

ACUTE RENAL FAILURE

ABSTRACT.—Although a wide variety of disease processes can result in a failure of renal excretory function, the vast majority of cases with “acute renal failure” (ARF) are due to the syndrome of acute tubular necrosis (ATN). The syndrome is usually initiated by an acute injury to the proximal renal tubular epithelial cells by ischemic or nephrotoxic events. This is followed by progressive and often rapid increases in the concentration of blood urea nitrogen (BUN) and serum creatinine. In the average case, the failure of renal excretory function persists for 1 to 3 weeks, to be followed by recovery. Oliguria (urine volume less than 400 ml) is present in about half of the patients. The pathogenesis of the retention of nitrogenous waste in human ATN is the subject of controversy, but the balance of data in most patients suggests that the predominant mechanism is a profound secondary vasoconstriction in response to tubular cell injury. This may represent a teleologically appropriate response to prevent catastrophic losses of fluid that would occur, if the normally high rates of glomerular filtration continued, in the face of reduced tubular reabsorptive capacity. The mechanisms by which the tubular cell injury is communicated to the vasculature, and the mediators of the hemodynamic changes, remain to be established.

The differential diagnosis in a patient with ARF, usually involves exclusion of an obstruction to the urinary tract as an initial step. The next step is to differentiate the patients with ATN from those who have renal hypoperfusion in response to events in the systemic circulation, but who otherwise have functionally and structurally intact kidneys, i.e., prerenal ARF. The kidneys of patients with prerenal ARF exhibit the normal renal response to an acute reduction in renal blood

flow and glomerular filtration rate (GFR). This consists of avid reabsorption of the filtered salt and H₂O, so that a small amount of concentrated and NaCl-poor urine is elaborated. The tubular cell injury in ATN syndromes prevents this response from maximally occurring, so that the urine is isosmotic and relatively rich in NaCl. This difference in the character and composition of urine forms the basis for the separation of patients with prerenal ARF from those with ATN. The differentiation is important because of its implication for management.

Additionally, prerenal ARF markedly enhances the susceptibility of patients to develop ATN with additional renal injury. Experimental studies suggest that this is due to enhanced salt and H₂O absorption in the proximal nephron, which increases nephrotoxin concentrations in the tubular lumen. The slower transit times allow more prolonged exposure of tubular epithelium to nephrotoxins and increases the likelihood of nephron obstruction. Conversely, interventions such as saline expansion or mannitol administration, which decrease proximal reabsorption and increase volume flow through the proximal nephron, ameliorate the severity of ATN. However, it needs to be emphasized that plasma volume expansion per se has little protective effect in the absence of renal vasodilation and decreased proximal tubular reabsorption, as might occur in patients with preexistent cardiac, hepatic, or renal disease. A variety of pharmacologic agents have been reported to ameliorate the severity of ATN, especially when administered prior to or simultaneous with the initiating injury. However, no controlled clinical studies have been performed to test their efficacy, and their use is not recommended because of potential side effects.

The management of established ATN is primarily addressed to minimizing the inevitable changes in body fluid volume and composition and to prevention of uremic complications. Dialysis is a reasonably effective substitute for renal excretory function until recovery occurs. However, the combined loss of the homeostatic regulatory ability and excretory function of the kidneys in ARF further complicates the already complex management of many of the underlying diseases. This is reflected in the high mortality (50%) that continues to be associated with the syndrome of ARF.

It should be emphasized that most patients die with ARF and not of ARF.



IN BRIEF

Acute renal failure (ARF) is defined clinically as any acute reduction in renal excretory function sufficient to result in retention of nitrogenous waste.

CLASSIFICATION

The disease processes that cause ARF can be separated into three major categories: (1) inadequate blood flow to functionally and structurally intact kidneys (prerenal ARF); (2) renal parenchymal diseases (intrinsic ARF); and (3) diseases causing obstruction to the outflow of urine (postrenal ARF). The causes of intrinsic ARF can be further subdivided based on the anatomical site of injury in the kidney: large blood vessels, microvasculature (arterioles and/or glomeruli), tubules, and interstitium. However, in the vast majority of patients with ARF, the failure of renal excretory function results from an acute injury to the renal tubular epithelial cells caused by either ischemic or nephrotoxic mechanisms. The resulting clinical syndrome has been termed acute tubular necrosis (ATN). The terms "ATN" and "intrinsic ARF" are often used interchangeably.

In the usual case, progressive and fairly rapid increases in the concentration of blood urea nitrogen (BUN) (10 to 20 mg/dl) and serum creatinine (0.5 to 2 mg/dl) occur following a clearly defined event, usually in patients hospitalized for other underlying diseases. Often there is an associated decrease in urine volume. However, recent studies have emphasized that approximately half of the patients may not be oliguric (urine volume less than 400 ml/dl). The nonoliguric form of ATN in general reflects a less severe renal injury. The failure of excretory function in the average case persists for 1 to 3 weeks (the maintenance phase), followed by a recovery phase during which gradual increases in urine volume and fall in the BUN and serum creatinine concentrations occur. In some severe cases, the maintenance phase can last as long as a few months. Recovery is usually complete in a majority of cases, at least as judged by attainment of normal serum creatinine values.

PATHOGENESIS OF ATN SYNDROME

Although acute tubular cell injury is the initiating event in ATN, the precise mechanisms by which nitrogenous waste is retained are the subject of ongoing controversy. There is very often a poor cor-

relation between the extent of morphological injury and the severity of the clinical syndrome. The proposed pathogenetic mechanisms can be broadly classified into two categories: (1) tubular mechanisms involving "backleak" of the glomerular filtrate across damaged tubular basement membranes and/or obstruction of individual nephrons with proteinaceous casts and necrotic cell debris; and (2) hemodynamic mechanisms involving intense preglomerular vasoconstriction causing a decrease in renal blood flow (RBF) and glomerular filtration rate (GFR) and/or a decrease in the filtration coefficient (K_f), which is a product of the glomerular capillary hydraulic conductivity and surface area. Experimental studies attempting to assess the relative contributions of these pathogenetic mechanisms have yielded variable and often contradictory results. Moreover, there are reasons for caution in extrapolating the experimental data to human ATN. None of the animal models is entirely satisfactory in reproducing the morphological and functional characteristics of human ATN. A persistent marked decline in RBF is characteristic of human ATN but not of experimental ATN. In our opinion, the balance of data in human ATN syndromes suggests that hemodynamic mechanisms predominate, with a significant but variable contribution by obstructive and a minor contribution by "backleak" mechanisms.

THE CONCEPT OF "ACUTE RENAL SUCCESS"

While the term "acute renal failure" refers to the failure of excretion of nitrogenous waste, a persuasive case can be made that the marked reduction in glomerular filtration responsible for retention of waste in the ATN syndrome represents a teleologic success in allowing survival of the organism. The hallmark of the ATN syndrome is tubular cell injury and in vitro studies have demonstrated a marked reduction in tubular reabsorptive ability. As the entire extracellular fluid volume in man is filtered in approximately 2½ hours, survival is dependent on the reabsorption of 99% of the filtered Na and H₂O. Continued normal glomerular filtration in the face of an even moderately impaired tubular reabsorptive ability would have devastating consequences for fluid volume homeostasis. Thus, a hemodynamically mediated reduction in GFR in response to tubular cell injury is not only an appropriate response but is critically necessary for survival. The success of this mechanism is attested to by the fact that, despite tubular cell injury, the total amount of H₂O and Na excreted even in nonoliguria is almost never enough to cause volume depletion. Despite the teleologic attractiveness of this concept, the evidence supporting it is largely indirect. The precise mechanisms by which tubular cell injury is communicated to the vasculature, and the mediators of the hemodynamic response, remain undefined.

Increased release of adenosine, as a consequence of the "energy deficit state" of renal tubular cells in ATN, has been recently proposed as a mediator of the hemodynamic changes. While there is evidence to support a role for adenosine-mediated hemodynamic changes in certain experimental ATN models, this is not true for other models. Therefore, there are other potential mediators of the hemodynamic changes that remain to be identified.



RELATIONSHIP OF PRERENAL HYPOPERFUSION TO ATN

Many observations, both in experimental animals and in human ATN, suggest that prerenal hypoperfusion markedly increases the predisposition to both ischemic (hypotensive) and nephrotoxic ATN. The increased proximal reabsorption, characteristic of prerenal hypoperfusion states, leads to the development of a higher concentration of nephrotoxin in the tubular lumen and to an increased transit time with prolonged exposure of the tubular epithelium to potentially toxic agents, with resultant tubular injury. Slow proximal flow rates are also likely to be associated with a greater potential for nephron obstruction.

DIFFERENTIAL DIAGNOSIS

Obstruction can be responsible for a readily reversible syndrome of ARF in a significant percentage of patients. Partial obstruction may be associated with a wide range of urine volumes, and exclusion of obstructive ARF by ultrasonography is, therefore, an early step in the differential diagnosis.

Once obstructive ARF is excluded, the differentiation among the other possible etiologies of ARF is based on the characteristic pathophysiologic mechanisms and/or responses of the kidney associated with each of the categories. These are reflected in the changes in the volume, nature, and composition of urine that is elaborated. Analyses of the urine chemistries and osmolalities and a routine urinalysis, with careful microscopic examination of the sediment, in addition to the history and physical findings, are central to the differential diagnostic process. The glomerular and vasculitic processes severe enough to cause ARF are almost invariably associated with evidence of glomerular capillary injury in the form of proteinuria, hematuria, and an often active sediment with red blood cell casts. Although the etiologic agents responsible for ATN and acute interstitial nephritis (AIN) are different, the pathophysiologic mechanisms responsible for failure of excretory function are probably similar. This is reflected in the similar composition of urine in ATN and AIN. Therefore, clinically the differential diagnosis primarily involves the separation of prerenal ARF with functionally and structur-

ally intact kidneys, from the ATN and AIN syndromes with associated injury to the tubules and/or interstitium. The differentiation is important because of the obvious implications for management. This differentiation is based on the fact that the normal response of the kidneys to an acute reduction in GFR is to retain salt and H₂O avidly, so that small volumes of concentrated and NaCl-poor urine are excreted. This functional response can only be maximally achieved in the presence of preserved tubular integrity and is therefore observed in prerenal states. However, in ATN syndromes with associated tubular cell injury, the urine tends to be isosmotic and relatively rich in NaCl. This is reflected in qualitative parameters such as urinary osmolality or urinary sodium concentration. The quantitative parameters of H₂O and Na excretion ([U/P]Cr, and FE_{Na}), especially the latter, are more useful for differentiation. A classification can be established in the vast majority of patients with ARF based on an interpretation of these urinary parameters in the context of the systemic hemodynamic status of the patient.

PREVENTION OF ATN SYNDROMES

Identification of patients at risk and avoiding the events that cause ATN, if possible, are the most practical approaches. Any preexistent prerenal hypoperfusion should be corrected. However, it should be recognized that volume expansion per se is not protective in the absence of renal vasodilation and decreased proximal reabsorption. A misplaced emphasis on volume expansion in patients with preexistent cardiac, hepatic, or renal disease may only add the stress of volume overload without resulting in the desired solute diuresis. Other measures such as afterload reduction or inotropic agents may be of greater benefit in such patients. Induction of an osmotic diuresis with mannitol has been helpful in certain selected circumstances. These include its administration before amphotericin B or cisplatin administration, during high-risk surgery, or in the early stages of rhabdomyolysis before ATN is established. Experimental observations also suggest that a state of high fluid flow through the proximal nephron needs to be maintained before, during, and for at least several hours after the anticipated renal insult. Loop diuretics have also been used as potential protective agents, but there is no convincing evidence that they are effective.

The use of several pharmacologic agents has been associated with partial amelioration of ATN in certain experimental models, especially when these agents have been used prior to, or simultaneously with the initiating injury. To date, there are no controlled clinical studies, and the use of these agents is not recommended until such studies are performed as they have the potential for serious hypotension or other side effects.

MANAGEMENT OF ESTABLISHED ARF

It is important to recognize that the kidneys are the primary effector site for the regulation and composition of body fluids. This regulatory function is severely impaired in ARF and, therefore, in effect the body becomes a relatively "closed system." This further complicates the already complex management of many of the underlying disease processes. Frequent clinical and biochemical monitoring is necessary to minimize the inevitable alterations in body fluid volume and composition. Acid-base and fluid and electrolyte problems are frequent in addition to the complications of uremia, which are related to retention of nitrogenous waste. Uremia (BUN greater than 100 mg/dl) affects the function of most organ systems, gastrointestinal hemorrhage and infections being the major cause of morbidity and mortality. The availability of the various "dialytic" modalities has provided a reasonably effective substitute for renal excretory function. The general goal in the management of the patient with the ATN syndrome is to "buy time" during which the damaged kidney can heal and recover.

PROGNOSIS

Despite the availability of dialysis, the mortality in ARF continues to average about 50%. This primarily reflects the seriousness of the associated illnesses, as the mortality tends to be much lower in younger patients without complications. It should be emphasized that most patients die with ARF and not of ARF. Patients who survive the acute illness generally recover almost complete renal function, except for those with cortical necrosis or with very severe ischemic injury to the renal parenchyma.



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Paul C. Churchill, Ph.D. obtained undergraduate and graduate degrees at the University of Michigan in Ann Arbor (B.S., Biophysics; Ph.D., Physiology). After postdoctoral studies in Switzerland (Department of Pharmacology, University of Lausanne), he joined the faculty of the Department of Physiology at the University of Michigan. Two years later, he joined the faculty of the Department of Physiology at Wayne State University in Detroit, 50 miles away, and has been there ever since. He has done research on the mechanisms controlling renin secretion, as well as on the mediation and significance of the hemodynamic changes in acute renal failure.

ACUTE RENAL FAILURE

The syndrome of acute renal failure (ARF), defined clinically as an acute reduction in renal function sufficient to result in retention of nitrogenous waste, occurs in diverse clinical settings and has a varied and complex pathogenesis. Since the kidneys are the primary effector site for maintenance of the constancy of the "milieu interior," an impairment of the regulatory ability of the kidneys threatens the volume and composition of the body fluids. The pervasive effects of such changes in the "milieu interior" on the function of almost all body systems as well as the impaired ability of the kidneys to respond appropriately to additional homeostatic challenges further complicate the already complex management of many of the underlying disease processes. This is reflected in the continued high morbidity and mortality that is associated with the syndrome of ARF despite major technical advances in dialytic techniques. This monograph is intended to provide a broad conceptual framework to the understanding of the mechanisms that result in retention of nitrogenous waste and a diagnostic and therapeutic approach to deal with the consequences of such retention.

ANATOMICAL AND PATHOPHYSIOLOGIC CLASSIFICATION

By definition, the hallmark of ARF syndromes is retention of nitrogenous waste, i.e., an impairment of the process by which such waste is normally eliminated in the urine. Although ARF results in the accumulation of several products of protein breakdown in the body (such as guanidines, phenols and phenolic acids, aliphatic and aromatic amines, indoles, and hippurates), the clinical diagnosis and management of the syndrome rests primarily on the increases in the plasma levels of two final products of protein and muscle metabolism that are eliminated by the kidney through glomerular filtration, i.e., urea and creatinine. This is appropriate because of the ease of their determination as well as the fairly good correlation of their blood levels and/or rate of accumulation with the severity of the clinical syndrome. The criteria for diagnosing acute vs. subacute or chronic renal failure are somewhat arbitrary. Most nephrologists ac-

cept an increase in serum creatinine level of 0.5 mg/dl/day and a rise in blood urea nitrogen (BUN) level of 10 mg/dl/day over at least a few days as satisfying the definition of ARF. However, these criteria are not absolute and are adapted to the individual patient's size and muscle mass, as will be discussed subsequently.

Figure 1 is a simplified diagrammatic representation of the four major steps involved in the urinary elimination of nitrogenous waste: (1) delivery of nitrogenous waste to the glomerular capillaries via an adequate renal blood flow; (2) appropriate formation of plasma ultrafiltrate containing urea nitrogen and creatinine; (3) normal tubular handling of the ultrafiltrate in its passage through the nephron into the collecting system; and (4) excretion of the final urine through a nonobstructed urinary tract. Acute renal failure occurs when there is a disease process that interferes with any of these four steps. Diseases that only affect step 1 are classified under the category of pre-renal ARF; they result from an inadequate blood flow to a functionally intact kidney. Similarly, diseases that affect step 4, i.e., diseases that cause obstruction to outflow of urine, are classified under post-

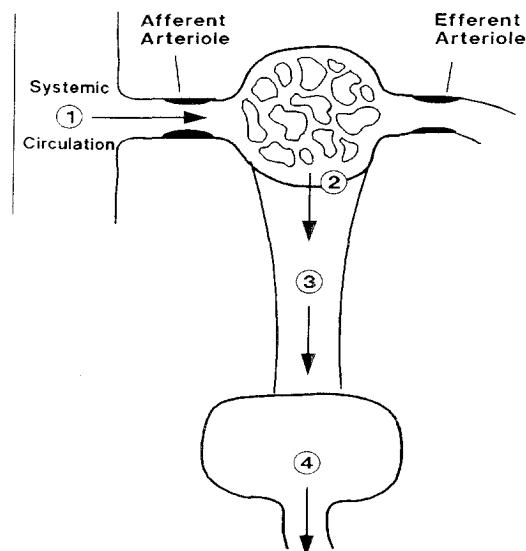


FIG 1.

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ANATOMIC CLASSIFICATION OF ARF SYNDROMES

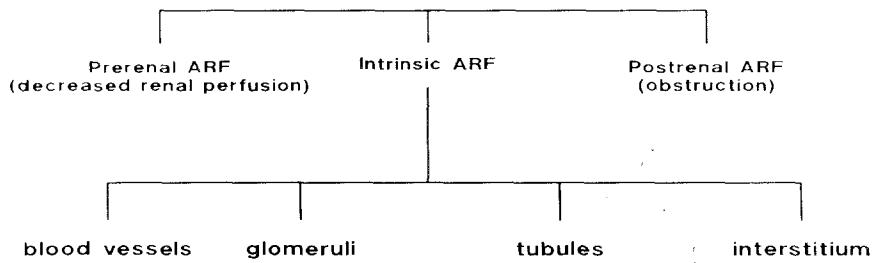


FIG 2.

