Acute Renal Success

The Unexpected Logic of Oliguria in Acute Renal Failure*

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The clinical condition known as acute renal failure is recognized by the onset of oliguria, its course is marked by the persistence of oliguria, and recovery is heralded by the advent of diuresis. The dramatic character of oliguria has made it the focus of attention for the physician. Oliguria was viewed as the primary event and therapy was directed to measures to restore urine flow rate to normal. Little thought has been given to the concept that the kidney may be acting appropriately in making a small volume of urine or that oliguria may be the necessary consequence of a functional adaptation protecting the patient from a graver danger.

A PARTICULAR POINT OF VIEW

Experimental research during the last decade [1–9] has provided new insight into the functional alterations and adaptations in the kidney during acute renal failure; we would like to discuss the condition from a rather particular point of view. Our thesis is that the oliguria of acute *reversible* renal failure results from the operation of an intrarenal regulating mechanism present in the normal kidney and working, in the case of acute renal failure, to the immediate benefit of the patient. The immediate benefit is life-saving, as will be shown; certain long-term effects are less desirable.

THE INHERENT DANGER OF OUR HIGH FILTRATION RATE

The kidney has a reputation for sensible behavior. As the exacting guardian of our internal environment, it has been credited with discriminatory activity in the selection of filtered plasma constituents for reabsorption or excretion. The large glomerular filtration rate, a heritage from our aquatic ancestors, has been retained in the mammalian kidney because it serves its important function of continuously reprocessing the plasma. In this reprocessing, the entire circulating plasma volume is filtered and reabsorbed twice an hour. As a means of adjusting the body fluid composition, the function is effective but it contains an inherent danger—that of severe fluid loss if the reabsorptive mechanism should fail.

DISTINCTIVE FEATURE OF TUBULAR REABSORPTION

The coupled events of filtration and reabsorption occur at the capillary end of all vascular beds and are accomplished in most regions by purely physical forces, the balance between hydrostatic and colloid oncotic pressures first described by Starling. By and large, the composition of filtrate and reabsorbate is the same, and no discrimination

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is exercised (Figure 1). In the kidney, however, a layer of epithelial cells (the tubular wall) is interposed between the site of filtration and that of re-entry of the filtrate to the blood stream. This distinctive addition to the system refines the reabsorptive process and enables a degree of selectivity in solute excretion (Figure 1). Salt and water are reabsorbed in large volumes, creatinine and urea for the most part are excreted. Tubular cell activity defines the composition of both reabsorbate and final urine. Selectivity ends at the basal surface of tubular cells, and re-entry into the vascular compartment is accomplished, as in the peripheral circulation, by Starling forces, without further discrimination as to composition.

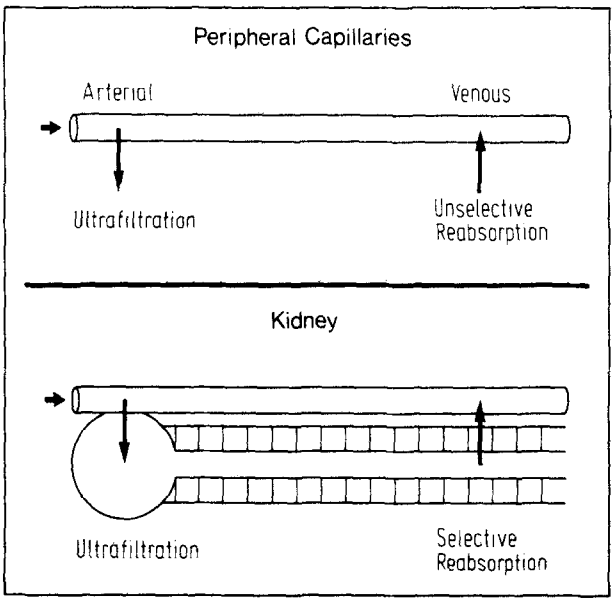

Figure 1. *Schematic representation of fluid movement across the capillaries in the peripheral circulation and in the kidney. The extravascular fluid movement is determined in peripheral capillaries by physical forces (Starling mechanism) and, hence, is unselective, whereas, in the kidney, energy for a discriminating reabsorptive process is supplied by an interposed cell layer (tubular cells).*

GLOMERULAR FILTRATION RATE AND TUBULAR REABSORPTION ARE SEPARATELY POWERED

The energy source for glomerular filtration, the left ventricle, is distinct from the metabolic energy of reabsorption, generated locally by the tubular epithelial cells. It is this locally-produced energy that brings to the blind force of filtration the refinement of differential selectivity in the reabsorptive process. Although the energies of these two basic renal operations are independently derived, they must be adaptively coupled to one another. The adaptive coupling is described phenomenologically as tubuloglomerular balance [12–15], a process by which the rate of tubular reabsorption sets the filtration rate. This setting is imperative since failure of reabsorptive function in the presence of continued filtration would result in a devastating loss of body fluids.

