higher rates of solute excretion would require enhanced volumes of water reabsorption to attain the same urine osmotic concentration (2,13,14). He fur-

![Figure 1](https://example.com/figure1.png)

**Figure 1.** Effect of solute load on water abstraction and urinary osmotic concentration during hydropenia. $C_{osm}$, solute clearance; $U_{osm}V$, urinary solute excretion rate; $P_{osm}$, plasma osmolality.
ther observed that, at low urine flow rates in the antidiuretic state, solute-free water reabsorption was limited by a maximal attainable urine to plasma osmotic ratio (2,13-15). Under these conditions, \( T_{W} \) was directly proportional to the urine flow rate (2,13-15). Conversely, at high urine flow rates induced by osmotic diuresis in the antidiuretic state, the rate of reabsorption of solute-free water reached a constant maximal limit \( (T_{W,C}) \). With further osmotic diuresis, the solute concentration of the urine decreased and approached that of plasma (2,13-15).

Finally, Smith's unique ability to create new concepts enabled him to integrate the work of Hargitay, Kuhn, and Wirz on countercurrent exchange and multiplication into a hypothesis (involving the vasa recta and loop of Henle) that explains the mechanism by which urinary osmotic concentration is achieved (16).

**UREA CLEARANCE**

Smith objected to the use of absolute urea clearance as an estimate of filtration rate, arguing that the excretion of urea was affected by urine volume (2,17). At maximum urine flow rates, the clearance of urea is approximately 60% of the inulin clearance (2,17). Because urea is completely filtered, he argued that the difference between the urea and inulin clearance reflected back-diffusion of urea into the blood through the tubules (2,17). He pointed to the fact that urea is among the most diffusible of organic substances. At low urine flow rates, the ratio of urea to creatinine clearance declines, consistent with the hypothesis that the back-diffusion of urea occurs as the urine is concentrated in its passage down the tubules and that prolonged contact allows enhanced back-diffusion (2,17).

Smith developed a model of urea handling by the kidney on the basis of observations made in humans and dogs over a wide range of urine flow rates (17). The urea/inulin clearance ratio (equivalent to the fraction of filtered urea that is excreted) was measured, and the value was plotted against the ratio of urinary to plasma concentrations of inulin \( (U/P) \) (which expresses the degree to which the urine is concentrated by the reabsorption of water) (17). This curve was found to be linear with a break in the slope at a \( U/P \) inulin ratio of 10 (17). The significance of this finding can only be understood in the context of the model of water reabsorption formulated by Smith (2,4). He divided the water reabsorptive process into two distinct components. The first, obligatory water reabsorption, involved the isosmotic passive reabsorption of water in the proximal tubule, made possible by the active proximal reabsorption of solute (2,4). The second process, facultative reabsorption of water, occurs in the most distal segments of the tubule and collecting duct and is responsible for the osmotic concentration of the urine (2,4). Water reabsorption that occurred at a \( U/P \) inulin ratio below 10 was attributed to obligatory reabsorption, whereas water reabsorption that occurred at a \( U/P \) inulin ratio above 10 was attributed to facultative reabsorption (2,4). Returning to our original discussion, Smith divided the plot of urea/inulin clearance versus \( U/P \) inulin into two phases at the point where the slope changed, corresponding to a \( U/P \) inulin ratio of 10 (17). Because the slope of the curve was steeper in the early phase, it was suggested that the proximal tubule is more permeable to urea than is the distal system (17).

Because 1-[urea/inulin clearance] gives the fraction of filtered urea that is reabsorbed, it could be calculated that 40% of filtered urea diffused back into the blood as passive water reabsorption in the proximal tubule progressively concentrates inulin from a \( U/P \) ratio of 1 to a ratio of 8 (17). Extrapolation of Smith's experimental curve to a urea/inulin clearance ratio of 1 corresponded to a \( U/P \) inulin ratio of 1.