The two stages of the anatomical separation of the causes of ARF syndromes are shown (see text for details).

renal ARF, since they only secondarily affect the function of the kidneys. On the other hand, disease processes that primarily affect steps 2 and 3 represent injury to renal parenchyma itself and are therefore classified under intrinsic ARF. This separation of the causes of retention of nitrogenous waste into prerenal, postrenal, and intrinsic ARF categories is the first stage in the differential diagnosis of ARF¹ and is presented in Figure 2 and Table 1.

The second stage in the differential diagnosis involves a further differentiation of the disease processes causing intrinsic ARF after prerenal and postrenal causes of ARF are eliminated. This is best achieved by considering the different potential anatomical sites of injury to the renal parenchyma: (1) blood vessels; (2) glomerular capillaries, (3) tubules, and (4) interstitium. Diseases that affect the blood vessels and glomeruli include organic vascular diseases, vascular occlusion syndromes, malignant hypertension, microangiopathic syndromes with cortical necrosis, and the various forms of primary and secondary acute glomerulonephritides. Acute tubular cell injury is the hallmark of all syndromes classified under the category of acute tubular necrosis (ATN), whether caused by ischemia or a nephrotoxin. All forms of acute interstitial nephritis, whether caused by allergic or toxic mechanisms, are examples of acute injury primarily to the interstitium with associated retention of nitrogenous waste. In general, each of these categories and subcategories of disorders is associated with distinct and characteristic pathophysiologic mechanisms and/or responses of the kidney. Identification of these responses, along with the associated extrarenal systemic manifestations forms the basis of the classification and differentiation of these

TABLE 1.

Etiopathogenetic Classification of Acute Renal Failure

PRERENAL ARF	
Renal vasoconstriction in response to systemic hemodynamics	
Intravascular volume depletion	
Exogenous losses and/or hemorrhage	
"Third space" sequestration	
Decreased effective circulating volume	
Peripheral vasodilatation	
Reduced cardiac output	
Primary renal vasoconstriction	
Hepatorenal syndrome	
Drug-induced-NSAIDS, cyclosporine	
Hypercalcemia	
INTRINSIC ARF	
Large vessel disease (renal arterial or venous thrombosis)	
Microvascular disease (arterioles and/or glomeruli)	
Acute nephritic syndromes	
Vasculitic syndromes	
Cortical necrosis (HUS, TTP, eclampsia, postpartum ARF)	
Scleroderma	
Malignant hypertension	
Atheroembolic disease	
Acute tubular necrosis (ATN)	
Postischemic ATN	
Nephrotoxic ATN	
Acute interstitial nephritis	
Allergic	
Immunologic	
Infectious	
Toxic	
POSTRENAL (OBSTRUCTIVE) ARF	

ARF = acute renal failure; NSAIDS = nonsteroidal anti-inflammatory drugs; HUS = hemolytic-uremic syndrome; TTP = thrombotic thrombocytopenic purpura.

disorders. An appreciation of the underlying pathogenetic mechanisms that result in the characteristic changes in the nature and composition of the urine helps in the formulation of an appropriate diagnostic approach and is therefore discussed first.

PHYSIOLOGY OF EXCRETION OF NITROGEN WASTE

Before the characteristic pathophysiology of the major categories of ARF are considered, it is useful to briefly review the normal regulation of the steps involved in the elimination of nitrogenous waste.

Renal Blood Flow.—The blood flow to the kidneys is determined by the perfusion pressure, i.e., the mean arterial pressure (MAP), and

the renal vascular resistance (RVR). Unlike the systemic capillaries, the glomerular capillaries are interposed between two resistance arterioles rather than an arteriole and a venule (Fig 3). These two arterioles, the preglomerular afferent arteriole and the postglomerular efferent arteriole, arranged in series, are the major sites of vascular resistance in the kidney and the sum of their individual resistances, therefore, determines the renal blood flow (RBF) for any given MAP. In general, changes in MAP within the autoregulatory range are associated with proportionate changes in renovascular resistance such that RBF is maintained constant (Fig 4). These resistance changes occur at the level of the afferent arteriole and are precise so that glomerular capillary pressure is also kept constant and the filtration fraction, i.e., the fraction of plasma that is ultrafiltered through a single passage through the glomerular capillaries, stays constant. Therefore, this results in concurrent autoregulation of glomerular filtration rate (GFR) as well.

Glomerular Filtration Rate.—The rate of formation of plasma ultrafiltrate at the glomerular capillaries is governed by the Starling forces operating across the glomerular capillaries (Fig 5) and is expressed by the following equation:

$$GFR = K_f (P_{Gc} - P_{BS} - \pi_g)$$

where P_{Gc} = glomerular capillary hydrostatic pressure; P_{BS} = Bowman's space or tubular hydrostatic pressure; π_g = oncotic pressure of plasma in the glomerular capillaries. The K_f is defined as the filtration coefficient and is a product of two variables: the hydraulic conductivity, which is the volume flow per unit time per unit of driv-

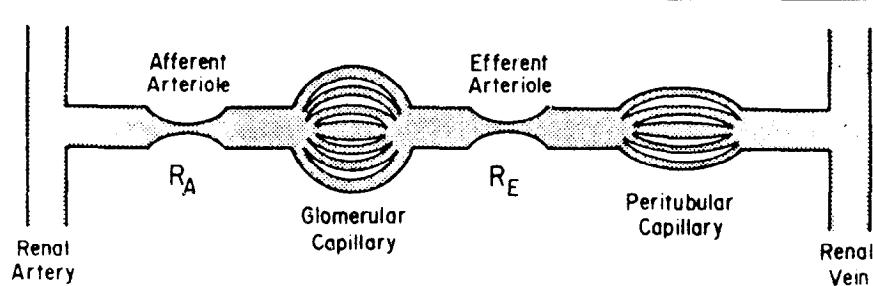


FIG 3.

A schematic drawing of the anatomical arrangement of the resistance arterioles (afferent and efferent) and the separation of the capillary networks responsible for ultrafiltration (glomerular) and reabsorption (peritubular) in the kidney. R_A = afferent arteriole resistance; R_E = efferent arteriolar resistance. (From Marsh DJ: Glomerular filtration and renal blood flow, in *Renal Physiology*. New York, Raven Press, 1983. Used by permission.)

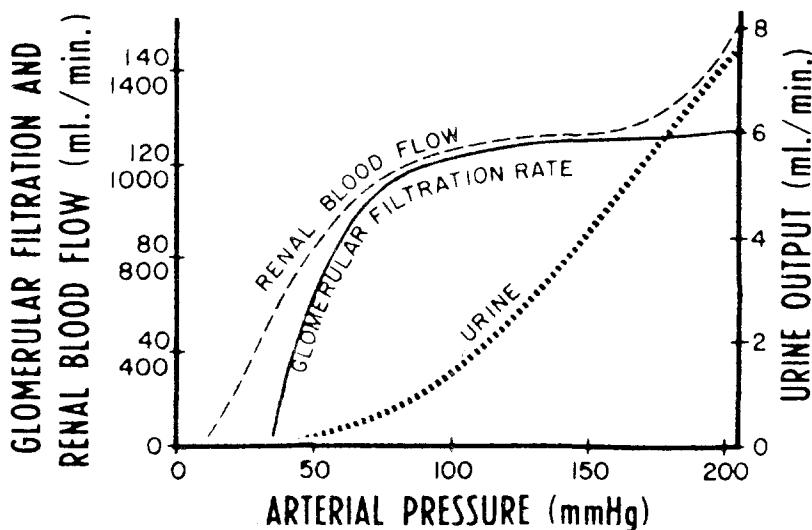
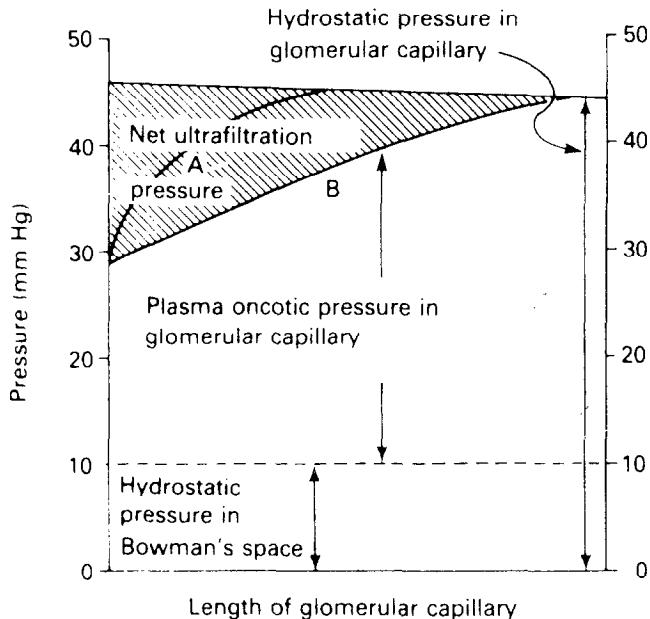


FIG 4.

Autoregulation of renal blood flow and glomerular filtration rate during mean arterial pressure (MAP) changes between 75 and 150 mm Hg. Urine output varies directly with MAP and is not autoregulated. (From Guyton AC: Formation of urine by the kidney: Glomerular filtration, tubular function, and plasma clearance, in *Human Physiology and Mechanisms of Disease*. Philadelphia, WB Saunders Co, 1982. Used by permission.)

ing force per unit of available surface area, and S_f , which is the total surface area available for filtration. The K_f can therefore be expressed for individual glomeruli (nl/minute per mm Hg) or per gram of total kidney weight (ml/minute per mm Hg). The caliber of the preglomerular and postglomerular resistance vessels regulates both the glomerular blood flow and the P_{Gc} . The resistances of these arterioles, therefore, along with P_{BS} and K_f , constitute the primary intrarenal determinants of GFR. Under normal circumstances, P_{Gc} varies little over the entire length of glomerular capillaries, and as protein free filtrate is formed, the π_g increases and the net ultrafiltration pressure ($P_{Gc} - [P_{BS} + \pi_g]$) decreases. Therefore, the amount of fluid filtered across the length of capillary progressively decreases toward the efferent arteriolar end (see Fig 5). The increase in colloid oncotic pressure of the plasma at the end of glomerular capillaries is directly proportional to the volume of plasma that is ultrafiltered by the glomerular capillaries during a single pass, i.e., the filtration fraction (ratio of GFR to renal plasma flow).

Interrelationship of Filtration Fraction and Salt and H_2O Reabsorption.—The anatomical arrangement of the other major capillary



Balance of Mean Values

Hydrostatic pressure in glomerular capillary	45 mm Hg
Hydrostatic pressure in Bowman's space	10
Plasma oncotic pressure in glomerular capillary	27
Oncotic pressure of fluid in Bowman's space	0*
Net ultrafiltration pressure	8 mm Hg

FIG 5.

Starling forces involved in glomerular ultrafiltration in rats (specific values vary with species). As shown, ultrafiltration pressure declines in glomerular capillaries, mainly because plasma oncotic pressure rises. It is not yet known at what point in the capillary the sum of the hydrostatic pressure in Bowman's space and of plasma oncotic pressure exactly balances the hydrostatic pressure in the glomerular capillary. In some species such as dog or man, this point, called filtration equilibrium, may not be reached. In those species in which it is attained, the pattern for the rise in plasma oncotic pressure as a function of capillary length is not known precisely, and it can vary. For example, an increase in the rate of which plasma enters the glomerular capillary will lead to a change in the pattern from curve A to curve B, and consequently to a rise in the mean net ultrafiltration pressure. The concentration of protein in Bowman's space fluid is negligibly small; the estimated oncotic pressure is perhaps 0.3 mm Hg. (Data from Brenner BM, Troy JL, Daugherty TM: *J Clin Invest* 1971; 50:1776.) (From Valtin H: Glomerular filtration, in *Renal Function, Mechanisms Preserving Fluid and Solute Balance in Health*. Boston, Little Brown & Co, 1983. Used by permission.)

network in the kidney, the peritubular capillaries, has been previously shown (see Fig 3). These capillaries arise from the efferent arteriole. The favorable Starling forces (decreased hydrostatic and increased colloid osmotic pressures) account for their ability to remove from the interstitium the large amount of fluid reabsorbed by the proximal nephron. Thus, unlike the systemic capillaries where both outward filtration and inward reabsorption occur across the same capillary, in the kidney the capillaries that are responsible for ultrafiltration (glomerular) are anatomically separated from the reabsorptive capillaries (peritubular) by the efferent arteriole. This unique anatomical arrangement allows the Starling forces to be independently controlled in the peritubular capillary network by changes in efferent arteriolar resistance. This has important implications for both salt and H_2O homeostasis and the ability to excrete nitrogenous waste.

While resistance changes at either afferent or efferent arteriole have directionally similar effects on RBF, they tend to have opposite effects on GFR. As can readily be appreciated from Figure 6, P_{Gc} and, therefore, GFR is affected in opposite directions by resistance changes in the afferent and efferent arteriole. Afferent arteriolar constriction decreases RBF. The reduced P_{Gc} leads to a fall in filtration fraction (FF), and therefore GFR decreases disproportionately more

Resistance in Arterioles	RBF	GFR	PGC
Control	↔↔↔	↔↔↔	↔↔↔
Decreased in Afferent	↑↑↑	↑↑↑	↑↑↑
Increased in Afferent	↓↓↓	↓↓↓	↓↓↓
Decreased in Efferent	↑↑↑	↓↓↓	↓↓↓
Increased in Efferent	↓↓↓	↑↑↑	↑↑↑

FIG 6.

Changes in renal blood flow (RBF), glomerular filtration rate (GFR), and glomerular capillary hydrostatic pressure (P_{Gc}) that will occur when resistance is altered in either the afferent or the efferent arterioles, provided that renal perfusion pressure does not change (see text for details). (Adapted from Valtin H: Renal hemodynamics and oxygen consumption, in Valtin H (ed): *Renal Function, Mechanisms Preserving Fluid and Solute Balance in Health*. Boston, Little, Brown & Co, 1983. Used by permission.)

than RBF. In contrast, although efferent arteriolar constriction decreases RBF, it increases P_{GC} and therefore FF and GFR. However, when efferent arteriolar constriction is severe, and a marked reduction in RBF occurs, GFR can decline despite an elevated FF.

Figure 7 illustrates the effect of efferent arteriolar constriction and dilatation on salt and H_2O reabsorption by the proximal nephron. Efferent arteriolar constriction leads to decreases in peritubular capillary hydrostatic pressure, which tends to increase capillary reabsorption. Furthermore, the increased FF at the glomerular capillaries causes a more marked increase in the protein concentration (oncotic pressure) of the peritubular blood, which also leads to enhanced capillary reabsorption. Enhanced capillary reabsorption leads to enhanced proximal tubular reabsorption, perhaps by minimizing any passive backflux of reabsorbate from the interstitium into the tubular fluid. Efferent arteriolar dilatation has opposite effects on peritubular capillary Starling forces, and this results in decreased proximal reabsorption. In general, the higher the FF, the greater the peritubular oncotic pressure and the Starling forces favoring proximal tubular reabsorption. Additionally, acute decreases in both MAP and/or GFR in the presence of preserved tubular integrity lead to decreases in salt and H_2O excretion by the kidney (see Fig 4), al-

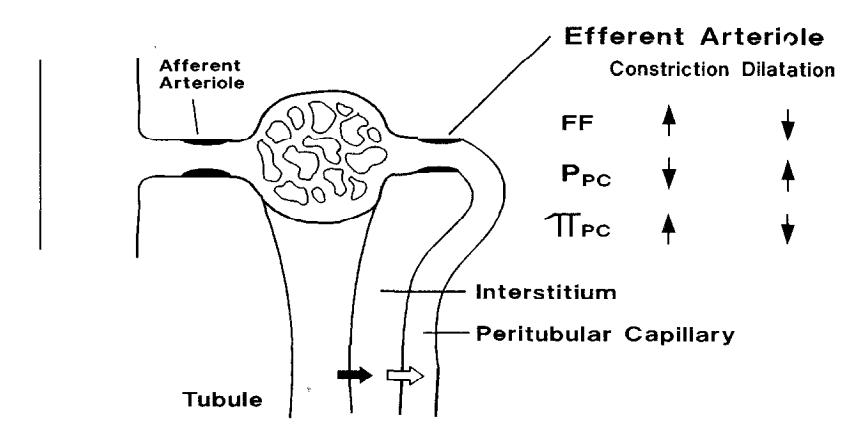


FIG 7.

A schematic representation of the effects of efferent arteriolar constriction and dilatation on the filtration fraction (FF) and the Starling forces in the peritubular capillaries. P_{PC} = hydrostatic pressure in the peritubular capillaries; π_{PC} = oncotic pressure in the peritubular capillaries. Normally $\pi_{PC} > P_{PC}$. The greater this difference, the more fluid is reabsorbed by the peritubular capillaries from the interstitium surrounding the proximal tubule. Enhanced removal of fluid from the interstitium by the peritubular capillaries promotes proximal tubular reabsorption, probably by minimizing any passive backleak of reabsorbate into the proximal tubule from the interstitium.

though all the efferent pathways and target sites for this response have not been defined. This enhanced avidity for salt and H₂O retention in the face of acute reduction in GFR by the kidney can be achieved maximally only in the presence of preserved tubular integrity; this has important implications in the differential diagnosis of ARF (*vide infra*).

Tubular Handling of Nitrogenous Waste.—While both urea and creatinine are freely filtered at the glomerulus, creatinine is not reabsorbed in the absence of severe tubular injury, whereas urea is reabsorbed to a variable extent. In general, urea reabsorption varies directly with salt and H₂O reabsorption. Therefore, the more avid the salt and H₂O conservation by the kidney, the more urea is reabsorbed and less is excreted. Thus, the clearance of urea is reduced out of proportion to the reduction in GFR (i.e., creatinine clearance). This causes a disproportionate increase in the level of BUN.

PATHOPHYSIOLOGY OF ACUTE RENAL FAILURE

The characteristic pathophysiologic mechanisms associated with the major categories of ARF are described next in the sequence in which the differential diagnosis is considered.