A LINK BETWEEN FILTRATION AND REABSORPTION

In most systemic capillaries, filtration and reabsorption are intrinsically joined. The hydrostatic force that results in filtration at the arterial end of a capillary provides the energy for reabsorption by concentrating colloids. The opposing filtration pressure is dissipated by the high resistance of the capillaries, and colloid oncotic pressure becomes increasingly effective, favoring reabsorption.

What mechanism exists to adjust filtration rate to reabsorptive capacity in the nephron? To be effective it should comprise monitoring and reacting components by which some sensing device reads a signal reflecting the adequacy of reabsorption and initiates a response at the glomerular level. The structural basis for such a system has been found in every mammalian nephron examined [16–19] and is embodied in the juxtaglomerular apparatus (Figure 2). The juxtaglomerular apparatus joins a late segment of each nephron to the vascular pole of its own glomerulus. At the end of the thick ascending limb of Henle's loop, where the nephron returns to its glomerulus, the cells of the tubular wall are differentiated into the *macula densa* cells and lie in intimate apposition to the walls of the glomerular arterioles. Here the cells of the media are transformed to large secretory-type cells filled with electron-dense granules (renin). This anatomic arrangement is ideally suited to monitor an intratubular event (reabsorption) and to initiate a response (filtration).

FEEDBACK CONTROL OF GLOMERULAR FILTRATION RATE—THE SIGNAL

The signal that is read by the tubular component (macula densa) of the juxtaglomerular apparatus is the sodium chloride concentration of tubular fluid at that site [10,11,14,21]. Present evidence more specifically favors chloride ion concentration as the definitive signal [22], and the concentration of this ion here is related to the reabsorptive activity of the entire nephron. The largest volume of filtrate is reabsorbed proximally, at a chloride concentration close to the plasma value. Filtrate arriving at the site of the *macula densa* has, under normal conditions, lost over 80 per cent of its original volume and its sodium chloride concentration is, for the first time along the nephron, below plasma value—about one-seventh in fact [1,23,25]. This low chloride concentration is established by the thick ascending limb of Henle's loop, the cells of which actively transport chloride [26] without equivalent water.

An increased signal, reporting imbalance between filtration and reabsorption, can be induced experi-