**SODIUM EXCRETION**

Smith recognized that sodium homeostasis was conditioned by a variety of factors including filtration rate, glomerulotubular balance, and a host of physiologic mechanisms that governed proximal, distal, and collecting duct behavior vis à vis sodium reabsorption (2,18). He developed a model of the tubular handling of sodium based on observations made in dogs undergoing osmotic diuresis (18). During mannitol-induced osmotic diuresis, almost two-thirds of the filtered water was excreted in the urine at the time of a natriuresis, which was proportionally much less (2,18). He argued that, during osmotic diuresis, the urine flow rate is so great that the distal tubule effects little change in the composition of the tubular fluid, so that the composition of bladder urine could be equated with that of fluid at the end of the proximal tubule (2,18). On the basis of the observation that more water than salt was excreted under these experimental conditions, he concluded that the reabsorption of sodium in the proximal tubule was an active process and not merely a result of the passive diffusion of sodium in response to water reabsorption (2,18). Because the osmotic pressure of the urine approaches that of plasma during osmotic diuresis, he also concluded that proximal reabsorption was isosmotic with the plasma (2,18). To explain these observations, he argued that sodium was actively reabsorbed in the proximal tubule against a concentration gradient and that water passively diffused from the tubular fluid to maintain an osmotic \( U/P \) ratio of 1 (2,18).

Smith reasoned that the active proximal reabsorption of sodium would be impaired by the development of a concentration gradient between tubular and interstitial fluid (2,18,19). Under normal conditions, this gradient should remain small because of the rapid passive diffusion of water, and yet, he believed that sodium reabsorption in the proximal tubule was incomplete because the diffusion of water was not fast
enough to prevent the development of a sodium concentration gradient and because the presence of other osmotically active substances in the tubular fluid (i.e., urea or mannitol) retarded water reabsorption (2,18,19). In fact, he found that sodium reabsorption was reduced during osmotic diuresis, under conditions in which proximal water reabsorption was greatly retarded and proximal tubular sodium concentration declined (2,18,19).

Smith believed that sodium reabsorption in the distal tubule was also an active process insofar as a nearly sodium-free urine could be generated on a sodium-restricted diet (2,18). Because seven-eighths of filtered water is reabsorbed in the proximal tubule, he argued that an identical fraction of the filtered sodium is reabsorbed proximally so that only one-eighth of the filtered sodium is delivered to the distal tubule. He viewed the proximal tubule as being responsible for the bulk reabsorption of salt and water, with fine adjustments occurring in the distal tubule and collecting duct, subject to a variety of homeostatic mechanisms (2,18).

Smith recognized that sodium reabsorption is conditioned by the level of glomerular filtration (2,18,19). Absolute proximal sodium reabsorption was found to vary directly in response to changes in GFR, a form of glomerular-tubular balance, presumably reflecting alterations in sodium concentration gradients between proximal tubular and interstitial fluid (2,18,19). He suggested that sodium reabsorption in the distal tubule was modulated by both changes in the delivered load of sodium and changes in transport capacity (2,18,19). Expansion of the extracellular volume by increasing the filtration rate would increase the delivery of sodium to the distal tubule (2,18,19). Conversely, a reduction in the extracellular volume would decrease GFR and absolute delivery distally (2,18,19). Although he postulated a possible Tm for distal and collecting duct sodium reabsorption, he believed that the precise control of distal sodium handling depended on mechanisms that were still undefined in his time (and incidentally remain so). Through operation of the supraoptic-hypophysial/antiuretic hormone system, he proposed that sodium retention (or loss) would lead to the retention (or loss) of water until the osmotic pressure of the plasma is restored (20).

CLINICAL PRESENTATION #1

A 22-yr-old man with a 5-yr history of bipolar affective disorder was referred for nephrology consultation because of polyuria and polydipsia. The patient had been treated with lithium carbonate, 600 mg twice daily, for the previous 8 yr.