POSTRENAL (OBSTRUCTIVE) ARF

Obstruction to the flow of urine can be the underlying etiology in up to 15% of patients with the ARF syndrome.¹ Therefore, unless the cause of ARF is immediately apparent, obstruction to the flow of urine must be considered in all cases of unexplained ARF, regardless of the urine volume. Although complete obstruction is an obvious differential diagnostic category in patients with a history of total suppression of urine output, partial obstruction can be associated with a wide range of urine volumes and compositions, depending upon the acuteness and the completeness of the obstruction. If the obstruction only involves one kidney, the functional reserve of the contralateral kidney is usually enough to prevent progressive retention of nitrogenous waste. Therefore, obstruction has to be bilateral or distal to the urinary bladder to result in the syndrome of ARF. Obviously, obstruction of the urinary tract at any site, in the case of a solitary functioning kidney, results in ARF. Such obstruction most often results from congenital abnormalities in children, prostatic hypertrophy in men, and gynecologic problems in women.

Pathophysiology

The initial hemodynamic response to obstruction is an increase in RBF due to preglomerular vasodilation that is thought to be me-

diated by myogenic and prostaglandin mechanisms.¹⁻⁵ However, 24 to 48 hours later, vasoconstriction supervenes and RBF decreases. Thromboxane A₂ may be responsible for the vasoconstriction, although the evidence supporting its role is conflicting. In any case, acute partial obstruction causes a rapid increase in intratubular pressure (P_{BS}), which decreases the net glomerular filtration pressure and therefore decreases the GFR. The initial response of the nephron is to increase salt and H₂O reabsorption from the smaller volume of slowly flowing filtrate, so that small amounts of concentrated and NaCl-poor urine are elaborated during this early phase of partial obstruction. However, if the obstruction lasts longer than 24 to 48 hours, the tubules tend to dilate. Salt and H₂O reabsorption decrease, possibly as a result of the sustained exposure of tubular epithelium to increased intraluminal pressures, such that the final urine during this phase tends to be hypotonic or isotonic and is relatively rich in NaCl. The increased intraluminal pressure and dilation of the distal nephron and collecting system might also account for other disturbances in distal nephron function. The most prominent of these is the loss of normal responsiveness to antidiuretic hormone (ADH), resulting in impairment of H₂O reabsorption. In some patients, the distal tubular function of urine acidification and potassium secretion are also impaired, resulting in hyperkalemic distal renal tubular acidosis. This impairment of distal nephron function can sometimes persist for a variable period of time after the relief of obstruction. Although precise information in human obstructive ARF is not available, clinical impression suggests that relief of obstruction, even after 1 to 2 weeks of complete obstruction, is associated with almost full restoration of function in the absence of infection.¹ Recovery is more variable after longer durations of obstruction. Because of the potential for surgical relief of the obstructive process and because the volume and the composition of urine can mimic either prerenal or ATN syndromes, exclusion of obstructive ARF is an important early step in the differential diagnosis.

PRERENAL ARF SYNDROMES

The hallmark of these clinical states is a decreased blood flow to structurally intact kidneys (see Table 1). The causes for this inadequate perfusion can be classified into two major categories^{4,5}: (1) The first category, which includes most of the clinical examples of pre-renal ARF, can be broadly viewed as disorders in which the renal hypoperfusion is an appropriate response to the deranged systemic hemodynamics. These include states of true intravascular depletion, due to either external losses or internal translocation of fluids. Renal hypoperfusion may also result from decreases in effective circulatory volume or from decreased cardiac output. The compensatory re-

sponses triggered by such circulatory stress include release of vasoactive substances, both locally (renin-angiotensin) and systemically (catecholamines), that promote arteriolar constriction primarily in the renal, splanchnic, and musculocutaneous circulatory beds, so as to maintain blood pressure and perfusion to the more vital tissues. (2) The second group of clinical entities consists of those in which the renal vasoconstriction seems to be inappropriate to the general hemodynamic status. These renal hemodynamic changes may be caused by some unidentified humoral factor, as has been postulated in the hepatorenal syndrome, or by pharmacologic agents such as the nonsteroidal anti-inflammatory drugs (NSAIDS) and cyclosporine.

Pathophysiology of Group (1) Disorders

The decreased RBF in the clinical states of the group (1) disorders is due to a predominant increase in the resistance of postglomerular efferent arterioles, attributed to activation of the sympathetic nervous system, the renin-angiotensin system, and possibly other mechanisms.⁴⁻⁷ This predominant efferent arteriolar constriction results in an increase in the FF so that GFR is compromised less than RBF, and salt and H₂O reabsorption by the proximal nephron is increased. This hemodynamic response can be considered a teleologically appropriate response of a structurally and functionally intact kidney, attempting to maintain its excretory function in the face of a decreased RBF, and at the same time attempting to conserve Na and H₂O so as to restore circulatory volume and/or cardiac output. The activation of the sympathetic nervous system, the renin-angiotensin aldosterone system, and the release of ADH, directly and indirectly, lead to avid Na and H₂O reabsorption in segments of the nephron beyond the proximal tubule. This avid Na and H₂O transport, indicative of normal tubular integrity in the presence of reduced GFR, is the basis for the use of urine chemistries to diagnose prerenal states (*vide infra*).

Pathophysiology of Group (2) Disorders

The renal hemodynamics in group (2) disorders are similar to those just described, although afferent arteriolar constriction may be more prominent than efferent arteriolar constriction.⁸⁻¹⁰ The acute reduction in RBF and GFR in the presence of preserved tubular integrity is associated with increased salt and H₂O retention, which may be inappropriate to the volume status of the patient. While the mediators of the vasoconstriction in the hepatorenal syndrome have not been identified, the NSAIDS are considered to promote vasoconstriction by blocking the vasodilatory prostaglandins. This hemodynamic effect of NSAIDS is of particular importance in the setting of preexistent functional compromise of the kidneys, whether pro-

duced by other prerenal factors or by renal parenchymal diseases. The NSAIDS can additionally induce ARF by tubular mechanisms discussed later. Cyclosporine is another therapeutic agent that has the ability to cause ARF by causing renal hypoperfusion as well as tubulointerstitial injury.

An essential feature of the disease states, belonging to both groups (1) and (2), is that once the prerenal stimulus for this pathophysiological state is removed and the RBF is restored to normal, the GFR also recovers and the functionally intact kidneys start eliminating the nitrogenous waste appropriately.

INTRINSIC (PARENCHYMAL) ARF SYNDROMES

Large Vessel Occlusion Syndromes

The ARF occurring as a consequence of the diseases of the larger blood vessels is usually secondary to an occlusive process (thrombotic or embolic) with or without evidence of preexistent renal vascular disease.^{1,11} The site of the disease process may be the major arteries (thus interfering with renal blood supply) or the major renal veins (resulting in vascular congestion and stasis); these often require invasive radiologic investigations for confirmation.

Microvascular Disease (Arterioles and/or Glomeruli)

These states share the common feature of morphological disease of the arterioles and glomeruli.^{1,11-14} The injury may be due to an inflammatory response (various glomerulonephritic and/or vasculitic syndromes), due to intravascular thrombi formation (thrombotic microangiopathy syndromes), or due to direct barotrauma (malignant hypertension). When nephritic and vasculitic syndromes present with the ARF syndrome, they are usually associated with a rapidly progressive course that is morphologically accompanied by exuberant crescent formation in the glomeruli. More often the rate of rise in the level of BUN and creatinine is slower in these disease states, therefore excluding them from the category of ARF. Frequently, the acute renal failure syndrome is superimposed on these disorders by other insults such as the use of NSAIDS or other drug-induced interstitial nephritides. While the precise etiology and the mediators may vary among the various clinical syndromes grouped under this category and are the subject of ongoing investigation and controversy, the pathophysiology and clinical expression of these syndromes are usually remarkably similar. The injury to the glomerular capillaries is associated with a breach in the integrity of the barrier function of the capillary wall that normally restricts the passage of protein and blood into the urinary space. Therefore, the diagnostic hallmark of these diseases is the presence of proteinuria and hematuria, and an active urine sediment with red blood cell casts. The

differential diagnosis among the various disease states under this category is based on the evidence of other associated clinical manifestations of systemic disease and the histologic changes in the kidney. This differentiation often requires a renal biopsy.

The group of entities classified under the microangiopathic syndromes usually do present with a severe ARF syndrome. The complete interruption of vascular supply to parts of the kidney by intraluminal thrombi in the arterioles and glomerular capillaries results in patchy cortical necrosis of variable severity. Patients may be anuric during the acute stage. The precise pathogenesis of these clinical disorders remains to be defined; however, they all seem to involve abnormalities of platelet and vessel wall interaction, probably precipitated by endothelial injury. The renal crisis of scleroderma and malignant hypertension also seem to share similar pathogenetic pathways. The diagnostic hallmark of these entities is evidence of fragmented erythrocytes on the peripheral smear (schistocytes), often accompanied by thrombocytopenia. The systemic manifestations are the basis of differentiating the individual disease entities classified under this category. The small amounts of urine that are produced are concentrated, NaCl-poor, and contain blood, protein, and often an active urinary sediment.

The pathogenesis of the retention of nitrogenous waste in these syndromes is due to a reduction in RBF (because of the increased resistance of the injured microvasculature), and an impairment in GFR over and beyond the reduction in RBF. This disproportionate reduction in GFR is probably due to both a reduction in the glomerular surface area available for filtration and an actual impairment of the ability of the glomerular capillary walls to act as ultrafilters. These two functions are expressed in the mathematical term " K_f " in the equation for GFR discussed earlier. The acute reduction in GFR in these syndromes, usually in the presence of preserved tubular integrity, is also almost invariably associated with avid Na and H₂O retention by as yet incompletely understood mechanisms, leading to edema formation, vascular congestion, and hypertension. The one notable exception to this pathophysiologic sequence and clinical presentation is renal atheroembolic disease, which is discussed separately in a subsequent section.

The Acute Tubular Necrosis Syndromes

These syndromes include the vast majority of patients with ARF (especially that acquired in the hospital), and the term ATN is often used interchangeably with ARF. The clinical syndrome is characterized by an abrupt onset of retention of nitrogenous waste usually initiated by a clearly defined event. Often this acute retention of nitrogenous waste is accompanied by oliguria (urine volume less than or equal to 400 ml/day). Indeed, in the earlier descriptions of the

syndrome, oliguria was considered an essential feature.¹⁵ However, over the past decade it has been recognized that the syndrome occurs in association with a wide range of urinary volumes, and recent studies indicate that up to 50% of patients have what has been termed "nonoliguric ARF" (urine volumes usually 0.5 to 2.5 L/24 hours).¹⁶⁻¹⁹ The pathogenetic mechanisms for retention of nitrogenous waste are similar in both oliguric and nonoliguric ARF, and the difference in urine volume probably merely reflects the severity of injury.^{4,5,16-19} While it is generally agreed that the hallmark of these syndromes is evidence of disruption of the structural and/or functional integrity of tubular epithelial cells as a result of ischemic or toxic injury,^{4,5,20} the pathogenesis of the retention of nitrogenous waste remains an extremely controversial subject.

The term ATN derives from meticulous morphological and microdissection studies of Oliver and his co-workers who demonstrated that the syndrome was characterized by areas of necrosis of tubular epithelium, often accompanied by loss of basement membrane (tubulorrhexis).²¹ Because of the striking morphological normalcy of the microvasculature and glomerular capillaries, it was believed that the glomerular ultrafiltrate was formed normally, but that during its passage down the nephron, filtered H₂O and solutes including inulin and creatinine were reabsorbed across the damaged and denuded basement membranes (Fig 8, A). This "backleak" of filtrate could account for the decreased clearances of inulin and creatinine in the presence of preserved GFR. Another tubular mechanism for oliguria and retention of nitrogenous waste was suggested by the frequent presence of cast formation in dilated tubules, consistent with obstruction of individual nephrons.²¹ Myoglobin and hemoglobin containing casts were especially evident in patients with ARF associated with crush injuries or mismatched transfusions. Obstruction of individual nephrons was thought to result in increased proximal hydrostatic pressure (P_{BS}) and therefore to result in failure of filtration in individual nephrons, analogous to what is observed with urinary tract obstruction at the whole kidney level (see Fig 8, B).

The predominance of these two tubular mechanisms in the retention of nitrogenous waste was subsequently questioned on the basis of morphological findings at autopsy in patients with the ATN syndromes. There was often a significant lack of correlation between degree of morphological injury and the severity of the clinical retention of nitrogenous waste that had preceded death.^{4,22} Based on studies in humans that showed a marked reduction in RBF in both ischemic and nephrotoxic forms of ATN,²³ it was proposed that vasoconstriction accounted for the decreases in both RBF and GFR and was the major mechanism for retention of nitrogenous waste²³⁻²⁵ (see Fig 8, C). Over the past 20 years a great deal of investigative work

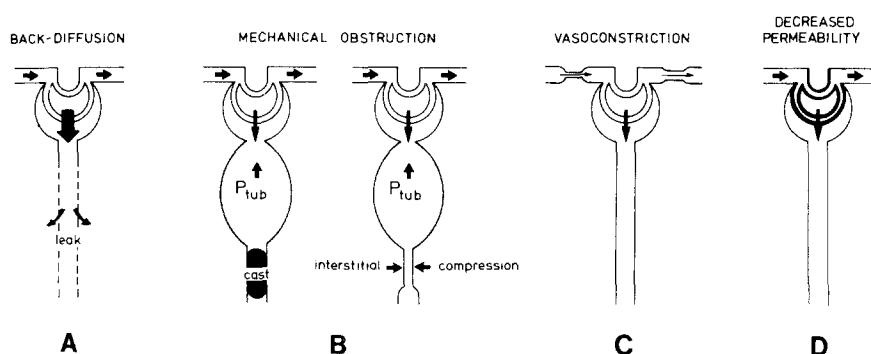


FIG 8.

Proposed pathophysiological mechanisms responsible for the excretory dysfunction of the kidney during ARF. **A**, filtered fluid and solutes are lost from the tubular system back into the circulation. **B**, reduced glomerular filtration due to increased tubular pressure caused by intratubular cast formation or tubular compression. **C**, reduced glomerular filtration due to preferential afferent arteriolar vasoconstriction. **D**, reduced glomerular filtration due to decreased filtering area and/or permeability of glomerular capillaries. (From Thurau K, Mason J, Gstraunthaler G: Experimental acute renal failure, in Seldin DW, Giebisch G, (eds): *The Kidney: Physiology and Pathophysiology*. New York, Raven Press, 1985. Used by permission.)

has been performed in experimental animals to clarify the relative contribution of these hemodynamic and tubular mechanisms in the pathogenesis of the syndrome of ATN.

Observations in Experimental Animal Models.—These studies have utilized a variety of methods to produce the syndrome. They can be classified broadly by two well-defined initiating factors: renal-ischemia-mediated ARF and nephrotoxin-mediated ARF.²⁵⁻²⁷ Renal ischemia has been produced by mechanical occlusion of renal arteries and by cessation of renal blood flow with renal-arterial infusion of norepinephrine. Many agents have been used to produce nephrotoxic injury including HgCl₂, uranyl nitrate, cisplatin, cyclosporine, and antibiotics such as gentamicin. Myoglobinuric ARF, produced by intramuscular administration of 50% glycerol is an example of combines ischemic (due to volume shifts into muscles) and toxic injury (direct toxicity of myoglobin).

Following the induction of ARF, the course of the resulting ARF has been divided into initiation, maintenance, and recovery phases, similar to what is observed in the clinical context.²⁵⁻²⁷ These divisions are based on the concept that different pathogenic factors may be involved during the different phases. The pathogenic factors thought to contribute to the retention of nitrogenous wastes have been classified into two broad categories: (1) tubular factors, consist-

ing of backleak of glomerular filtrate and tubular obstruction, and (2) hemodynamic factors, consisting of a decrease in and a redistribution of RBF and a decrease in K_f . These mechanisms are illustrated (see Fig 8, A-D).

The precise contribution of these four mechanisms to the retention of nitrogenous waste depends on the experimental model and on the time of the investigations during the course of ATN. One notable feature of most experimental models is the marked heterogeneity of individual nephrons, both morphologically and functionally, as revealed by micropuncture studies.^{19-22, 24-29}

TUBULAR MECHANISMS.—Although variable in degree, evidence of functional and/or morphological tubular cell injury is invariably present in all experimental models of ATN and seems to be the initiating event in the cascade of complex and interrelated pathogenic mechanisms.

Morphology. The kidneys are enlarged and edematous. The cortices appear pale while the medulla looks hyperemic with prominent engorgement of the vasa recta. The morphologic patterns of ischemic and nephrotoxic damage are illustrated in Figure 9.^{20, 28, 29} In both types, the straight segment of the proximal nephron seems to be most vulnerable. This probably reflects its high metabolic energy requirement and/or intrarenal concentration and uptake of toxins. In ischemic models, there is early plasma membrane bleb formation, shedding, and impaction in the straight segments of proximal tubules, which later undergo patchy necrosis (see Fig 9). Disruption of the tubular basement membrane (tubulorrhexis) is often also noted. The severity of injury is roughly proportional to the duration of ischemia. In the nephrotoxic models, the necrosis is more diffuse and confluent but usually without tubulorrhexis. Subsequently, well-organized casts are often present in the distal tubular lumina in both types of ATN models. The pathogenesis of cast formation is unknown. They seem to arise from the interaction of a glycoprotein secreted by the thick ascending limb of the loop of Henle (Tamm-Horsfall protein), sloughed microvilli, and cellular debris. In models characterized by pigmenturia (myoglobinuria, hemoglobinuria), these proteins seem to interact with Tamm-Horsfall protein and precipitate out into the casts. Whether these casts are truly obstructive or merely reflect the decreased and sluggish urine flow is the subject of considerable controversy.