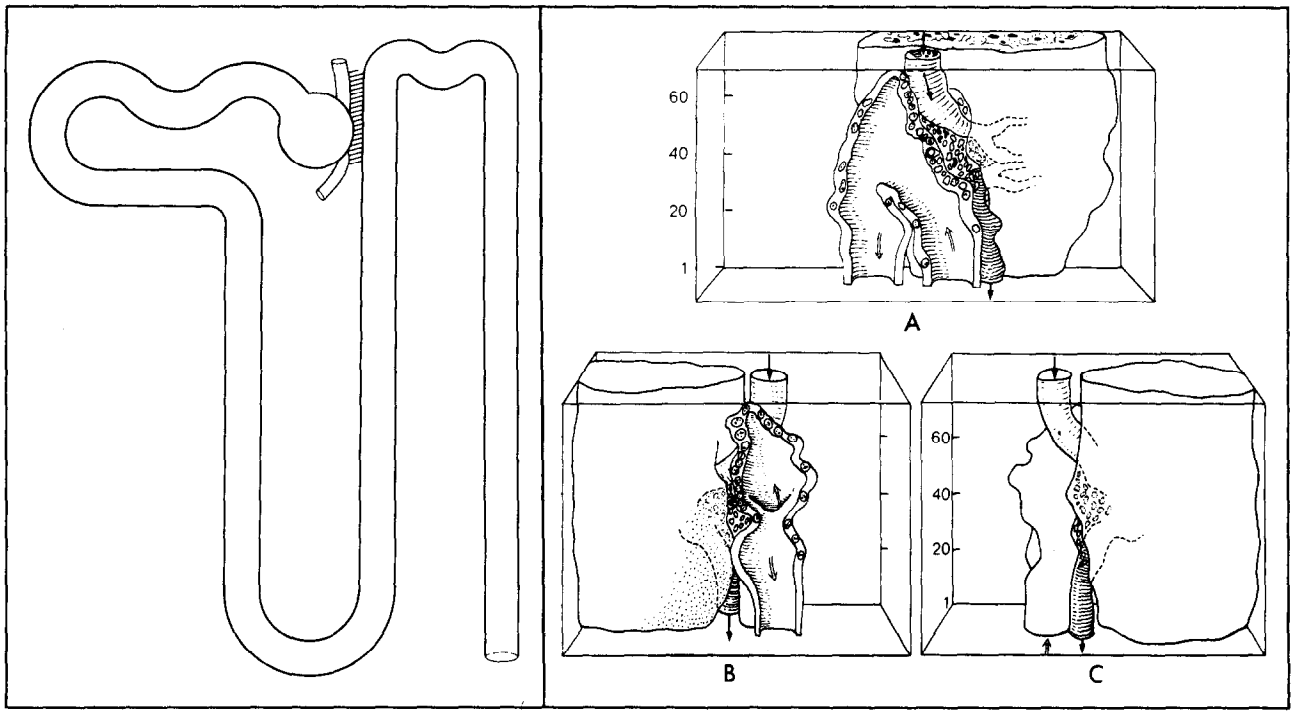

Figure 2. ***Left,*** *schematic representation of the anatomic relationship of the juxtaglomerular apparatus (hatched area) within the single nephron unit. The juxtaglomerular apparatus forms a functional link between the end of Henle's loop and the vascular pole of the glomerulus of the same nephron.* ***Right,*** *scale reconstruction (190:1) of the vascular pole of a human glomerulus with juxtaglomerular apparatus from 1.9 μ thick, Giemsa-stained serial sections.* ***A,*** *from above,* ***B,*** *from the left,* ***C,*** *from the right. The flow direction of blood* ***(closed arrows)*** *and urine* ***(open arrows)*** *is indicated. The Goormaghtigh cells in the angle between the two arterioles, the cell nuclei of the macula densa and in the remaining part of the tubule are shown. The arteriolar component of the apparatus is not shown. In the background (A) of the vascular pole and to its left and right (B and C) is the outer surface of Bowman's capsule [20].*

mentally in two ways: (1) One is by augmenting the perfusion rate through the nephron, a condition simulating increased glomerular filtration rate. This leads to an increase in sodium chloride concentration at the *macula densa* [14,23,24] since tubular reabsorptive activity does not increase in proportion to the increased tubular flow rate. (2) Another is by reducing the tubular reabsorptive capacity. Here, the increased sodium chloride concentration at the *macula densa* reflects the failure of the tubular epithelium to reabsorb [1,11]. Either maneuver causes an imbalance between solute load to the nephron and reabsorptive capacity of tubular cells.

FEEDBACK CONTROL OF GLOMERULAR FILTRATION RATE—THE RESPONSE

The appropriate response to a signal reporting reabsorptive failure is reduction in filtration rate; this has been found in experimental animals with induced acute renal failure [5] and in the clinical condition in man [27]. Filtration rate is reduced by vasoconstriction of the glomerular arterioles and, possibly, by retraction of the glomerular tuft [28,29], activities that simultaneously reduce renal blood flow [30–32]. Evidence is accumulating that the vasoactive material is angiotensin II, locally formed at the site of the juxtaglomerular apparatus and acting in situ. It has been shown that the juxtaglomerular apparatus is supplied with all the components necessary to manufacture and to degrade angiotensin II [35]. Converting enzyme inhibitors reduce the intensity of the response [36] as does depletion of renal renin [10,34–39].