Laboratory evaluation revealed a BUN of 23 mg/dL, a serum creatinine of 1.6 mg/dL, a creatinine clearance of 60 mL/min, a serum osmolality of 290 mosmol/kg H₂O, and a 24-h urinary volume of 3,500 mL with a solute concentration of 200 mosmol/kg H₂O (700 mosmol/24 h). Urinary osmolarity deter-

minded after 24 h of fluid deprivation was 466 mosmol/kg H₂O. Simultaneous plasma osmolarity had increased to 302 mosmol/kg H₂O. Urine osmolarity was essentially unchanged after the administration of 5 U of vasopressin.

DISCUSSION #1

This patient is unable to concentrate his urine maximally after prolonged fluid deprivation as compared with healthy subjects who can generally achieve a urine osmolarity of at least 800 mosmol/kg H₂O. During antiuresis and the formation of a concentrated urine, the osmotic pressure of the urine is raised above that of plasma by abstraction of solute-free water from the isosmotic glomerular filtrate. At usual solute loads in normal subjects, the maximal urinary solute concentration (Uosm) is achieved as the collecting duct fluid comes into equilibrium with medullary hypertonicity in response to antidiuretic hormone (ADH) (Figure 1). When urine flow rate is varied over a wide range by inducing an osmotic diuresis during hydropenia, Zak et al. (14) showed that the urine-concentrating mechanism can be assessed additionally by plotting C同盟 against urine flow rate (V). If the glomerular filtrate were to undergo no concentration or dilution, then V would equal C同盟 throughout the range of urinary flow rates. However, during antiuresis, V is less than C同盟 by a value equal to the volume of solute-free H₂O reabsorption, designated as TₐH₂O. At high urine flow rates induced by osmotic diuresis during hydropenia, TₐH₂O reaches a limiting maximal value, which can be designated TmₐH₂O. As a result, at sufficiently high solute loads, the plot of C同盟 versus V forms a straight line with a slope of 1, which is displaced from the line of identity by a constant value equal to TₐH₂O. It is apparent from this plot that Uosm will decrease progressively with increasing solute loads and that concentrating ability will be defined under these circumstances in terms of TmₐH₂O rather than maximal Uosm.

Were the patient described here induced to undergo an osmotic diuresis during hydropenia, TmₐH₂O would be reduced as a consequence of his underlying chronic renal disease and the resultant reduction in the number of functioning nephrons that normally contributes to water abstraction. This would result in a displacement of the straight line plot of C同盟 versus V toward the line of identity at high urine flow rates.

Solute load per nephron increases in proportion to the reduction of renal mass under steady-state conditions in all forms of chronic renal disease. This solute diuresis is manifested by a reduction in maximal Uosm, which becomes increasingly evident as renal disease advances and surviving nephrons ultimately function at a C同盟 that exceeds their TmₐH₂O. In patients with acute glomerulonephritis studied by Baldwin et al. (15), GFR was found to be reduced without significant impairment in TmₐH₂O, reflecting glomerular injury without nephron loss and sparing of
the concentrating mechanism. In most patients with chronic glomerulonephritis, $Tm^{\text{H}_2\text{O}}$ was reduced in proportion to the impairment in GFR, suggesting the loss of entire nephrons. In contrast, in patients with acute renal failure, $Tm^{\text{H}_2\text{O}}$ was reduced out of proportion to the reduction in GFR, reflecting primary destruction of tubulointerstitial structures (ATN). Lithium nephrotoxicity in the patient under discussion would be expected to reduce $Tm^{\text{H}_2\text{O}}$ out of proportion to the patient’s decline in nephron number. Because lithium primarily affects the renal interstitial structures and presumably limits the ability to achieve medullary hypertonicity, both maximal $U_{\text{osm}}$ and $Tm^{\text{H}_2\text{O}}$ would be affected to a greater extent than in primary glomerular diseases.