Mechanisms of Tubular Cell Injury. Recent studies have provided evidence that both ischemia and nephrotoxins cause damage to cellular and intracellular organellar membranes through activation of degradative mechanisms and/or impairment of synthetic pathways.^{4, 5, 30, 31} This results in a host of biochemical derangements in

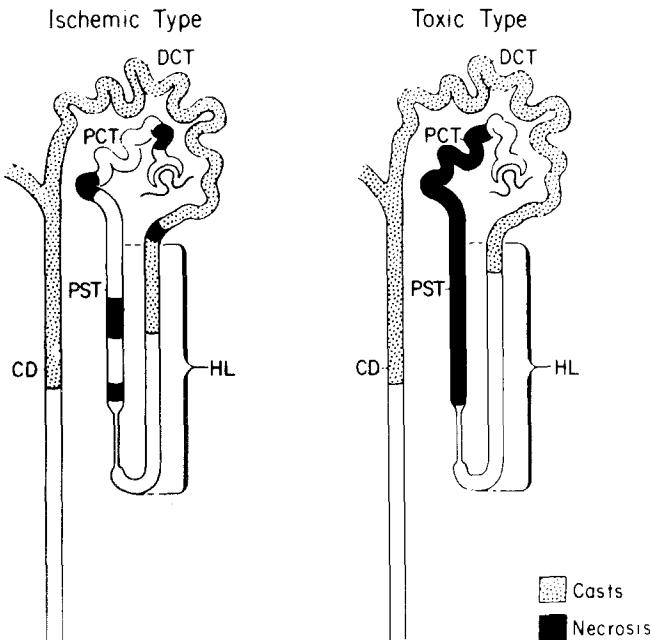


FIG 9.

Tubule damage in human ARF. In the more common ischemic type of ATN, necrosis is patchy. Short lengths of tubules are affected, the straight segments of the proximal tubule being the most vulnerable. Rupturing of necrotic tubule segments may occur (i.e., tubulorrhexis). In ATN caused by nephrotoxins, extensive necrosis is present along proximal tubule segments and tubulorrhexis usually does not occur. In both ischemic and nephrotoxic types, the lumina of the distal nephrons are occupied by casts. *PCT* = proximal convoluted tubule; *PST* = proximal straight tubule; *HL* = Henle's loop; *DCT* = distal convoluted tubule; *CD* = collecting duct. (From Robbins SL, Cotran RS: *Pathologic Basis of Disease*, ed 2. Adapted from *Microdissections* by J Oliver. Philadelphia, WB Saunders Co, 1979, p 1150. Used by permission.)

the renal tubular cell, including a marked decline in adenosine triphosphate (ATP) levels, a fall in intracellular pH, release of free fatty acids, and defective transmembrane ion transport with disruption of cellular cation homeostasis and cellular calcium overload. The relative importance of these intracellular events in causing cell injury and death is the subject of extensive ongoing investigations.

This recent focus on the mechanisms of cellular injury has undoubtedly provided important information. However, the results of these studies have demonstrated that the pathways for renal tubular cell injury and death are remarkably similar to those in other organ systems, such as the heart and the liver. The mechanisms by which the renal tubular cell injury translates into the manifestation of

whole organ failure, i.e., retention of nitrogenous waste, has remained obscure beyond what was proposed by Oliver and his colleagues.²¹ Although the morphological findings and some micro-puncture studies provide support for both backleak and nephron obstruction as pathogenetic mechanisms, studies assessing the relative importance of these mechanisms, in the various stages of the different experimental ARF models, have yielded variable and often contradictory results.^{24-29, 32-37} Obstruction seems to play a role during the early stages of ischemic models, since directly measured intratubular pressures are markedly elevated. Although these pressures tend to normalize subsequently, this cannot be used as evidence of resolution of obstruction; tubular dilatation and secondary hemodynamic changes (afferent arteriolar constriction, decreased glomerular blood flow, and glomerular filtration rate) may decrease the intratubular fluid pressure and mask the existence of significant obstruction.^{38, 39} Backleak of glomerular filtrate does occur in severe ischemic and nephrotoxic models, but its significance is probably minor in most models. The estimates of backleak of inulin have averaged about 50%. If the measured clearance of inulin (or creatinine) is less than 5% of normal, as it often is, without backleak the clearance would still be only 10% of normal. Therefore, backleak can account for only a very minor part of the overall reduction in filtration. There is some limited data in human ATN about the possible contribution of these mechanisms, which is discussed later.

HEMODYNAMIC CHANGES.—The changes which have been described have varied with the species, the model of ARF, the phase, and the methodology used for measurements.^{24-27, 32-36, 40-42} However, there is a general pattern. The RBF is decreased during the initiation phases of both ischemic and nephrotoxic models of ARF, albeit to variable degrees. Decreased RBF is accompanied by decreased GFR, suggesting afferent arteriolar constriction as the major component of increased renovascular resistance, in contrast to the efferent arteriolar constriction in prerenal ARF. In some models, K_f is reduced, and this may contribute to the disproportionately greater reduction in GFR than in RBF that is often observed. During the maintenance phase, RBF tends to recover spontaneously, but this is not accompanied by recovery of GFR. The recovery of RBF without recovery of GFR, i.e., the low filtration fraction, could result from tubular obstruction and/or backleak of filtrate or it could result from hemodynamic changes such as a decrease in K_f and/or efferent arteriolar dilation coupled with afferent arteriolar constriction. In addition, there is evidence for a redistribution of RBF from outer to inner cortex during both initiation and maintenance phases in several ischemic and nephrotoxic models. The relative contribution of these individual factors to the low GFR and filtration fraction in the different models is unknown.

Pathogenic Significance of the Hemodynamic Changes. The significance of hemodynamic changes in ATN remains controversial. The observation that RBF recovers spontaneously without a recovery in GFR has been used to argue a minor role for hemodynamic changes. Additionally, the ability of saline loading or of vasodilators to increase RBF without increasing GFR has been interpreted as evidence against major significance. However, such observations are less than definitive. Increased RBF without a corresponding increase in GFR could theoretically result from efferent arteriolar dilation in the presence of maintained afferent constriction; a priori efferent dilatation would not be expected to increase the GFR.

Observations in Humans.—Although experimental animal studies have provided insights into the possible pathogenesis of ATN syndromes, there are reasons for caution in extrapolating the data to humans. None of the animal models is entirely satisfactory in reproducing the morphological and functional characteristics of human ATN syndromes.^{20, 43, 44} Oliguria is usually not a feature of most experimental models of ARF. Moreover, in both ischemic and nephrotoxic human ATN, there is an invariable 50% to 70% reduction in RBF. This reduction in RBF is demonstrable by various techniques; it primarily affects the outer cortex and it persists for the duration of the maintenance phase, in contrast to findings in experimental animals.^{43, 45} Oken has persuasively argued that these decreases in RBF are quite capable of accounting for the suppression of filtration in human ARF, provided that the reduction in RBF is due to a predominant increase in the resistance of the preglomerular vasculature (interlobular arteries and afferent arterioles) with either no change or dilatation of the efferent arterioles.⁴³ The primary importance of hemodynamic mechanisms for retention of nitrogenous waste has been questioned on the basis of the observation that comparable reductions in RBF in chronic renal failure do not lead to similar suppression of filtration or in oliguria.⁴⁰ However, this analogy is inappropriate and misleading. Chronic renal failure is characterized pathologically and functionally by totally unperfused and obsolescent nephron populations coexisting with hyperperfused and hyperfunctioning nephron units.

Recently Myers and Moran have attempted to assess the contribution of the various pathogenetic mechanisms in human ARF by using indirect techniques of fractional clearances of dextrans of different molecular sizes and inulin transit time through the urinary space.⁴⁴ They have interpreted their data as providing evidence of a prominent role for both tubular backleak and obstruction of individual nephrons, which was more widespread in patients with the severest ATN syndrome. However, a critical evaluation of their data shows that backleak can at best account for only a fraction of the

total decrease in whole kidney GFR in severe ATN.^{20,43,46} Similarly, their conclusions about the contribution of obstructive mechanisms are based on a mathematical model that has serious limitations and does not really permit the role of obstruction to be defined independently of urine flow rates.⁴⁶ This is not to say that nephron obstruction can or does not play a pathogenetic role in human ARF, only that good supportive evidence is lacking. The finding of normal wedge renal venous pressures (an indirect index of proximal tubular pressures) in ATN syndromes argues against a significant proportion of obstructed nephrons in most patients⁴³, although these measurements have been usually obtained during the maintenance phase and do not exclude a role for nephron obstruction earlier in the course. Moreover, nephron obstruction per se can cause secondary hemodynamic changes.^{38,39}

Thus, in our opinion, the balance of data in human ATN syndromes suggests that hemodynamic mechanisms predominate with a significant but variable contribution by obstructive and a minor contribution by backleak mechanisms in the majority of patients with ATN. However, the term "vasomotor nephropathy"^{24,33,43} may not be appropriate, because it is the tubular cell injury that is the prerequisite event in initiating the syndrome of ATN. Additionally, in certain specific clinical states, these tubular mechanisms may indeed play a more important role. For example, nephron obstruction may have a more prominent role in acute uric acid nephropathy, myeloma kidney, or during oxalate deposition.⁴⁷⁻⁴⁹

The Concept of "Acute Renal Success".—In its essential form, this concept states that when there is tubular injury and impaired reabsorptive capacity, a reduction in GFR is not only an appropriate response but is critically necessary for the survival of the organism. The devastating consequences of a continued normal GFR in the presence of even moderate impairment of reabsorptive capacity is readily appreciated when one considers that the entire extracellular fluid volume is filtered every 2 to 2½ hours. This concept of a linkage between tubular reabsorptive capacity and GFR in the setting of ATN syndromes was first suggested by Brandt-Rehberg in 1929⁵⁰: "Es bedeutet hier, daß jede Schädigung der Tubuli, die eine Einschränkung in der Resorptionsfähigkeit dieser Gebilde bewirkt, auch eine sofortige Herabsetzung der Glomerulkfunktion 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"). This concept, to which we subscribe, has been most forcefully articulated by Thurau and Boylan leading to the suggestion that teleologically, "acute renal failure" may indeed represent "acute renal success."⁵¹ The syndrome of ATN could therefore be considered as a more ex-

treme example of clinical situations in which the need for volume preservation overrides the need for preservation of composition of the body fluids.

The evidence supporting a close relationship between tubular injury and its attendant reduced reabsorptive ability, on the one hand, and the decreased GFR, on the other, is largely indirect. In vitro assessments of tubular reabsorptive ability by microdissected nephron segments have shown that it is reduced by 50% to 70%,⁵² yet fractional excretion of salt and H₂O in vivo never even approaches that figure.^{1,4,5,53,54} Clinical measurements of tubular reabsorptive capacity in ATN syndromes, as indicated by the fraction of filtered Na that is excreted (FE_{Na}), have with few exceptions been less than 10% and in most cases less than 5%. This marked discrepancy between the transport defects found in vitro and in vivo can most readily be reconciled by a primary reduction in the filtered load of Na, which is roughly matched to the tubular reabsorptive ability. The finding that greater than 90% to 95% of filtered Na is reabsorbed in ATN states provides compelling but indirect evidence that the decreases in GFR are closely coupled to tubular reabsorptive ability; the statistical odds are enormously against such a finding if the two were independent phenomena. Indeed, the total amount of Na and H₂O excreted even in nonoliguric ATN is almost never enough to cause significant volume depletion. Similarly, glucosuria and bicarbonaturia are notably absent in ATN despite the often striking morphological injury to their reabsorptive sites, i.e., the proximal nephron. The ability of the renal tubular cells to heal and regenerate, as indicated by complete recovery of renal function in most patients, would be meaningless unless catastrophic losses of body fluids were prevented during the acute phase of the injury. Despite the teleologic attractiveness of this concept, the mechanism by which the severity of functional tubular injury is communicated to the vasculature, as well as the mediators of this hemodynamic response, remains speculative.

The most often cited mechanism is the activation of a tubuloglomerular feedback (TGF) system.^{4,35,36,51,55} Phenomenologically, TGF is the sensitivity of single nephron glomerular filtration rate to changes in the flow of tubular fluid in the macula densa region of the tubule. Micropuncture studies have established that increasing tubular fluid flow rate in this region leads to a decrease in the filtration rate of the same nephron, which is mediated by afferent arteriolar constriction and possibly by a decreased K_f.^{55,56} The role of this system in normal physiologic regulation of GFR, its activation during ATN syndromes, the nature of the afferent signal at the macula densa, the efferent signal from the macula densa, and the vasoactive mediator—all remain ill-defined and the subject of controversy. The renin-angiotensin system via local generation of angiotensin II has been proposed to be the mediator of hemodynamic changes in both TGF

and in ATN syndromes.^{23-27, 44, 51, 55} However, several observations exclude any major role of the renin-angiotensin system in ATN.^{18, 41, 57-62} Churchill and Bidani have proposed that adenosine may mediate, at least in part, these hemodynamic changes of ATN.⁶³ According to this hypothesis, the energy deficit state of ATN (impaired oxidative phosphorylation, due to hypoxic ischemic or nephrotoxic tubular cell injury) leads to decreased cellular ATP levels and increased adenosine production and release; adenosine acts on the afferent and efferent arterioles to produce the hemodynamic changes. Several experimental observations are consistent with this hypothesis. Renal ischemia results in decreased cellular ATP levels and increased adenosine production and release.^{64, 65} Nephrotoxic injury of renal tubular cells also decreases cellular ATP levels, but it is not known if this is accompanied by increased adenosine production and release. The hemodynamic changes seen after administration of adenosine and adenosine analogs strikingly mimic the hemodynamic changes of experimental ATN. These include variable changes in RBF and its distribution, but consistent decreases in FF and GFR.^{54, 64} It is of interest that sodium loading, which attenuates the renal hemodynamic effects of adenosine, also ameliorates the severity of experimental ATN; conversely, sodium deprivation potentiates both the renal hemodynamic responses to adenosine and the severity of experimental ATN.^{24, 56, 57, 60, 61}

Pharmacologic manipulation of the renal adenosine system in experimental models of ischemic ATN has provided additional support for the hypothesis that adenosine mediates, at least in part, the hemodynamic changes, and that these changes are of pathogenic significance. Theophylline, a competitive adenosine receptor antagonist, has protective effects on RBF and GFR in the rat, both during the initiation and maintenance phases in an ischemic ATN model.^{66, 67} Moreover, dipyridamole blocks cellular adenosine uptake, thereby increasing the concentration and potentiating the effect of extracellular adenosine,⁶⁵ and dipyridamole potentiates the reductions in GFR and RBF during the initiation phase of postischemic ARF in rats; these effects of dipyridamole are reversed by theophylline.⁶⁸ Ischemia is considered to play a significant role in glycerol-induced myoglobinuric ARF in rats, and in this model also theophylline has protective effects that are dose-dependent and independent of any effects on sodium excretion.⁶⁹ Theophylline is also protective against acute reduction in GFR caused by endotoxin and amphotericin B.^{70, 71} On the other hand, adenosine does not seem to be the mediator in other experimental models of ARF. Thus, theophylline is not protective in cyclosporine or HgCl₂-induced ARF.^{64, 72} These data suggest that there are additional, as yet unidentified, mediators of hemodynamic changes in the ATN syndromes.

Another pathway to the production of hemodynamic changes, in

response to tubular events at the single nephron level, is the hemodynamic response to nephron obstruction that was mentioned earlier. It has been demonstrated in micropuncture studies that the hemodynamic changes that occur at the whole kidney level after induction of acute obstruction are mimicked by similar changes when obstruction is produced in a single nephron.^{38,39} Twenty-four hours following placement of an obstructive block in the nephron, the glomerular blood flow to that nephron declines. This increased resistance is confined to that nephron and is due to predominantly afferent arteriolar constriction with the associated decline in P_{Gc} . The afferent and efferent pathways, or the vasoactive mediator of this response, have not been completely defined.

Based on recent studies in the isolated perfused kidney, a somewhat different teleologic and pathogenetic perspective has recently been offered by Brezis et al.⁷³ and Epstein and Brown.⁷⁴ They have suggested that the thick ascending limb of the loop of Henle (TAL) is particularly susceptible to hypoxic (ischemic) injury. This is thought to be a consequence of the combined effect of two factors: (1) countercurrent exchange of oxygen between the descending and ascending limbs of vasa recta, resulting in a sharp and progressive decline of oxygen tension from the cortex to the medulla; and (2) the high metabolic rate of the cells of the TAL. These investigators have provided evidence that the increased vulnerability of TAL in the isolated perfused kidney is related to oxygen demand for metabolic work since it is ameliorated by pharmacologic agents such as furosemide and ouabain, which reduce the metabolic work of TAL by inhibiting active transport. Based on these findings, these investigators have suggested that RBF and GFR are decreased in order to reduce the workload of TAL and protect it from ischemic necrosis. However, this concept is difficult to reconcile with the observations that saline or mannitol administration, which ameliorate the severity of both ischemic and nephrotoxic ARF, decreases proximal nephron reabsorption and increases the delivery of solute to the TAL.^{25,26,60,61,75-77} Since active reabsorption in the TAL is load dependent, these protective measures lead to an increased rather than a decreased metabolic workload of TAL, therefore contradicting the hypothesis. Conversely, states of decreased workload (e.g., prerenal hypoperfusion states with increased proximal reabsorption and decreased filtrate delivery to TAL) are associated with an increased predisposition to ischemic ATN.^{6,25,26,61,77} Thus, the relevance of the results in the isolated perfused kidney to ATN in the intact organism remains to be established.

RELATIONSHIP OF PRERENAL STATES TO ATN.—It has often been stated that if prerenal hypoperfusion is not treated promptly or adequately,

it progresses to ATN by causing ischemic injury. There is little convincing evidence to support a progression of prerenal hypoperfusion to ATN in the absence of additional renal insults. For example, patients with congestive heart failure or cirrhosis, with mild to moderate impairment of function, can continue in a state of prerenal hypoperfusion for months without ATN. Of course, these are chronic states of renal hypoperfusion, and it is possible that more acute and more extreme prerenal hypoperfusion could lead to ischemic injury.