Data have been furnished recently to confirm the intrarenal formation of angiotensin II [40] and its release primarily into the renal interstitium rather than into the blood [41]. Experimentally, when tubular fluid sodium chloride concentration of a single nephron is increased at the macula densa (Figure 3), the renin activity of the attached juxtaglomerular apparatus increases proportionately [21] and the filtration rate of that nephron decreases [14,42]. These findings together demonstrate the existence of a tubuloglomerular feedback mechanism whereby single nephron (and in the aggregate, whole kidney) glomerular filtration rate is regulated according to the efficiency of reabsorption. Brandt-Rehberg [12], who introduced creatinine as a

marker for the measurement of glomerular filtration rate, was to our knowledge, the first to point out the relationship between tubular reabsorptive capacity and the glomerular filtration rate when he wrote in 1929: "Es bedeutet hier, daß jede Schädigung der Tubuli, die eine Einschränkung in der Resorptionsfähigkeit dieser Gebilde bewirkt, auch eine sofortige Herabsetzung der Glomerulifunktion mit sich bringt." (Translation: This means that any damage to the tubules, which leads to a curtailment of their ability to reabsorb, will also lead to an immediate reduction in the function of the glomeruli.)

SEQUENCE LEADING TO OLIGURIA

Whatever the initiating cause of acute renal failure (toxic, ischemic, etc.), the injury affects tubular transport activity, that function of the kidney that depends on locally generated energy [3,33,34,43,44]. When tubular reabsorptive capacity and net volume reabsorption have been examined in animal models of acute renal failure they have been found to be significantly depressed [2,3,5,45–47]. The result is an increase in sodium chloride concentration of tubular fluid arriving at the *macula densa*. In addition, these experimental animals have been found to have increased renin activity in their juxtaglomerular apparatus [9,48–50] just as the renin activity in the single juxtaglomerular apparatus of normal kidneys increased when their macula densa segments were perfused with fluid of high sodium chloride concentration [21,35].

In acute renal failure, therefore, the feedback mechanism described and schematically illustrated in Figure 4, provides a means to maintain tubuloglomerular balance by reducing the glomerular filtration rate to a level compatible with the attenuated reabsorptive capacity. Both the sensing and response elements of the feedback mechanism have been found to be functionally intact in various models of acute renal failure [9].

GLOMERULAR DEFENSE OF VOLUME

Reduction in glomerular filtration rate to conform to diminished reabsorptive capacity means that the glomeruli have taken over the volume-conserving function normally exercised by the tubules. The importance of this reduction in glomerular filtration rate is made clearer by considering what might happen if the glomerular filtration rate remained normal and the tubular reabsorption were reduced by 50 per cent. Urinary volume and sodium excretion would be half the filtered load. In man, the result would be a urinary volume loss of approximately 60 ml/min and, unless salt and water loss could be replaced, the organism would lose its last sodium ion within a few hours. Volume conservation by reversible glomerular shutdown is immediately effective