Tubular resistance to the hydro-osmotic action of ADH (or vasopressin) has also been described in patients on lithium, giving a form of nephrogenic diabetes insipidus. Strictly speaking, this term may be used with certainty only when it is shown that the urine cannot be brought up to a level iso-osmotic with the plasma, because the exclusive role of ADH with regard to water transport by the distal tubule and collecting duct is permissive. Although lithium-induced renal resistance to ADH probably does play some role in reducing maximal concentrating ability (partial nephrogenic diabetes insipidus), such an effect cannot be separated from impairment of the tubular mechanism underlying this function, i.e., production of a hyperosmotic medulla. Resolution of this problem is further complicated by a potential reduction of medullary hypertonicity resulting from polydipsia.

At an intermediate urine flow rate (0.6 to 5 mL/min) induced by osmotic diuresis during hydropenia, urine-concentrating mechanisms are defined by a “transition zone” lying between the zone in which $Tm^{\text{H}_2\text{O}}$ limits urinary concentrating capacity (high V) and the zone where the maximal osmotic $U/P$ ration limits concentrating ability (low V). As the urine flow increases during osmotic diuresis in the antidiuretic state, the osmotic $U/P$ ratio will decrease asymptotically from its maximal value (Figure 1).

In clinical practice under usual prevailing solute loads, urine flow rates under hydropenic conditions rarely exceed $Tm^{\text{H}_2\text{O}}$; therefore, the ability to concentrate the urine is not limited by $Tm^{\text{H}_2\text{O}}$, but by a maximal $U_{\text{osm}}$. At low urine flow rates during hydropenia, when the delivered load of isoosmotic urine is less than $Tm^{\text{H}_2\text{O}}$, concentration is achieved by the abstraction of a quantity of solute-free water that is less than $Tm^{\text{H}_2\text{O}}$. Under these circumstances, water reabsorption is limited by a maximal urine to plasma osmotic gradient across the renal tubule that is dependent on medullary hypertonicity and urea recycling. Water reabsorption proceeds until the maximum osmotic $U/P$ ratio is achieved. Thus, the urine-concentrating ability during overnight fluid deprivation in our patient is determined by the maximum osmotic $U/P$ ratio that he can achieve. It may be postulated that lithium’s functional and structural effects on interstitial and tubular structures (most important, Henle’s loop) limit medullary hyperosmolality. In addition, as a consequence of our patient’s reduced GFR, an increased solute load is delivered to residual functioning nephrons. These nephrons are thus subject to an endogenous osmotic diuresis, which further depresses their maximal osmotic $U/P$ ratio.

Considering our patient’s ability to achieve a maximal urinary $U_{\text{osm}}$ of 466 mosmol/kg $H_2$O, it should be possible for him to excrete his 24-h solute load of 700 mosmol in 1,500 mL of urine. His output of 3,500 mL must be taken as evidence of somewhat exaggerated thirst rather than a reflection of his impaired urinary concentrating ability. The relatively minor elevation of his BUN as compared with serum creatinine (which is doubled) may be viewed as a corollary of his polyuria, which would maximize urea clearance. The increase in serum osmolality after 24-h fluid deprivation can be attributed to his 1,500-mL obligatory urine volume coupled with insensible fluid loss.

**CLINICAL PRESENTATION #2**

A 90-yr-old man was admitted to the hospital with fever and confusion. Physical examination revealed a systolic blood pressure of 60 mm Hg, a temperature of 102°F, and bilateral pulmonary infiltrates. The admission BUN was 60 mg/dL, and the serum creatinine was 2.5 mg/dL. Urine osmolality was 700 mosmol/kg $H_2$O, urine sodium was 15 mEq/dL, and the $U/P$ creatinine ratio was 68. The patient was hydrated with intravenous normal saline at a rate of 100 mL/h and was begun on empiric therapy with cefotaxin. He remained hypotensive despite $\alpha$-norepinephrine infusion. Twenty-four hours later, the serum creatinine had risen to 3.6 mg/dL and the BUN has increased to 70 mg/dL. Urine output during this 24 h totaled 350 mL. Repeat urine osmolality was 306 mosmol/kg $H_2$O, urine sodium was 56 mEq/L, and the $U/P$ creatinine ratio was 12.