On the other hand, there is a great deal of evidence that prerenal hypoperfusion states result in a markedly increased predisposition to both ischemic and nephrotoxic ATN. For ischemic ATN, the critical event often seems to be the occurrence of significant hypotension that, probably by causing tubular cell injury, changes the predominant efferent arteriolar constriction of a prerenal state to the predominant afferent arteriolar constriction of the ATN syndrome. A similar increased incidence and severity of nephrotoxic ATN has been observed after dehydration or volume depletion, both in humans and experimental animals.^{1,4,5,25-27} The precise reasons have not been defined. The two major interlinked characteristics of prerenal states are renal hypoperfusion and an increased salt and H₂O avidity of the kidney. Studies in experimental animals suggest that the latter may be the more important factor. Most of the experimental manipulations that have been found to be protective are associated with an increased rate of salt and H₂O excretion by the kidney, just prior to, during, and following the initiation of ATN.^{25-26,60-62,75-78} It is important to recognize that it is not urine flow per se that is important. Brattleboro rats with diabetes insipidus excrete large volumes of urine but have the same if not increased susceptibility to ATN.⁷⁹ These studies strongly imply that an increased solute and H₂O flow through the proximal rather than the distal nephron is the critical component of protection. It is likely that the increased proximal salt and H₂O reabsorption in prerenal states lead to development of higher concentration of nephrotoxins, a slower transit time, and therefore longer exposure of tubular epithelium to potentially toxic agents, with resultant greater tubular injury.^{4,5,19,60,77,78} Slow proximal flow rates would also be associated with an increased likelihood of nephron obstruction. This interpretation would also account for the experimental observations that volume expansion per se confers limited protection, independent of the induction of a solute diuresis.^{75,80} It is also possible that volume expansion may modify the release of putative mediators of the hemodynamic changes or modify the vascular response to their release, but, at present, definitive evidence is lacking. These findings have important implications for prophylactic measures against ATN in susceptible individuals, as discussed subsequently.

Acute Interstitial Nephritis

About 10% to 15% of the patients with ARF syndrome have acute interstitial nephritis (AIN) as their etiologic basis.^{1,4,5,49,81} This category includes a large heterogenous group of disorders. A variety of pharmacologic, toxic, infectious, immunologic, and hereditary mechanisms can injure the interstitium. However, the etiologies that are most often involved in acute interstitial nephritis with an associated ARF syndrome are related to drugs and sometimes to infections in certain susceptible individuals such as diabetics or pregnant patients. Pathogenetically, the drug-associated interstitial nephritides can be separated into two broad categories: (1) Those that are mediated by hypersensitivity to penicillins, sulfonamides, or related drugs. These are characterized by interstitial edema and eosinophil infiltration and are often accompanied by evidence of systemic hypersensitivity responses such as fever, urticarial rashes, and peripheral eosinophilia. (2) Those that are presumably mediated by other immunologic mechanisms although the details of the pathogenesis have not been defined. The cellular infiltrate in this latter case is composed of plasma cells and other mononuclear cells but without eosinophils. Similar immunologic mechanisms may be involved in other non drug-related interstitial nephritides such as those associated with certain infections or sarcoidosis.

Although the etiologic mechanisms in AIN are different as compared to the purely tubular injury syndromes, there are certain morphological and functional similarities. Evidence of tubular cell injury is often present in AIN. Conversely, interstitial inflammation and mononuclear cell infiltrates are often seen in ATN syndromes. Indeed the retention of nitrogenous waste in AIN is probably related to mechanisms that are similar if not the same as in the ATN syndromes, as suggested by the fact that urinary composition is similar in the two disorders (*vide infra*). Although hematuria and proteinuria are often noted in AIN, they are usually mild, unlike the acute nephritic and vasculitic syndromes. Moreover, the urine sediment in AIN often shows evidence of epithelial or mixed cell casts but no red blood cell casts. Additionally, eosinophils are often present in the urine when hypersensitivity mechanisms are involved. Evidence of tubular dysfunction in the form of renal tubular acidosis or glycosuria, etc., may also be noted on occasion. The recognition of these disorders is important since removal of the offending agent is associated with recovery or improvement in renal function when this process is superimposed on other renal diseases. Steroids have been stated to hasten recovery in selected cases, but controlled studies have not been done.

DIFFERENTIAL DIAGNOSIS

It is beyond the scope of this monograph to enumerate and discuss all the possible factors in the history, the physical findings, and the laboratory tests that impact on the differential diagnosis of the syndrome of ARF. Instead the pertinent clinical aspects and the laboratory tests that are central to the process of differential diagnosis are emphasized.

HISTORY AND PHYSICAL EXAMINATION

Most episodes of ARF occur in hospitalized patients, and therefore some of the pertinent data are easily obtainable. However, some patients have elevated levels of BUN and serum creatinine at presentation. In both groups, particular attention should be paid to acuteness of the syndrome and the possible precipitating events, especially those related to changes in fluid volume status. The signs, symptoms, and laboratory findings indicative of the presence and nature of preexistent renal disease should be specifically sought during history-taking. The presence of nocturia is a particularly valuable sign of chronic renal insufficiency because of the loss of ability to concentrate the urine. Inquiries should be made about changes in urine volume, frequency, and voiding patterns. During physical examination, an assessment of the body fluid volume status is critical to differentiating between the possible etiologic mechanisms and to interpretation of the urine chemistries. In certain complex clinical situations, a chest x-ray film and measurement of central venous pressures or pulmonary capillary wedge pressures may be required. Evidence of an obstructive process, such as an enlarged distended bladder, should be carefully sought.

URINE VOLUMES

Although a wide range of urine volumes can be associated with the ARF syndromes, urine volume still provides very valuable information.^{1, 4, 5, 13, 19} Persistent anuria (urine volume less than 50 ml/day) is typically observed with obstruction of the major renal arteries or with complete obstruction of the urinary tract. It is also a characteristic of the clinical syndromes associated with cortical necrosis. Although transient anuria can be seen on occasion with prerenal ARF or ATN syndromes, the presence of anuria, unless it is very transient, should lead one to suspect vascular occlusion or cortical necrosis.

EXCLUSION OF OBSTRUCTIVE ARF

When the cause for acute retention of nitrogenous waste is not immediately obvious after history-taking and physical examination, obstruction to the urinary outflow tract should be considered in every patient regardless of the urine volume. This is best done by ultrasonography. It is simple, noninvasive, and sensitive enough to detect dilatation of the urinary tract within 24 to 36 hours of the onset of obstruction. It also provides information about other possible anatomical abnormalities as well as kidney size. Small kidneys indicate that a chronic disease process has been present, with possible acute exacerbation. If evidence of obstruction is found, other radiologic or invasive procedures are often required to establish the specific cause and initiate treatment.

URINARY "DIAGNOSTIC INDICES"

Interpretation of urine chemistries and osmolalities, a routine urinalysis, and a careful microscopic examination of the urinary sediment are central to the diagnostic process.

The term "diagnostic indices" is used in deference to traditional usage.^{1, 4, 5, 16, 17, 53, 54} In our opinion, the term is inappropriate and encourages a nonanalytic approach to the interpretation of these parameters. The urine chemistries and osmolalities are best interpreted as reflecting the functional response of the kidneys to a particular disturbance of body fluid volume and/or composition in a given patient. The first step is to assess if the response of the kidneys is appropriate or inappropriate to the homeostatic stress or to systemic hemodynamics. If the response is appropriate, it usually indicates a problem outside the kidney. On the other hand, if the response is inappropriate, the next issue is to ascertain if the inappropriate response is due to renal disease per se or due to factors preventing an appropriate response by normal kidneys. This is illustrated by the hypothetical case of a patient with diabetes mellitus who presents to the emergency room with signs of dehydration and plasma volume depletion and yet is producing relatively copious volumes of urine. Clearly this lack of oliguria is inappropriate in a patient with clinical volume depletion. A urinalysis reveals the presence of large amounts of glucose, indicating that the lack of oliguria is due to the solute diuresis that is preventing the kidneys from responding appropriately to volume depletion. This approach to interpretation of urine chemistries requires that the homeostatic challenge to either the volume or the composition of the body fluids be defined first by clinical parameters, such as history, physical findings, and other ancillary data. The urine chemistries are next interpreted as indicating the functional renal response. It is inappro-

priate and potentially dangerous to make judgments about the volume and/or composition of body fluids based on urine chemistries, and yet this is done regrettably too often. For example, if a patient is excreting a small volume of concentrated and NaCl-poor urine, the patient's volume status cannot be inferred on the basis of this response, since patients with congestive heart failure, acute glomerulonephritis, or true volume depletion elaborate a similar urine.

If obstructive ARF has been excluded, the primary task of differential diagnosis is to separate the prerenal syndromes with functionally and structurally intact kidneys from the diseases states in which there is injury to the kidneys, i.e., ATN syndromes. This differentiation is based on the fact that in prerenal states with preserved tubular integrity, the urine exhibits evidence of avid salt and water retention by the kidney in response to decreased GFR, while the tubular cell injury in the ATN syndromes prevents this response from occurring.

Figure 10 presents the major urinary parameters ("diagnostic indices") used to differentiate between prerenal ARF and ATN syndromes. The urinary Na concentration and urinary osmolality are qualitative indices of Na and H₂O absorption, while urinary to plasma creatinine ratios and fractional excretion of sodium are quantitative parameters.

URINARY NA CONCENTRATION

The urinary Na concentration (U_{Na}) is an index of the ability of the tubular epithelium to reabsorb Na against concentration gradients. This process normally occurs distal to the thick ascending limb of the loop of Henle, and therefore U_{Na} is primarily a test of functional tubular integrity of those nephron segments. During states of avid Na reabsorption, the kidney with a functionally intact tubular epithelium is able to lower U_{Na} to less than 20 and often to less than 10 mEq/L. Therefore, a U_{Na} of less than 20 mEq/L is indicative of preserved tubular integrity and therefore of a prerenal ARF. A U_{Na} of greater than 40 mEq/L is considered indicative of tubular injury and therefore of ATN. Values between 20 and 40 mEq/L are considered nondiagnostic.

URINARY OSMOLALITY

This qualitative index tests the function of those segments of the nephron that are involved in the concentrating process. A detailed discussion of the concentrating mechanism is beyond the scope of this monograph, but urinary osmolality (U_{Osm}) reflects the tonicity of the medullary interstitium during ARF states, which in turn depends

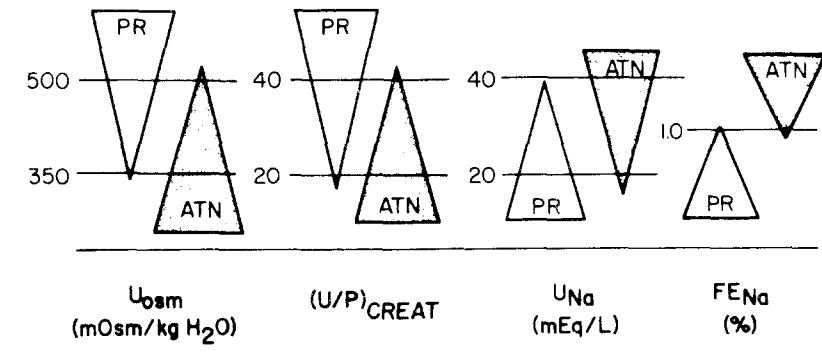


FIG 10.

Common urinary indices in acute renal failure. The horizontal axis displays four laboratory tests and the units used to differentiate functional prerenal ARF (*PR*) azotemia from acute tubular necrosis (*ATN*). The vertical axis depicts values that define the nondiagnostic zones of overlap between the designated values and diagnostic areas of nonoverlap above and below the designated values. (From Humes HD: *Acute renal failure*, in Humes HD (ed): *Pathophysiology of Electrolyte and Renal Disorders*. New York, Churchill Livingstone Inc, 1986. Based on an adaptation from Basti CP, Rudnick MR, Narins RG: Diagnostic approaches to acute renal failure, in Brenner BM, Stein JH (eds): *Acute Renal Failure*. New York, Churchill Livingstone, 1980, p 17. Used by permission.) As discussed in the text, the ratio of urine osmolality to plasma osmolality ($[U/P]Osm$) is a better index of renal concentrating ability and therefore for separation of prerenal ARF from ATN. The urinary to plasma creatinine ratio ($[U/P] CREAT$) is a quantitative index of fractional excretion of H_2O , i.e., the percentage of water that is excreted by the kidney (FE_{H_2O}).

$$FE_{H_2O} = \frac{H_2O \text{ Excreted}}{H_2O \text{ Filtered}} \times 100$$

Since the quantity of H_2O excreted is the urine volume (V), while the amount of H_2O filtered is the GFR (i.e., creatinine clearance; $[U/P]Cr \times V$)

$$FE_{H_2O} = \frac{V}{[U/P]Cr \times V} \times 100 = \frac{100}{[U/P]Cr}$$

Fractional excretion of sodium (FE_{Na}) is similarly derived:

$$FE_{Na} = \frac{\text{Amount of Na excreted}}{\text{Amount of Na filtered}}$$

The amount of Na excreted = Na concentration in the urine (U_{Na}) \times volume of urine (V); the amount of Na filtered = Na concentration in the plasma (P_{Na}) \times GFR.

$$FE_{Na} = \frac{U_{Na}V}{P_{Na} \times [U/P]Cr \times V} \times 100 = [U/P]Na/[U/P]Cr \times 100$$

FE_{Na} is the most useful parameter to separate prerenal ARF from ATN as it has the least diagnostic overlap. Another urinary index termed the "renal failure index" (RFI) has been used and recommended for separation of prerenal ARF and ATN. It is calculated as follows: (Continued.)

FIG 10 (cont.).

$$RFI = U_{Na}/[U/P]Cr \times 100$$

As can be noted by comparing this calculation to the derivation of FE_{Na} , the only difference between the two parameters is that the P_{Na} has been left out of the calculation for RFI. Therefore, in our opinion, RFI does not provide any more useful information and is physiologically meaningless.

upon water-free solute extraction in the loop of Henle. Under conditions of increased solute reabsorption such as prerenal ARF, the ratio of urine osmolality to plasma osmolality $[U/P]Osm$ is significantly greater than 1. The cutoff point for $[U/P]Osm$ used to diagnose prerenal ARF is greater than 1.35, while in ATN the ratio is less than 1.1. Intermediate values are considered nondiagnostic. It is important to appreciate that regardless of the etiology, as GFR declines progressively, the amount of solute delivered to the loop of Henle also declines progressively; the net decrease in the amount of solute transported into the medullary interstitium results in a decrease in the maximal urinary osmolality, even in prerenal ARF. This is the reason for accepting a $[U/P]Osm$ ratio of greater than 1.35, rather than a ratio of greater than 3, which would be the expected value with a normal maximal urinary osmolality of greater than 1,000 mOsm. Therefore, a loss of concentrating ability in ARF states does not necessarily indicate injury to TAL and, therefore, on occasion, overlapping values of $[U/P]Osm$ may be seen (see Fig 10).

URINARY TO PLASMA CREATININE RATIO

For clinical purposes creatinine is neither secreted nor reabsorbed. Therefore, the increase in concentration of creatinine in the tubular fluid is directly related to the amount of H_2O reabsorbed and urinary to plasma creatinine ratio $[U/P]Cr$ is a quantitative index of total water absorption by the kidneys, as explained previously (see Fig 10, legend). Therefore, $[U/P]Cr$ greater than 40 implies that less than 2.5% of filtered H_2O is being excreted and greater than 97.5% of filtered H_2O is being reabsorbed, and suggests prerenal ARF. A value of $[U/P]Osm$ of less than 20 is considered to be indicative of ATN and implies that more than 5% of H_2O is excreted, while 95% is reabsorbed and suggests ATN. Values of $[U/P]Cr$ between 20 and 40 are considered nondiagnostic.

FRACTIONAL EXCRETION OF SODIUM

While the three previous tests are able to separate prerenal ARF from ATN syndromes in about 80% of the patients, the values are intermediate in 20% of the patients. The fractional excretion of so-

dium (FE_{Na}) is considered to have a greater discriminatory ability, allowing separation of prerenal ARF from ATN in more than 90% of the patients. It is a quantitative index of the total sodium reabsorption by the kidney. A value of less than 1% (more than 99% reabsorption) indicates prerenal ARF, while a value greater than 1% (less than 99% reabsorption) indicates an ATN syndrome, although some authors have recommended an FE_{Na} greater than 2% as a cutoff point to diagnose ATN. For all practical purposes, FE_{Na} of 1% excludes a prerenal state unless there is coexistent solute diuresis (glucose, mannitol), prior diuretic administration, or preexistent chronic renal disease with superimposed prerenal ARF. On the other hand, the ATN syndromes will occasionally present with an FE_{Na} of less than 1%. This is usually observed early in the course of certain specific kinds of ATN syndromes; the two most notable examples are rhabdomyolysis and radiocontrast-media-induced ARF. An FE_{Na} of less than 1% can also be seen on occasion during the course of ATN, if an intense prerenal state (decreased effective circulating volume and/or decreased cardiac output) is superimposed on the ATN syndrome.

The overlap of urinary "diagnostic indices" often occurring in a nonoliguric setting has led to statements that these indices are of limited value in differentiating the various diagnostic categories especially in the nonoliguric patient. In our opinion, these conclusions are overstated. While it is true that the underlying etiology of ARF is uncertain in occasional patients, most of the problems stem from emphasizing the exceptions and from an insistence on interpretation of these parameters as absolute "diagnostic indices" rather than as an index of the renal response in the context of the individual patient's hemodynamic status. For example, nonoliguria in the face of decreasing GFR per se indicates an impairment of the ability of the kidney to respond appropriately. Therefore, if the extrarenal causes of nonoliguria (solute diuresis, diuretics, lack of ADH) can be excluded, the diagnosis is in all likelihood an ATN syndrome, regardless of the urinary diagnostic indices. Conversely, it is not surprising that, on occasion, an ATN syndrome can be associated with prerenal urinary diagnostic indices. After all, the difference between $[U/P]Cr$ of 20 or 40 only implies a difference of 2.5% in fractional H_2O absorption (95% vs. 97.5%). Similarly, the differences in FE_{Na} in prerenal ARF and ATN often only represent a difference in fractional reabsorption of sodium of 1% (99% vs. 98%). As discussed in the section dealing with the concept of acute renal success, the GFR seems to be closely linked to Na reabsorptive ability in ATN. If additional decrements in GFR (and filtered load of Na) are produced by a superimposed hemodynamic mechanism, the injured tubules are able to more completely reabsorb the decreased filtered load of Na. The examples cited earlier, in which an FE_{Na} of less than 1% is observed in asso-

ciation with an ATN syndrome, are precisely the ones in which such hemodynamic changes are known to occur, i.e., contrast media, rhabdomyolysis, and ATN with a superimposed intense prerenal stimulus. Therefore, the finding of somewhat unexpected urinary parameters in a given patient with ARF should initiate a search for the reasons of the renal response rather than a literal application of diagnostic indices in order to attach a diagnostic label on the patient.