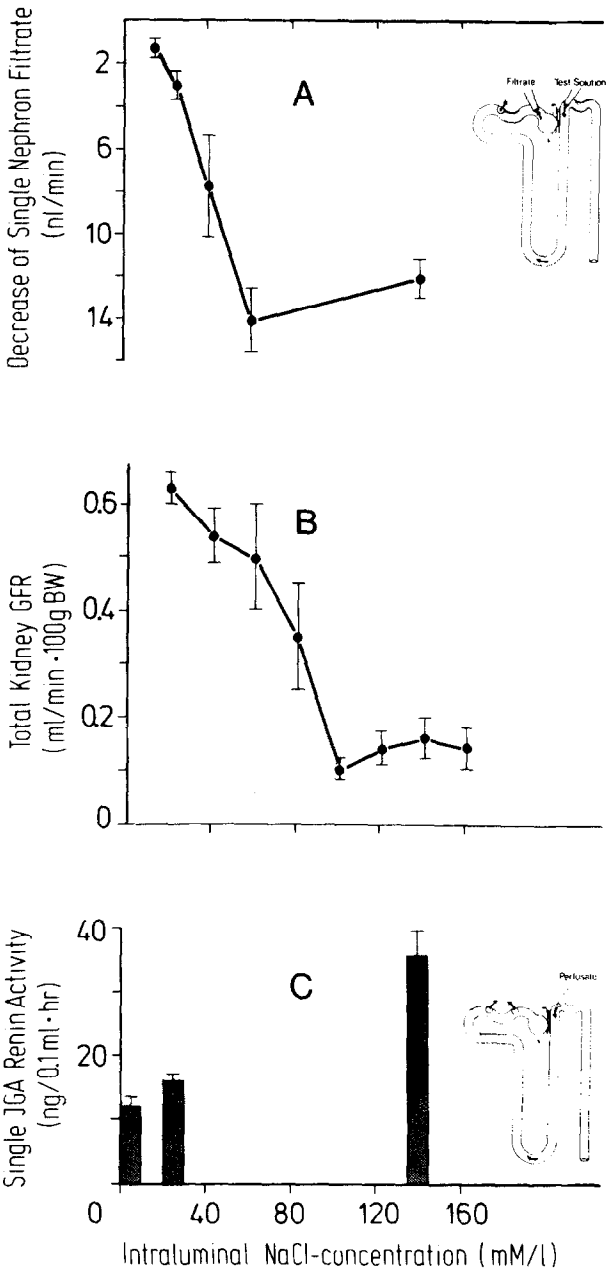

Figure 3. *The relationship of glomerular filtration rate (GFR) (solid line) and renin activity in the juxtaglomerular apparatus (JGA) (solid bars) to the sodium chloride concentration in tubular fluid of early distal tubule.* ***A,*** *in the normal rat kidney, retrograde perfusion of a macula densa segment with increasing sodium chloride concentration is associated with a progressive fall in simultaneously measured single nephron filtration rate (after 22).* ***B,*** *in the normal and postischemic rat kidney, total kidney filtration rate correlates closely with sodium$^+$ concentration in the early distal tubular fluid (after 1).* ***C,*** *in the normal rat kidney, retrogade perfusion of the macula densa segment with sodium chloride-free mannitol or with 140 mmol sodium chloride and determination of renin activity in the attached juxtaglomerular cell complex. Renin activity associated with 25 mmol sodium chloride (middle bar) was obtained from juxtaglomerular apparatus of nephrons naturally perfused from the glomerulus [21].*

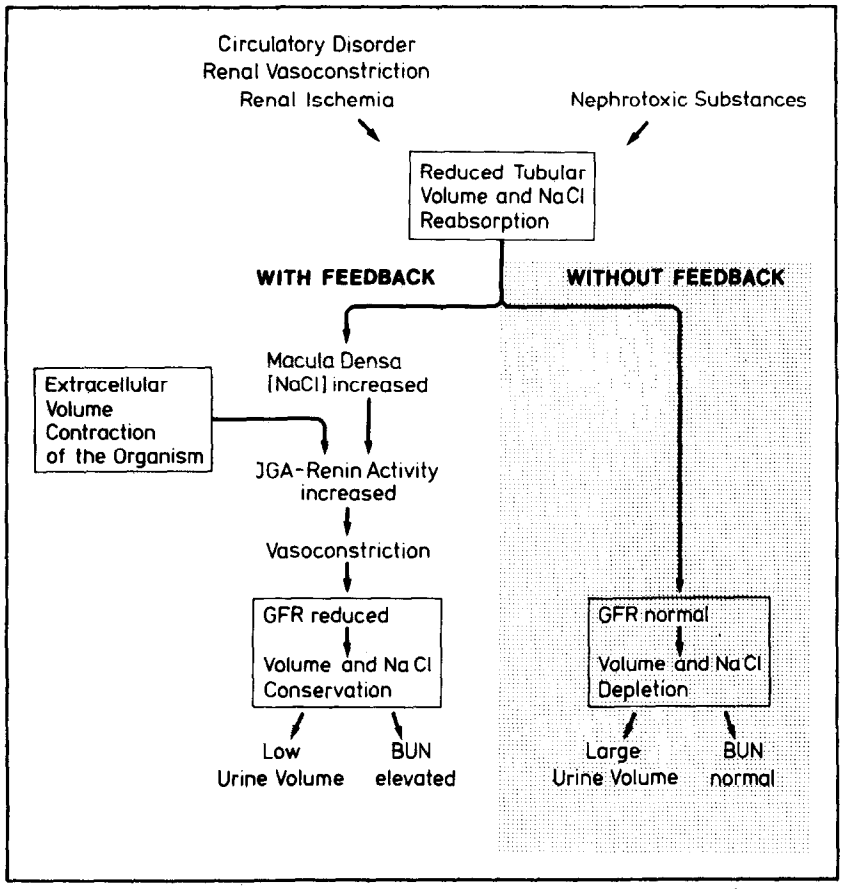

Figure 4. *Diagram illustrating the postulated effect of the presence or absence of tubuloglomerular feedback on urine volume and blood urea nitrogen in the inadequately reabsorbing tubules of an acute renal failure kidney.*

and therefore life-saving. It has the disadvantage of being indiscriminate; consequently nitrogenous wastes and other materials regularly cleared by filtration are retained. The immediate threat of death by hypovolemia is averted at the expense of the regulation of body fluid composition. This decision allows the organism time to repair structure and function of the damaged tubules.