**DISCUSSION #2**

This elderly patient presented with hypotension and renal functional impairment in a setting of sepsis. The mechanisms responsible for hemodynamically mediated renal functional impairment were studied by Smith and coworkers, who showed that the response of the renal microvasculature to endogenous vasoconstrictors parallels that observed with exogenous agents and with orthostatic hypotension. In studies of the renal circulation in humans, Smith found that upright tilting in healthy individuals elicited renal vasoconstriction and attributed this response to reflex excitation of neurogenic pathways (1,2,10). In addition, he demonstrated that the administration of moderate doses of adrenalin raised systemic blood pressure and reduced RPF while leaving the GFR unchanged. He concluded that the rise in filtration fraction after adrenalin resulted from predominant
constriction of the efferent arteriole, which elevated intraglomerular pressure sufficiently to maintain GFR despite a decline in RBF. With larger doses of adrenalin, afferent constriction predominated and the filtration rate fell. The initial fall in GFR in our patient resulted from reduced RBF (and glomerular capillary pressure, \(P_{GC}\)) due to a markedly depressed perfusion pressure combined with afferent and efferent arteriolar constriction.

Smith recognized that renal ischemia was a primary factor in the evolution to ATN in patients such as ours. He reasoned that in ATN both filtration and reabsorption fell to minimal levels and argued against the concept of primary back-diffusion in the face of continued filtration, although he acknowledged possible contributions of tubular obstruction and back-leak.

Avid sodium retention was a feature of the early phase of our patient's illness. Smith was aware that the renal handling of sodium was conditioned by a variety of influences including GFR, physical factors, adrenal cortical hormones, and others that remain undefined. In studies performed in healthy subjects, absolute proximal sodium reabsorption was found to vary directly in response to changes in GFR, giving rise to the concept of glomerulotubular balance. Smith suggested that sodium reabsorption in the distal tubule was modulated by both changes in the delivered load of sodium and changes in transport capacity. A reduction in renal perfusion, which decreases glomerular filtration, results in a decline in the distal delivery of sodium, increased distal reabsorption, and markedly decreased excretion. The precise mechanisms that determine distal sodium handling remain poorly understood. We know now that tubuloglomerular feedback undoubtedly plays a major role in the physiology and pathophysiology of sodium homeostasis (21).

In our patient with hypotension and renal ischemia before the ATN phase, decreased sodium and water excretion will be associated with a decline in urea clearance out of proportion to GFR, reflecting a larger fraction of urea reabsorption at low urine flow rates. An acute reduction in glomerular filtration with preservation of tubular function accounts for his increased sodium and water reabsorption and the generation of a steep urea gradient.

Chasis and Smith (17) studied urea handling in patients with chronic glomerulonephritis. In early glomerulonephritis, the urea/inulin clearance ratio at a given \(V\) was similar to that of healthy subjects. However, in advanced disease, osmotic diuresis in the remaining nephrons reduces water reabsorption and decreases the \(U/P\) inulin ratio below that of healthy subjects; as a result, urea clearance (\(C_{urea}\)) approaches GFR. Urea handling in our patient as he progressed to ATN resembles in some respects that observed in the adapted diuretic nephrons undergoing solute diuresis in patients with chronic glomerulonephritis. With widespread nephron destruction, the reduced volume of glomerular filtrate is altered, but minimally. As it traverses the tubules, minimal urea gradients are created and urea clearance approaches that of inulin.

The characteristic functional manifestations that reflect the transition from renal ischemia to ATN are evident in this case. The further marked decline in GFR and the disruption of tubular function bring the urinary constituents closer to those of plasma. The \(U/P\) creatinine ratio declines as the fraction of sodium, other solutes, and isosmotic water reabsorption plummets. The ability to concentrate the urine osmotically is lost as well, further depressing \(U/P\) creatinine.

REFERENCES