While the above mentioned urinary parameters are the major tests used, there are other additional tests that are of use in patients with ARF.

BUN/CREATININE RATIO

The normal BUN/creatinine (Cr) ratio is 10 to 15. In prerenal ARF it is often elevated above 20. As alluded to before, the reason for this disproportionate elevation of BUN is that the intense salt and H₂O absorption in prerenal ARF is also accompanied by an increased passive reabsorption of urea, leading to a disproportionately greater reduction in urea clearance than in creatinine clearance. However, it should be appreciated that a similar elevation of BUN/Cr ratio occurs in ARF secondary to nephritic and vasculitic syndromes with preserved tubular integrity and increased Na and H₂O absorption. Another factor that influences this ratio is the relative rate of production of BUN and creatinine. Creatinine is the product of muscle metabolism and therefore it is a function of the patient's muscle mass; consequently, the basal ratio tends to be higher in children and in very old patients, and this applies during ARF. Similarly, the BUN/Cr ratio may be increased by primary increases in protein breakdown and BUN production, as in catabolic patients with ATN syndromes. In this situation, an examination of ratios of urea nitrogen clearance to creatinine clearance, i.e., the fractional clearance of urea nitrogen (FC_{UN}), helps in differentiating the etiology of the elevated BUN/Cr ratio. This is calculated as: FC_{UN} = [U/P]UN/[U/P]Cr × 100. If the fractional clearance of BUN is less than 30%, it indicates increased urea reabsorption that is associated with the avid Na and H₂O reabsorption seen in prerenal states. If the fractional clearance of BUN is greater than 50%, it indicates that the primary reason for the elevated BUN/Cr ratio is increased protein breakdown and not urea reabsorption, and, therefore, this suggests an ATN syndrome.

Fractional excretion of chloride usually provides the same information as FE_{Na} and may in fact be a better test in the presence of alkalosis and bicarbonaturia that can cause an excretion of Na⁺ as the obligate cation with HCO₃[−] despite volume depletion. A high K⁺/Na⁺ ratio in the urine usually indicates preserved distal secretory ability for potassium and suggests a prerenal state with elevated aldosterone.

ROUTINE URINALYSIS

Analysis of a freshly voided urine sample combined with a careful examination of the urinary sediment provides additional critical information for the differential diagnosis of ARF syndromes. It is of major importance in the diagnosis of intrinsic ARF secondary to diseases of the microvasculature and glomerular capillaries. The vasculitic and nephritic syndromes severe enough to cause ARF are invariably associated with significant proteinuria, hematuria, and usually an active sediment with red blood cell casts. A urine that tests positive for blood but does not have enough red blood cells on microscopic examination suggests the presence of myoglobinuria or hemoglobinuria as the etiology of ARF syndrome. Similarly, the presence of epithelial cell, white blood cell, or mixed cellular casts suggests tubulointerstitial injury. Additional valuable diagnostic clues may include the presence of glucose, suggesting either a solute diuresis or proximal tubular injury. Similarly, urine pH indicates acidifying ability and can suggest the presence of distal renal tubular acidosis as is sometimes observed in interstitial nephritis or in obstruction. The specific gravity of the urine, while it may be an easily measurable index of the concentrating ability of the kidney, is often very misleading in the presence of glucosuria, proteinuria, or contrast media. Therefore, it is recommended that urine and plasma osmolality be obtained to assess the concentrating ability of the kidney.

Figure 11 provides an overall summary of the differential diagnostic approach. This, combined with additional specific clinical and laboratory evaluations, is sufficient to establish an etiopathogenetic diagnosis in the vast majority of patients with the ARF syndrome.

CLINICAL COURSE OF ATN SYNDROMES

Since the classic description of the syndrome during World War II,¹⁵ the clinical pattern has changed over the years.^{1, 4, 5, 15-19, 44, 49, 81-83} The onset of clinical ATN may be abrupt (after an ischemic, hypotensive, or nephrotoxic event) or somewhat more insidious (after aminoglycoside administration). In about half the cases, oliguria (urine vol less than or equal to 400 ml/dl/day) is present before the increases in level of serum creatinine or BUN are noted. In patients with nonoliguric ATN, no significant change in urine volume may be noted. The daily increases in levels of BUN and serum creatinine vary between 10 and 25 mg/dl and 0.5 and 2.5 mg/dl, respectively, depending upon the size of the patient, the severity of ARF, and the presence or absence of a catabolic state such as sepsis or major surgery. Larger increases are usually associated with more severe disturbances in plasma composition such as hyperkalemia, hyper-

SUMMARY OF DIAGNOSTIC APPROACH TO ARF SYNDROMES

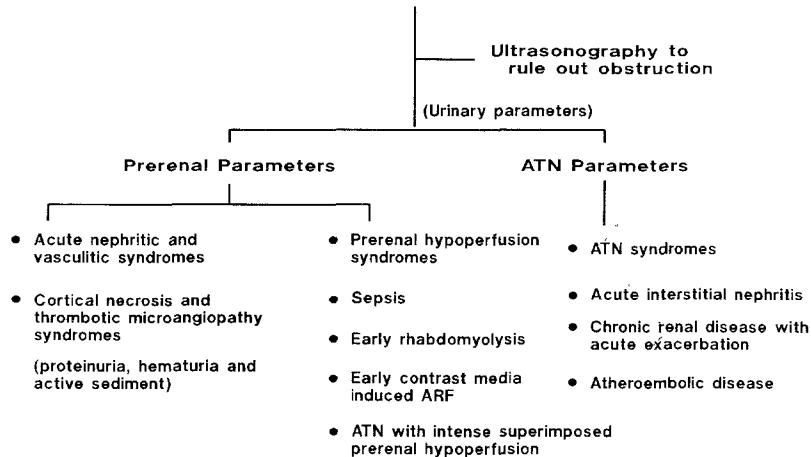


FIG 11.

Summary of the differential diagnostic categories of ARF syndromes (see text for details).

phosphatemia, hyperuricemia, and hypocalcemia. These disturbances should be anticipated and may indicate a need for early intervention with dialytic therapy. Renal excretory failure persists for an average of 7 to 21 days, although unusual cases lasting 3 to 6 months have been reported. The serum creatinine level typically follows a triphasic pattern, as shown in Figure 12. As illustrated, decreases in serum creatinine level usually lag behind recovery of GFR (see Fig 12). This lag in recovery of serum creatinine level is explained on the basis that increases in GFR at this stage are not of a sufficient magnitude to allow excretion of an amount of creatinine that exceeds the daily production. However, this increase in GFR is indicated by a progressive decrease in the rate of increase in serum creatinine level, and it is often accompanied by progressive increases in urine volume, especially in patients with oliguric ATN. In the typical case, urine volume increases gradually from day to day when significant volume expansion has been avoided during the oliguric stage. In an earlier era when patients were severely volume expanded by the time they reached the diuretic or recovery phase, massive diuresis (5 to 10 L/day) often ensued, with further complications in management. This is an unusual occurrence in the modern era since dialysis can prevent such major volume overloads. This increase in urine volume is not initially accompanied by significant changes in composition; this suggests that as the GFR is improving and the filtered load of Na is increasing, the tubules are able to reab-

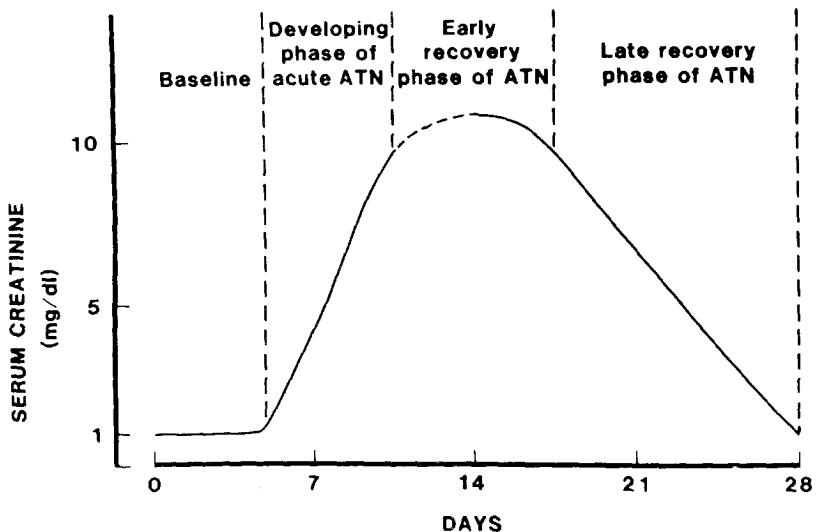


FIG 12.

Typical triphasic change in serum creatinine during developing, early recovery, and late recovery phases of acute tubular necrosis (ATN). During the early recovery period, the serum creatinine concentration may still rise as glomerular filtration rate improves. The rate of change in serum creatinine level, however, will be less (as noted by dashed lines). (From Humes HD: Acute Renal Failure, in Humes HD (ed): *Pathophysiology of Electrolyte and Renal Disorders*. New York, Churchill Livingstone Inc, 1986. Used by permission.)

sorb an increased amount of the filtered Na. This phenomenon again supports the concept of linkage between tubular reabsorptive ability and GFR during recovery in the vast majority of the patients, although, on occasion, problems with fluid volume homeostasis have been described during this phase.

These patterns are somewhat less distinct than in patients with nonoliguric ARF. Several studies have shown that GFR tends to be less severely depressed in these patients and therefore the excretory function is better preserved. This also results in fewer problems with fluid and electrolyte balance, which may account for the somewhat better prognosis of these patients.

SPECIFIC CLINICAL SYNDROMES OF ARF

It is beyond the scope of this monograph to describe in detail the clinical spectrum or the myriad syndromes of ARF. In the subsequent section, certain clinical syndromes of ARF are briefly described, emphasizing their unique characteristics that are important to diagnosis and management.

ARF SUPERIMPOSED ON CHRONIC RENAL DISEASE

This is a frequent differential diagnostic consideration, especially in patients who present with marked elevations in the levels of BUN and creatinine. The history and physical findings and the laboratory stigmata of chronic renal disease are of obvious importance in this situation. A rising serum creatinine level always indicates that at least a component of renal failure is acute, since chronic renal failure is associated with a steady state and stable serum creatinine values. The two most frequent offending factors for acute deterioration in renal function in patients with chronic renal disease are volume disturbance and drug nephrotoxicity. As can be seen in Figure 13, when renal function is significantly compromised, small changes in GFR result in marked changes in serum creatinine concentration. Therefore, acute and potentially reversible deterioration of renal function should always be considered, even in the presence of documented chronic renal insufficiency.

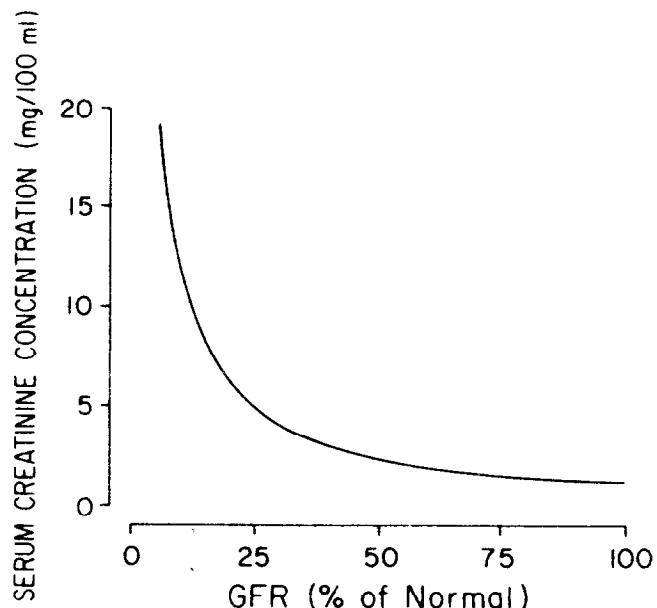


FIG 13.

Relationship between the glomerular filtration rate (*GFR*) and the serum creatinine concentration. Because of this relationship, when there is a significant preexistent decrease in *GFR*, small further declines in *GFR* result in marked changes in serum creatinine level. The graph is based on data obtained in adult patients. (Adapted from Valtin H: *Renal Dysfunction, Mechanisms Involved in Fluid and Solute Imbalance*. Boston, Little Brown & Co, 1979. Used by permission.)

SEPSIS

Sepsis, especially that due to gram-negative organisms, is often associated with the syndrome of ARF. A variety of pathogenetic mechanisms can mediate this ARF and need to be identified on an individual patient basis for appropriate management. (1) The most common mechanism, especially early in the course, involves a decrease in GFR due to a decrease in effective circulatory volume secondary to peripheral vasodilation and to an increased translocation of fluids into third spaces. (2) Evidence from experimental animals suggests that bacterial endotoxin can interact with the endothelium of the renal microvasculature, resulting in a persistent renal vasoconstriction and hypoperfusion that is not accompanied by significant morphological injury. The vasoactive mediators postulated to play roles include adenosine, platelet-activating factor, and leukotrienes.^{74, 84, 85} This mechanism is suggested when ARF is maintained and urinary diagnostic indices are persistently prerenal, despite restoration of an adequate circulatory volume. In animal studies both adenosine antagonists (theophylline) and platelet-activating factor antagonists have protective effects. However, no human data are available. (3) The disseminated intravascular coagulation (DIC) often associated with sepsis can lead to a microangiopathic process with fibrin deposition in the renal microvasculature and patchy cortical necrosis. This occurs in about 25% of the patients with DIC.¹³ (4) Sepsis-associated hypotension can result in an ATN syndrome. (5) Antibacterial agents, especially aminoglycosides can cause tubulointerstitial injury and result in an ATN syndrome.

HEPATOBILIARY DISEASE

Two distinct forms of ARF occur in these patients.^{1, 4, 5, 8}

Hepatorenal Syndrome

This form of ARF in patients with hepatic failure has an extremely high mortality. Over-aggressive use of diuretics and/or hypokalemia along with gastrointestinal hemorrhage have been postulated as precipitating factors but definitive evidence is lacking. It is characterized by intense and persistent renal vasoconstriction. A humoral mediator either formed or not metabolized by the liver has been postulated to cause the renal vasoconstriction. Patients are invariably oliguric and have a U_{Na} of less than 10 mEq/L. Hepatic failure can result in impaired urea synthesis and cause a disproportionately low level of BUN. The syndrome should be differentiated from impairment of renal function produced due to volume depletion, which can be ameliorated by restoration of an adequate circulatory volume. The functional and reversible nature of the vasoconstriction in the he-

patorenal syndrome is suggested by the fact that the syndrome is reversed on occasion by a LeVeen shunt and invariably by successful hepatic transplantation; moreover, kidneys removed from such patients function normally in transplant recipients. These data provide the basis for its classification in the prerenal ARF group.

ATN Syndromes

The increased incidence of ATN in these patients is due to multiple predisposing factors. Prerenal hypoperfusion is often present in these patients, and jaundice seems to be an additional independent risk factor. Studies in experimental animals suggest that obstructive jaundice heightens the sensitivity to a given degree of volume depletion. This increased sensitivity may account for the increased risk of postsurgical and cyclosporine-induced ARF in patients with poorly functioning liver transplants. Moreover, *in vitro* and *in vivo* studies suggest that bile acids and possibly other components of bile may have nephrotoxic potential.

RENAL CORTICAL NECROSIS

Renal cortical necrosis is potentially the severest form of ARF.^{1,4,5,13,14} Injury to the endothelium of the microvasculature with thrombotic occlusion seems to be the common pathogenetic pathway. More than 50% of the cases are associated with obstetric events including abruptio placentae, septic abortion, and during the postpartum state. This may be related to an increased susceptibility to thrombotic events during pregnancy. It occurs in about 25% of cases of disseminated intravascular coagulation (DIC) from any cause. It may be precipitated by certain antineoplastic agents such as mitomycin C. The onset can occur with devastating suddenness following a trivial viral illness, as in children with hemolytic uremic syndrome. Sometimes the onset is less acute, as in thrombotic thrombocytopenic purpura syndromes in which the central nervous system manifestations predominate. Evidence of a microangiopathic process is the diagnostic hallmark. Anuria is often present and may be persistent. Recognition of the syndrome is important because ARF usually persists for weeks and sometimes months. If the patients do not succumb during the acute stage, recovery is often incomplete unlike most ATN syndromes. The long-term outlook is also unfavorable; after a period of relative quiescence, hypertension, proteinuria, and progressive renal insufficiency often follow. There are recent reports that plasma exchange therapy is of benefit in a significant number of patients.

ATHEROEMBOLIC DISEASE

The ARF secondary to atheroembolic disease is probably more common than is recognized.^{11,86,87} It should be suspected in any patient with atherosclerotic disease. It usually follows an angiographic study or a surgical procedure, especially if related to aortic aneurysms, but it can occur spontaneously. Presence of peripheral eosinophilia has recently been emphasized as an important diagnostic clue. Evidence of atheroemboli in the retina and elsewhere in the systemic circulation provides further diagnostic support for atheroembolic disease as the cause of ARF. A renal biopsy can provide diagnostic confirmation. In a minority of patients following surgery, there is an acute onset of oliguria or anuria. More often, ARF develops insidiously and is nonoliguric. This more slowly progressive nonoliguric ARF is the characteristic pattern in renal atheroembolism following angiography or in spontaneous atheroembolism. This pattern of increase in serum creatinine level is unique for ARF syndromes and is illustrated in Figure 14 and contrasted with the pattern after contrast-media-induced ARF, which is one of the major differential diagnostic considerations. The progressive rise in creatinine level continues over weeks and months and results in eventual end-stage renal failure requiring chronic dialysis. The pathogenesis of this form of atheroembolic ARF is poorly understood. There is no specific treatment. Occasional long-term stabilization of function at an impaired level, and even recovery, have been described.