Nephron damage in acute renal failure is of quite variable severity. Many instances of tubular injury undoubtedly occur in which the reduction in glomerular filtration rate is moderate and retention insufficient to come to the clinician's attention. It is only when reabsorptive function is severely reduced that depression of the glomerular filtration rate leads to a degree of retention that is clinically relevant. The degree of retention in some measure, therefore, reflects the extent of tubular reabsorptive insufficiency.

LOSS OF CONCENTRATING ABILITY AND HIGH URINARY SODIUM

The distinctive defect in tubular sodium chloride reabsorption, here presented as the determinant of oliguria, has other effects on renal function, and these have provided diagnostic guides to the recognition of acute renal failure. Diminished urinary concentrating ability is characteristic [51]. For maximum efficiency, the concentrating process requires a filtration rate large enough to insure adequate delivery of solute to the countercurrent system and an intact function of loop transport of sodium chloride [52]. Both activities are prerequisite for the establishment of a medullary osmotic gradient, the basis of urinary concentration, and both activities are impaired in acute renal failure. The result is a small volume of isosmotic urine with a high sodium concentration, a combination found only in acute renal failure or end-stage renal disease. In balance studies of patients in acute renal failure, the mean urinary sodium concentration during the oliguric phase is often in excess of 85 meq/liter [53,63]. Values greater than 25 meq/liter during oliguria are considered diagnostic [54]. In contrast, prerenal oliguria, usually the result of dehydration or volume loss, is associated with avid sodium retention.

THE SIGNAL PERSISTS UNTIL HEALING

The persistence of oliguria long after removal of the precipitating cause of acute renal failure has always troubled the thoughtful physician as has the unexplained

appearance of diuresis. Both findings are readily accounted for in the present concept when we consider that as long as tubular reabsorptive capacity is interfered with, so long will sodium chloride concentration remain increased in tubular fluid and be monitored at the *macula densa.* The signal for reduced glomerular filtration rate and its correlated renal blood flow will persist until tubular function is restored. This is reflected in a decrease in urinary sodium concentration from high values in the first days of oliguria to lower values when urine flow is approaching normal (Figure 5). Healing of tubular cell injury requires from a few days to two or more weeks, depending on the severity of the lesion, and it is not surprising that the period of glomerular shutdown reflects this variability of time. As each nephron regains its reabsorptive function, the sodium chloride concentration of tubular fluid arriving at its *macula densa* is reduced and filtration to that nephron increases. Not uncommonly, in the restoration of tubular function, the glomerular filtration rate is not perfectly matched to reabsorptive capacity and a period of imbalance intervenes, manifested by polyuria. Salt wasting is characteristic of this phase [63] and replacement must be carefully matched to urinary loss. During functional maturation of regenerating tubules, small increases in the glomerular filtration rate result in large increments in urine flow and, until the capacity for maximum sodium salvage is restored, a period of negative balance is likely.

ACUTE RENAL FAILURE REDEFINED

So the accusation implied in the term "acute renal failure" is only partially just. Due to injury, the tubules have failed in their reabsorptive function but immediate massive volume loss has been prevented by the feedback mechanism of the juxtaglomerular apparatus, a fail-safe device that guards volume by indiscriminate retention. The system continues to operate, like a finger in the dike, until tubular function is reestablished. The scope and efficiency of this volume-conserving mechanism, the normal operation of which is scarcely discernible, are revealed only in the extraordinary condition of tubular failure.

A MODULATOR OF THE JUXTAGLOMERULAR APPARATUS SYSTEM

The system has another input in addition to the signal to the *macula densa* and that is the "state of fullness" of the extracellular space, i.e., the volume reserve of the organism. Volume expansion decreases renin activity in the juxtaglomerular apparatus [55] and this is coincident with a reduced gain of the feedback control system thereby reset to a lower level of responsiveness [10,37–39]. Hence reduction in glomerular filtration rate is less pronounced when the stimulus impinges on a system made less sensitive by volume expansion.