MYOGLOBINURIC AND HEMOGLOBINURIC ARF

Acute renal failure is a frequent occurrence after both acute traumatic rhabdomyolysis or the nontraumatic rhabdomyolysis associated with severe myopathies, heat strokes, viral infection, and potassium and phosphate depletion.^{1,4,5,15,82,88-90} The alcoholic patient is particularly susceptible. Intravenous infusions of myoglobin and hemoglobin cause little, if any, renal toxicity, suggesting that other factors are operative when clinical ARF develops. Rhabdomyolysis causes intravascular depletion as the damaged muscles release osmotically active solutes into the interstitium, leading to fluid shifts. That this plays an important pathogenetic role is suggested by the observations that the incidence and severity of myoglobinuric ARF is markedly increased by preexistent volume depletion and that in experimental animals vigorous volume replacement often aborts the expected ARF.^{62,91} The damaged muscles also release other substances that may have independent nephrotoxic potential. Similarly, hemolysis and hemoglobinuria appear to lead to ATN only in the presence of other complicating factors such as dehydration, shock and acidosis (transfusion reactions), and certain infections. Release

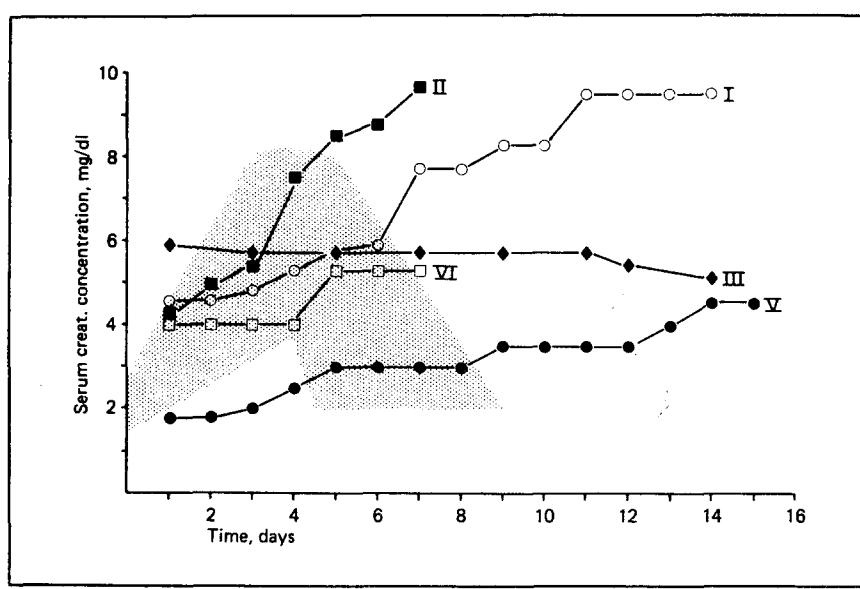


FIG 14.

The course of renal failure associated with atheroembolic renal disease in five patients is contrasted with that associated with contrast-media-induced ARF. (From Kasinath BS, et al: *Am J Nephrol* 1987; 7:173–177. Used by permission.)

of vasoactive mediators or red blood cell stroma may be additional contributory factors in the pathogenesis of the ARF. Both myoglobin and hemoglobin that is not bound to haptoglobin are filterable at the glomerulus. As fluid is reabsorbed, the concentrations of myoglobin and hemoglobin increase, leading to distal formation of pigmented casts in interaction with the Tamm-Horsfall protein. These may play an obstructive role. Since myoglobin is a much smaller molecule than hemoglobin, it is cleared more effectively so that both the plasma and urine are pigmented in hemoglobinuria, but only the urine is pigmented in myoglobinuria. More sophisticated tests for differentiating myoglobin and hemoglobin in the urine are usually not needed as the correct diagnosis can be made on other clinical grounds. In either case, the urine tests positive for "heme" by dipstick (ortholidine test), and examination of the urinary sediment reveals few red blood cells.

Clinically, rhabdomyolysis is associated with a marked elevation of creatinine phosphokinase (CPK), due to its release from injured muscle. The release of other constituents of the injured muscles such as creatinine and creatinine precursors, uric acid precursors, phosphorus, and potassium leads to rapid elevations of serum cre-

atinine level (more than 2 mg/dl; BUN/creatinine ratio may be less than 10), hyperkalemia, hyperuricemia, hyperphosphatemia, and hypocalcemia. These are indications for early and vigorous dialytic therapy. Similar biochemical changes may be seen in hemolytic states except for the changes in creatinine. Achievement of good hydration and solute diuresis seems to be protective. Although experimental studies suggest that mannitol and/or alkalinization of the urine may be of help, there are no controlled clinical studies showing their effectiveness. They are of no benefit once ARF develops, and there is potential for serious volume overload and alkalinization of plasma. The latter results in marked falls in the levels of ionized calcium that contributes its own morbidity. Therefore, if mannitol (25 gm as a single dose) is to be given or if alkalinization is attempted, this should be done before the onset of ARF. Urine pH should be checked after bolus administration of NaHCO₃ (50 to 100 mEq). If urine alkalinization is not achieved, it may be indicative of established ARF and repeated doses of NaHCO₃ should not be administered. Hypocalcemia is prominent during the acute stage because of its deposition in the injured tissue; hypercalcemia often occurs during recovery from ARF because of mobilization from the deposits.

AMINOGLYCOSIDES

All members of aminoglycosides have some potential for nephrotoxicity and ARF.^{1, 4, 5, 92, 93} Although increased excretion of a number of brush border and lysosomal enzymes occur within a few days of initiation of therapy, these changes correlate poorly with eventual ARF. Clinical ARF is usually seen during the second week of therapy, in about 10% of the patients, and correlates somewhat better with the degree of renal cortical accumulation of the drug. Clinically, the most important factors seem to be drug dosage and duration of therapy, with sustained elevation of trough levels being more injurious. Drug levels should be frequently monitored if possible, and adjustments should be made for preexistent or developing renal insufficiency. There is an increased risk in patients who receive repeated courses, even if separated by a few days or weeks. Once ARF is initiated, discontinuing therapy with the drug does not result in immediate recovery; rather ARF follows a typical course, with rising serum creatinine levels for the next several days before they reach a plateau and then fall to normal over the next week or two.

AMPHOTERICIN B

Renal toxicity of amphotericin B becomes more frequent and predictable with increasing cumulative doses beyond 2 to 3 gm.^{92, 93} Ini-

tial injury to the distal nephron results in an ADH-resistant nephrogenic diabetes insipidus, distal renal tubular acidosis, and potassium wasting with hypokalemia. These manifestations may be seen without major declines in the GFR. Evidence of proximal tubular injury is also seen in severe toxicity associated with an ARF syndrome. Direct renal vasoconstriction mediated by amphotericin B also contributes to the decreased GFR. Once ARF develops, the risk of continued therapy has to be balanced against the potential benefits. Recovery may be incomplete, and some of the tubular defects can persist long after GFR has recovered.

RADIOCONTRAST AGENTS

An increase in the incidence of radiocontrast-media-induced ARF has been noted during the past decade.^{1,4,5,92,94} This is attributable to a greater use of these agents for an increasing number of radiologic investigations in patients at risk, such as the sick and elderly. Other documented risk factors are the presence of diabetes, preexistent renal insufficiency, presence of myeloma or amyloidosis, and prior history of contrast-media-induced ARF. In this setting of increased risk, dehydration can be an additive risk factor. Three pathogenetic mechanisms may be involved: contrast-media-induced vasoconstriction, contrast-media-induced precipitation of Tamm-Horsfall protein, and possibly direct tubular toxicity.

Clinically, once ARF occurs, the pattern is fairly characteristic. Oliguria often occurs in the first 24 hours and may persist for a couple of days. Milder forms may be nonoliguric. Serum creatinine level reaches a peak within a week, followed by recovery (see Fig 14). Occasional irreversible injury has been described in patients with diabetes or preexistent renal disease.

The urinalysis is usually nonspecific. Although the specific gravity may be very high, the urine is isosmotic. During the oliguric phase, U_{Na} and FE_{Na} are low and suggestive of prerenal etiology because of the associated vasoconstriction, as discussed earlier.

NONSTEROIDAL ANTI-INFLAMMATORY DRUGS

NSAIDS have become an increasingly important cause of ARF, especially in patients with a preexistent functional renal compromise, i.e., prerenal states with decreased renal perfusion or preexistent glomerular or tubular disease.^{1,4,5,9,93} It has been postulated that these agents inhibit the vasodilatory prostaglandins that protect against undue and inappropriate vasoconstriction mediated by other vasoactive agents. These agents can also cause interstitial nephritis and ARF in patients without preexistent renal disease. Occasionally some of these patients also have a nephrotic syndrome that

may dominate the clinical presentation. Recovery from both processes occurs over several weeks after withdrawal of the drug.

CYCLOSPORINE

Cyclosporine, a potent immunosuppressive agent, produces dose-dependent decreases in RBF and GFR, probably by a direct effect on the vasculature.^{5, 10} There is some evidence, both in experimental animals and in man, that at least a component of the hemodynamic effect is mediated by an interaction of cyclosporine with renal nerves. These hemodynamic effects may be responsible at least in part for the worsening of hypertension seen with this agent. Additionally there is evidence that chronic long-term usage may be associated with functional and morphological toxicity to proximal and distal nephrons. Hyperkalemia is frequently observed, although its pathogenesis is poorly understood. There is also evidence that the nephrotoxicity of cyclosporine may be enhanced in the presence of other nephrotoxic agents such as aminoglycosides.

ARF ASSOCIATED WITH NEOPLASTIC DISORDERS^{5, 49, 95}

Multiple Myeloma

Acute renal failure occurs in about 2% to 8% of all patients with multiple myeloma. The pathogenesis of ARF is complex and probably multifactorial. The factors that are thought to be most important are related to deposition of light-chain dimers in the distal and collecting tubules. Such deposition is associated with tubular injury and atrophy with surrounding infiltrates of round cells and multinucleated giant cells. This characteristic appearance has been termed the "myeloma kidney." It is postulated that these light chains are directly nephrotoxic to the tubulointerstitium. The factors that have been considered to be of importance in the precipitation of these light chains are: (1) a total concentration of circulating immunoglobulin of more than 3.5 gm/dl; (2) lambda light chains are more likely to form dimers; (3) the more cationic the light chains, the greater the potential for precipitation and nephrotoxicity, possibly due to interaction with the anionic Tamm-Horsfall mucoprotein; (4) an acid urine favors precipitation; (5) dehydration by causing increased proximal salt and H₂O reabsorption results in higher concentrations in distal parts of the nephron; (6) the hyperviscosity itself can alter renal hemodynamics and cause increased proximal salt and H₂O reabsorption.

The other major factor that directly or indirectly contributes to ARF is hypercalcemia (vide infra). Additional factors that may contribute to ARF are hyperuricemia, infections, and contrast media.

In addition to the treatment of existent volume depletion, hypercalcemia, hyperuricemia, and maintenance of a relatively alkaline urine in myeloma patients at risk, plasmapheresis has been reported to be of benefit as an adjunct therapy for ARF.

Hypercalcemia

Acute renal failure has been described in various malignancies associated with severe hypercalcemia, multiple myeloma being the most frequent offender in hospitalized patients.^{4,49} However, severe hypercalcemia from any other nonmalignant disease can be associated with ARF. Hypercalcemia contributes to ARF by two distinct mechanisms.

Moderate chronic hypercalcemia decreases NaCl reabsorption in the loop of Henle and inhibits ADH action in the collecting tubules; both effects result in polyuria and a nephrogenic diabetes-insipidus-like state. The volume depletion resulting from these effects of hypercalcemia, and also from the often associated nausea, vomiting, and poor oral intake, predispose to ARF. Volume depletion also stimulates calcium reabsorption by the kidney and thus maintains hypercalcemia.

Severe hypercalcemia causes a reduction in RBF and GFR by direct effects of calcium on the renal microvasculature. The hemodynamic effects become marked when the serum calcium value exceeds 15 mg/dl and can result in "hypercalcemic crisis." Coma, oliguric ARF, and ventricular arrhythmias are characteristic features, and, if severe hypercalcemia is not treated on an emergency basis, it is uniformly fatal. The ARF results in a decrease in calcium excretion, leading to further hypercalcemia, which in turn causes further reductions in GFR, setting up a vicious cycle and contributing to the lethality of this disorder.

Since volume depletion perpetuates hypercalcemia, adequate hydration is an essential first step in the management of both acute and chronic hypercalcemia. If hypercalcemia is acute and symptomatic, loop diuretics should be administered to increase calcium excretion, with meticulous replacement of the ensuing fluid and electrolyte losses. Steroids should be given to decrease bone resorption and the gastrointestinal absorption of calcium. In cases with metastatic disease and bone resorption, mitamycin or calcitonin should be administered. Oral phosphate should be used to inhibit gastrointestinal absorption of calcium. In patients with ARF and/or a poor response to other modalities, dialysis, using fluids with a low calcium concentration, should be initiated. Hemodialysis is very effective in acutely reducing the serum calcium level and is the modality of choice in "hypercalcemic crisis."

Acute Uric Acid Nephropathy

Acute severe hyperuricemia resulting in ARF is usually seen when cell turnover is rapid and there is entry of nuclear proteins into the circulation. This usually occurs during treatment of myeloproliferative disorders. Massive amounts of uric acid are delivered to the distal nephron under these conditions. The decrease in pH and increase in concentration of urine that occurs in this part of the nephron reduce the solubility of uric acid, causing precipitation and nephron obstruction. The process should be suspected in the presence of serum uric acid levels of more than 20 mg/dl and/or a fractional excretion of uric acid of more than 100%.^{5,47,49}

Initiation of therapy with the xanthine oxidase inhibitor allopurinol, before the initiation of chemotherapy, will prevent most cases. Also, fluid volume replacement and induction of an alkaline diuresis with NaHCO₃ or acetazolamide (Diamox) will help prevent ARF. If ARF supervenes, hemodialysis is the treatment of choice, as it is extremely effective in acutely reducing uric acid levels.

Chemotherapeutic Agents

There is a growing list of chemotherapeutic agents that have the potential of causing nephrotoxicity.^{5,95} However, significant incidence of clinical ATN has been associated mainly with two agents: cisplatin and high-dose methotrexate. Adequate hydration and the maintenance of a brisk urine flow, in addition to alkalinization in the case of methotrexate, have resulted in a marked reduction in the incidence of ARF. Despite this reduction in the incidence of cisplatin-induced ATN, nephrotoxicity in the form of magnesium wasting, hypomagnesemia, and, occasionally, hypokalemia is still seen 10 to 14 days after chemotherapy in about 50% of the patients. Fortunately, this is easily treated, usually with oral magnesium supplementation, and it is not permanent.

Postoperative Acute Renal Failure

As expected, the incidence of ATN after major surgery varies with the nature and complexity of the surgery.^{4,18,44,96} It is most common after repair of aortic aneurysms, after cardiovascular surgery requiring extracorporeal circulation, and after major abdominal surgery. Acute tubular necrosis is likely to occur when the duration of suprarenal aortic cross-clamping exceeds 50 minutes or when cardiopulmonary bypass lasts longer than 160 minutes. Ischemia is thought to be the inciting event, although documented hemorrhage or hypotension can be incriminated in only 50% to 75% of the patients. In recent years, sepsis during the postoperative period has become a major cause of ARF in surgical patients. In general, postoperative ATN carries a high mortality that has shown little improvement over the years.

PREVENTION OF ATN SYNDROMES

No specific therapy is currently available for ATN syndromes. Therefore, the most effective approach is preventive, as a majority of cases occur in hospitalized patients. This requires identifying the patients at risk and avoiding the events that result in ARF. Even when such events are not avoidable, a recognition of the mechanisms by which ATN is produced by a given event or procedure can result in some amelioration of the severity of ATN in individual patients. The administration of allopurinol before initiating therapy of myeloproliferative disorders, following up levels of aminoglycosides in susceptible patients, and decreasing the dose of contrast media in patients with diabetes or multiple myeloma are obvious examples of this approach.

Several factors have been recognized that increase the predisposition to ATN. Preexistent prerenal hypoperfusion is the most important and potentially the most rectifiable of these, and it has been discussed earlier. An increased predisposition of patients with preexistent renal impairment has been observed in many clinical series.^{4, 5, 49, 94} The reasons are not clearly understood. In patients with glomerular or vascular diseases, this may be due to increased salt and H₂O reabsorption in the proximal nephron. An increased predisposition to nephrotoxic injury may be explainable on the basis of a greater nephrotoxin load per surviving nephron. An increased incidence and severity of ATN has also been noted in the elderly population. The reasons for this may be similar to those in patients with preexistent renal functional impairment. There is significant progressive nephron loss with advancing age, without a change in serum creatinine level because of concurrent loss of muscle mass. A rule of thumb for quantitating this loss of function is an approximate 10% loss of GFR for every decade after age 50. These patients also have a much higher incidence of vascular disease and arteriosclerosis, which may independently increase their risk. The latter may also be true for diabetic patients. It is possible that some of these risk factors are only associated with specific forms of ATN, but this has not been critically examined.

SPECIFIC PREVENTIVE MEASURES

Volume Expansion and Solute Diuresis

Although at present there are no specific measures that are consistently effective in preventing ATN, studies in experimental animals and empirical observations in humans have suggested that volume expansion is often successful in ameliorating the risk and severity of ATN. However, it should be clearly recognized that it is not the volume expansion per se, but rather the renal vasodilation and the as-

sociated decreased proximal reabsorption that are protective, i.e., the ability of the kidney to perceive the volume expansion and normally respond to it. This is often not achievable in patients with preexistent cardiac, hepatic, or renal diseases. Therefore, if volume expansion is attempted in these patients, it should be carefully monitored for the desired renal effects. A misplaced emphasis on continued volume expansion in the absence of an appropriate solute diuresis can be counterproductive in these patients. Such volume expansion adds the stress of fluid overload, which may precipitate or worsen congestive heart failure, exacerbate prerenal hypoperfusion, and therefore increase the risk of ATN. Other measures such as afterload reduction, administration of a low dose of dopamine (1 to 4 µg/kg/minute), or administration of other inotropic agents may be of greater benefit in such patients.

In experimental ATN, the use of mannitol has been associated with better protection than saline administration alone. Several factors may be involved: (1) mannitol leads to a greater volume flow through the proximal nephron because of its osmotic effects; (2) in renal hypoperfusion states, it has been shown to have greater renal vasodilatory effects; (3) it may minimize cell swelling after ischemia, although evidence is conflicting regarding this effect; (4) mannitol is a free radical scavenger and free radical injury has been postulated to play a role in ischemic ATN. The enthusiasm for the theoretical superiority of mannitol should be tempered by its greater potential for untoward plasma volume expansion. However, uncontrolled clinical observations suggest that it may be effective in certain selected circumstances. These include its administration before amphotericin B or cisplatin therapy, during high-risk surgery, or early in rhabdomyolysis before ATN becomes established.