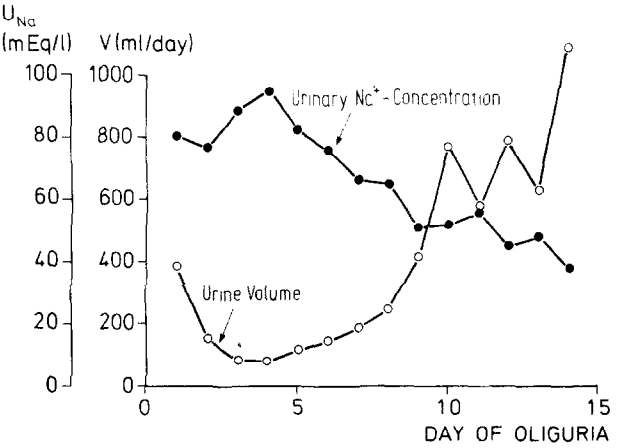

Figure 5. *Urinary sodium concentration and urine volume during the oliguric and recovery phases of acute renal failure in man (redrawn from data of [53]).*

In contrast, during volume depletion, renin activity in the juxtaglomerular apparatus is increased and a given increase in sodium chloride concentration at the *macula densa* results in a greater depression in the glomerular filtration rate than would occur in the normal or expanded state (Figure 4). The afferent pathway of this input is unknown but is thought by some to originate from baroreceptors in the walls of the glomerular arterioles [56] or from changes in ionic composition of juxtaglomerular apparatus cells associated with volume expansion or contraction [38].

THE LOGIC OF PROTECTION FROM GLOMERULAR SHUTDOWN

It follows that the likelihood of acute renal failure developing in a given situation is best minimized by a state of volume expansion. The consequent lowering of renin activity in the juxtaglomerular system prevents the kidney from reacting too intensely to tubular injury, that is, by too drastic a reduction in glomerular filtration rate and renal blood flow thus exacerbating the ischemic condition. The common clinical impression that patients whose extracellular volume is contracted are more prone to the development of acute renal failure was borne out by experiments in which volume expanded rats were significantly protected [57,58]. The efficacy of loop diuretics in some cases of acute renal failure is consistent with the ability of these diuretics to interfere with the perception and/or transmission of the signal at the *macula densa* [9,59].

POLYURIC ACUTE RENAL FAILURE

No system is infallible and we should expect cases of acute renal failure to occur in which the volume-preserving function of the feedback system does not properly respond. Whatever the cause (failure of *macula densa* to read the signal, enzyme defect, substrate in-

adequacy, etc.), reduced reabsorptive capacity in the presence of an uncontrolled filtration rate should result in massive volume loss.

A literature search in fact discovers cases of massive polyuria (45 to 70 liters/day approximating half or more of simultaneously measured filtration rate), in instances of tubular injury in which glomerular filtration rate was *not* curtailed [44,60]. *This* is complete renal failure wherein both tubular and glomerular volume-conserving mechanisms are bankrupt. It is of interest that one of these is a case of postobstructive nephropathy [60], a salt-losing state, in which the major defect in reabsorption is thought to occur in the proximal tubule [61,62]. Some ascending limb function is apparently spared since a dilute urine can be formed [61]; whether this fact or a direct compressive injury to the juxtaglomerular apparatus is responsible for failure of the feedback mechanism is presently speculative.

SUMMARY AND CONCLUSION

The magnitude of glomerular filtration imposes the necessity of a safety mechanism to protect the body from serious fluid loss if tubular reabsorption should fail. This need appears to be met by the juxtaglomerular apparatus which contains a sensing element to recognize tubular reabsorptive activity and a response component to adjust the glomerular filtration rate proportionately. The system is operating in acute renal failure and preserves body fluids by glomerular shutdown, with resulting oliguria. Once acute renal failure is manifest, rational therapy might be directed to an attempt to moderate the renal response, i.e., the degree of glomerular shutdown either at the level of signal perception or juxtaglomerular apparatus enzyme activity. Such methods are conjectural, but it may be possible in this way to adjust renal perfusion to a rate that is adequate to promote healing and a degree of excretory function without jeopardizing volume conservation. Dialysis and careful fluid balance will support the patient until healing is complete.

The basic pattern of the tubuloglomerular feedback system has been defined by experimental analysis. Many intricacies, especially details of signal transmission and the pathway leading to angiotensin II formation, remain as subjects for future investigation.

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