Loop diuretics have also been recommended as potential protective agents, but there is no convincing evidence that they are effective. The reason may be that the site of action of these agents is beyond the proximal nephron. Loop diuretics can actually increase proximal reabsorption after the initial diuresis by causing volume depletion. This may account for the fact that their use has been associated with protection, no effect, or even increased severity of experimental ATN.^{1, 4, 26, 69, 77} Therefore, in the clinical context, it is recommended that they be used to prevent serious volume expansion and/or to induce a diuresis that is then maintained by replacement of urinary losses. Repeated use should be avoided, as it results in hypokalemia, alkalosis, and increased proximal reabsorption.

Experimental observations also suggest that a state of high fluid flow through the proximal nephron should be maintained before, during, and for at least several hours (probably 24 hours) after, the anticipated renal insult.^{60–62, 77} It has been suggested that there is a poorly defined time frame between ischemic injury and onset of es-

tablished ATN, during which administration of volume and/or mannitol may be ameliorative.^{4, 18, 19, 77, 90} While there is some supportive evidence for this in experimental myoglobinuric ARF, it does not seem to be true of other experimental ARF models. Clinical data to support this concept are scant and if such measures are undertaken early in the course after renal injury, meticulous monitoring is mandatory to avoid volume overload. It has also been suggested that early use of mannitol or large doses of potent loop diuretics will convert an oliguric ARF to nonoliguric ARF and thereby improve prognosis. There are no controlled studies to support this concept, and it is likely that these measures only result in identification of patients with less severe ATN.^{1, 4, 19} There is almost unanimous agreement that once ATN is established, such measures do not provide any significant benefit.^{4, 97, 98}

Other Measures

The use of several pharmacologic agents has been associated with partial amelioration of ATN in certain experimental animal models, especially when these agents have been used prior to, or simultaneous with, the initiating injury. These include theophylline, calcium-channel blockers, chlorpromazine, clonidine, ATP-MgCl₂, synthetic atrial natriuretic factor, thromboxane-synthesis inhibitors, and low-dose dopamine.^{42, 66-70, 99-102} To date, there are no controlled clinical studies. Their use is not recommended until such studies are performed as these agents have the potential of serious hypotension or other side effects. Previous studies with vasodilator agents in human ARF have shown little benefit even when RBF was increased.^{42, 45, 101} However, these agents primarily cause a dilatation of the efferent arteriole, and therefore would not be expected to increase the GFR, as discussed previously. It is possible that agents capable of causing afferent arteriolar dilation (atrial natriuretic factor, theophylline, and calcium-channel blockers) may be of benefit in certain selected clinical situations, but this remains to be established.

MANAGEMENT OF ESTABLISHED ARF

The general principles of management of patients with ARF have not changed substantially since the pioneering study of Swann and Merrill.⁸³ The following section emphasizes the salient aspects of management that are related to the ARF syndrome itself or to its impact on the management of the underlying disorders. Some of the pertinent issues related to specific syndromes of ARF have been dealt with earlier. The complications of ARF per se are related to a compromise of the three major aspects of renal function: (1) regula-

tion of the volume and composition of body fluids, (2) excretion of nitrogenous waste, and (3) synthesis of certain essential hormones.

It is important to appreciate that under normal circumstances, it is the intact regulatory ability of the kidneys, combined with other homeostatic mechanisms, that allows the body to deal with a very wide range of exogenous intake or endogenous production of many substances. This provides the physician with a great deal of latitude and room for error without major untoward effects. In contrast, ARF results in an impairment of renal ability to regulate the internal milieu or to deal appropriately and adequately with additional homeostatic stresses. These sometimes result from the unavoidable events associated with the underlying disease, but very often they stem from iatrogenic causes. Additionally, nonrenal homeostatic mechanisms may be impaired due to the associated diseases of other organ systems. Therefore, fluids, electrolytes, and other therapies in effect are being administered in a relatively "closed system." All the skills and judgment of the physician are called upon to substitute for the normal homeostatic mechanisms in each individual patient. It is at best a poor exchange but can be made much worse in the absence of meticulous care and attention.

The relatively "closed system" that the body becomes in the absence of renal excretory function is primarily reflected in the retention of all the substances that are dependent on renal excretion, such as water, electrolytes, and end-products of protein metabolism. The principles of medical management, therefore, are to meet the nutritional and metabolic needs of the patient, while the underlying disease is being treated. This should be done in a manner that minimizes the inevitable alterations in the volume and composition of body fluids, with recognition and treatment of the consequences of these alterations in as safe and effective a manner as is possible. The goal is to "buy time" during which the damaged kidneys can heal and recover. Very often the ideal and optimal therapy cannot be achieved and the physician has to reconcile conflicting needs, weighing the risk and benefits of each intervention. Frequent clinical and biochemical monitoring of the patient is mandatory during this period.

General Fluid and Electrolyte Balance.—The principles of fluid and electrolyte therapy are the time-honored ones of (1) repair of existent deficits, (2) provision for normal losses, and (3) replacement of ongoing abnormal losses. This requires an accurate quantitation of each component. Whenever possible, the composition of abnormal fluid losses should be determined. The variable amount of insensible losses through sweat and respiration (500 to 1,200 ml) and the H_2O produced from normal endogenous catabolism (400 ml in patients without hypercatabolic states) should be taken into account

in deciding on fluid therapy. A general guideline for basal needs that must be adapted to the individual metabolic status is 500 ml plus urine output. However, obligate fluid administration because of vasoconstrictor agents, antibiotics, or nutritional needs prevents this goal from being met, except in the patients with relatively uncomplicated and brief ARF. The limitation of body weights in judging fluid balance should be recognized, as ongoing tissue catabolism in a patient without food intake causes a daily loss of 0.2 to 0.5 kg of real body weight. A stable body weight may therefore indicate a gradual expansion of total body fluids. Oliguric patients are particularly prone to develop volume overload and hyponatremia.

The distribution of body fluids into the plasma, extracellular, and intracellular compartments is often altered in critically ill patients. Additionally, there is often sequestration of body fluids into third spaces that sometimes makes it difficult to assess the plasma volume status clinically. In these patients, measurement of central venous and/or pulmonary capillary wedge pressures with a Swan-Ganz catheter is of great value in guiding fluid therapy.

Potassium Metabolism.—Potassium intake must be severely restricted in most patients with ARF; often this is sufficient to prevent hyperkalemia. However, patients who are hypercatabolic and acidotic (sepsis) or who have increased cell destruction (rhabdomyolysis, hemolysis, tumor lysis syndrome) often present with dangerous hyperkalemia and require emergency treatment in the form of glucose and insulin, NaHCO_3 , calcium salts, and potassium exchange resin (kayexalate) therapy. Long-term control in patients with ATN syndromes often requires dialysis. Hyperkalemia is unusual in patients with prerenal etiologies or those with glomerular and vascular diseases since tubular potassium secretory ability is preserved and increased levels of aldosterone are usually present. If hyperkalemia occurs in such patients, additional factors should be sought. These patients, as well as certain patients with interstitial nephritis, will often respond to large doses of loop diuretics with an increase in potassium excretion.

Acid-Base Balance.—Normally 1 to 2 mEq/kg of nonvolatile acids are produced every day from metabolic sources. Since the kidneys are responsible for the daily excretion of this acid load, H^+ accumulation is a predictable consequence of ARF, especially in ATN syndromes. Although patients with ATN are able to acidify their urine to a pH of 5.0 to 5.5, the net amount of H^+ excreted (bicarbonate generated) is too small to maintain H^+ balance. This usually results in a fall in bicarbonate concentration of 1 to 2 mEq/day. When acid production is increased due to the underlying diseases or hypercatabolism, the problem is magnified and larger falls in bicarbonate concentration are seen. The acidosis, because of the decreased

excretion of unmeasured anions such as sulfates, phosphates, and urates. However, acidemia is usually not progressive after bicarbonate levels fall to about 15 mEq/L, as the additional production of acid is buffered by bone salts. Therefore, NaHCO_3 is usually not required in the acute situation unless acidosis is severe and associated with hyperkalemia. In addition to the volume overload, NaHCO_3 therapy can have deleterious consequences on the level of ionized calcium (vide infra). When severe acidosis is present, it usually requires dialytic therapy.

Calcium and Phosphorus Balance.—The decreased excretion of phosphate by the kidney results in hyperphosphatemia. This results in a reciprocal decrease in the serum level of calcium and causes secondary hyperparathyroidism. Clinical manifestations of hypocalcemia are not usually seen in patients with untreated ARF because coexistent acidosis increases the fraction of the total calcium that is in the ionized form. Therefore, correction of the acidosis can precipitate tetany. Gastrointestinal absorption of calcium is decreased because of reduced synthesis of $1,25(\text{OH})_2 \text{Vit D}_3$ and this contributes further to the hypocalcemia. Despite the lower serum calcium levels, severe hyperphosphatemia can increase the calcium X phosphate product to more than 70. This increases the potential for metastatic calcification of tissues, including the cardiac conduction system. This danger limits the ability to administer calcium for hypocalcemia, unless phosphate levels are controlled first. Phosphate binders can be used to limit its absorption from the gastrointestinal tract, in patients who still have an oral intake. However, in other patients, dialysis may be the only effective way to maintain acceptable phosphate levels. Magnesium levels are also increased moderately in ARF but usually do not require any therapy beyond restriction of intake.

Hyperuricemia.—Uric acid levels are moderately elevated in most cases of ARF because of decreased excretion. This does not merit specific therapy except in states of excessive cell destruction, when therapy with allopurinol or dialysis may be necessary.

Complications of Uremia.—As alluded to before, the pathogenesis of the uremic syndrome is poorly understood and the uremic toxins have not been identified. Although increases in serum creatinine levels are a better marker of the severity of failure of glomerular filtration, increases in BUN values are usually a better marker of the severity of the uremic syndrome; this suggests that the uremic syndrome is somehow related to retention of breakdown products of protein metabolism. Empirical observations suggest that uremic symptoms correlate roughly with the level of BUN, and generally an increasing incidence is observed after the BUN level exceeds 100 mg/

dl. When the rate of increase is particularly rapid, uremic symptoms may be seen with a lower BUN level.

Gastrointestinal symptoms are among the more common manifestations and include anorexia, nausea, vomiting, and diarrhea in mild cases. In more severe cases, diffusive erosive gastritis, stress ulcers, or uremic colitis may be seen. Gastrointestinal hemorrhage is a major cause of morbidity and mortality in ARF.

Gastrointestinal bleeding is but one manifestation of a uremic bleeding diathesis. This is in large part due to defective platelet function and is reflected in a prolonged bleeding time. The pathogenesis of platelet dysfunction is not completely understood, but in some patients it is reversed by aggressive dialysis. Other patients have been helped by the administration of the vasopressin analogue desmopressin acetate (DDAVP). Anemia is another hematologic complication of uremia, and its pathogenesis includes hemodilution, gastrointestinal blood losses, decreased red blood cell survival, decreased erythropoietin production by the kidney, and partial resistance of the bone marrow to erythropoietin.

Neurologic complications are variable and range from altered mentation and lethargy to coma and seizures. Most of the cardio-pulmonary complications are related to volume overload or pneumonia but, on occasion, pericarditis, pleuritis, and ascites are also observed. The pathogenesis of this serositis is poorly understood. In general, most of these complications respond to dialysis.

Infections represent the second major cause of morbidity and mortality in ARF and occur in 50% to 75% of the patients.^{4,5,19} The presence of multiple vascular access lines is an important factor. Other frequent sites are the lungs, urinary tract, and wounds. A variety of abnormalities in the immune response and leukocyte function have been described, but their precise pathogenesis and relationship to infection in the uremic patient are poorly understood.

Dialysis.—Peritoneal or hemodialysis are both reasonably effective substitutes for renal excretory function, while awaiting recovery of renal function.⁴

The indications for dialysis are (1) emergent treatment for severe volume overload, hyperkalemia, and acidosis refractory to conventional management; (2) appearance of uremic symptoms; (3) acute uric acid nephropathy or the presence of other dialyzable nephrotoxins such as ethylene glycol. Early "prophylactic" dialysis has been advocated to prevent uremic complications from occurring. Despite the plausibility of the rationale, prospective studies have not shown a consistent benefit.^{4,103} At present, most nephrologists use an empirical approach that lies somewhere between early and vigorous prophylactic dialysis and waiting for the onset of uremic symptoms.

While dialytic therapy represents a major advance in treatment of ARF, it is not an entirely benign procedure, and each modality carries its own relative benefits and risks. Peritoneal dialysis is relatively more safe and hemodynamically gentler on the patient, and therefore can be performed in the presence of hemodynamic instability.¹⁰⁴ It is quite effective for fluid removal, but its ability to remove potassium and uric acid is more limited. Peritonitis is the major complication with its use. On the other hand, hemodialysis is the modality of choice for rapid correction of hyperuricemia or removal of toxins. However, such vigorous change in the composition of the blood sometimes causes neurologic signs and symptoms referred to as "disequilibrium syndrome." Vascular lines of access to systemic circulation and anticoagulation are needed for hemodialysis, with the attendant risks of bleeding, thrombosis, and infections. Hypotension and cardiovascular instability are frequent and therefore limit the use of hemodialysis in patients with hemodynamic instability. Recently, the modality of continuous arteriovenous hemofiltration has been introduced in such patients. Large volumes of fluid are ultrafiltered through high efficiency dialyzers with concurrent replacement by saline solutions.¹⁰⁵

Nutritional Considerations.—The ideal goal of maintaining positive caloric and nitrogen balance is difficult to achieve in patients with ARF.^{4, 106, 107} The major limitations arise from (1) the amount of fluid that can be administered without causing serious volume overload and (2) the risk of excessive retention of nitrogen breakdown products and solutes that can occur when a positive nitrogen balance is attempted.

Minimal caloric needs can be met by providing at least 100 gm of carbohydrate per 24 hours. This markedly reduces endogenous protein catabolism and therefore limits the increases in levels of BUN, creatinine, phosphorus, potassium, uric acid, and the uremic symptomatology. This can be achieved either enterally or by intravenous (IV) administration of 500 ml of 20% glucose. It is probably desirable to attempt to provide additional calories that further reduce the need for protein as an energy source, although an optimal caloric intake has not been established and probably varies with the metabolic status of the patient. In any case, probably no more than 1,500 to 2,000 calories are either necessary or achievable without significant cost in volume and solute loads. The source of these additional calories should be a mix of carbohydrate, fat, and protein if enteral nutrition is possible. The protein source should provide the essential amino acids and probably should not exceed 20 to 40 gm/day.

In case enteral nutrition is not feasible, parenteral alimentation with a mixture of glucose and essential amino acids can achieve a positive nitrogen balance. The initial reports suggested that this was

associated with a reduction in mortality in patients with severe complicated illnesses, but subsequent studies have been unable to demonstrate an effect on mortality, even though a positive nitrogen balance was achieved. The potential benefits of a positive nitrogen balance must be weighed against the significant risks that are associated with parenteral hyperalimentation. The obligate daily administration of 1 to 3 L of fluid often requires more intensive dialysis with its attendant risks, the risk of sepsis from an indwelling central catheter and the solute loads that are imposed. In this context, it must be remembered that urine osmolality in ARF is relatively fixed at isosmolarity (300 mOsm/kg). This implies that with a 500-cc urine volume, only 150 mOsm can be excreted per day and that it would require a urine output of 2 L to excrete the average daily solute load (600 mOsm), even in the absence of a hypercatabolic state. Therefore, it is not difficult to see that solute retention is almost inevitable with either oliguria or with a hypercatabolic state. It may be counterproductive to provide protein supplements, even in hypercatabolic states, beyond the minimum necessary (probably 0.3 gm/kg) through parenteral hyperalimentation if this results in solute retention and a disproportionate elevation in the BUN level. Therefore a good index to follow when providing exogenous protein in parenteral or enteral hyperalimentation is to avoid disproportionate increases in BUN level (more than 15 to 20 mg/dl/day).

Altered Drug Metabolism.—Many drugs are excreted in the urine by glomerular filtration and/or tubular secretion. The impairment of both of these processes in ARF results in significant alterations in the pharmacokinetics of these drugs.^{4, 5, 101, 108} The consequent alterations in peak drug levels and/or duration of action increase the potential for drug toxicity. Therefore, many drugs should be avoided, or their dosage and frequency of administration should be adjusted. It must be emphasized that the formulas for adjusting drug dosage in renal failure are based on serum creatinine concentration. This is appropriate in patients with chronic renal failure and stable creatinine levels, because in such steady states serum creatinine is a reasonably accurate indicator of the creatinine clearance (i.e., GFR). This is obviously not true in ARF, when serum creatinine levels are changing and have little relationship to the GFR. Therefore, drugs should be administered based on monitoring of blood levels. If that is not possible, GFR of 5 ml/minute for (oliguric) and 10 ml/minute (nonoliguric) should be assumed in established ARF.

Avoidance of Hypotension and/or Other Nephrotoxic Injuries.—There is experimental evidence that RBF autoregulation is impaired in experimental ischemic ATN.^{109, 110} It has been suggested that impaired autoregulation makes the patient with ARF more susceptible to further ischemic injury, even with mild hypotension. The patho-

genesis of impaired autoregulation probably involves the persistent constriction of the afferent arteriole such that it does not dilate normally in response to decreases in perfusion pressure. However, despite the plausibility of this concept, empirical observation suggests that second episodes of ATN are uncommon during the maintenance or early recovery phases.¹⁹ Perhaps the recovering tubular epithelium is resistant to further injury by the same or different nephrotoxins.^{19, 111} However, this cross-resistance may not be uniform, and it is prudent to avoid further ischemic and/or nephrotoxic injury.

PROGNOSIS

Despite the impressive advances in dialytic techniques, the overall survival rate of patients with ARF has stayed around 50%, although some recent series have reported better results.^{4, 19, 44, 112, 113} It is difficult to analyze such overall mortality data, since the composition of patients, the etiology of ARF, the underlying illnesses, and the complications may all have major impact on survival rates. These analyses, however, do indicate that the patient population with ARF is presently older and generally has more serious associated illnesses. Since these factors are in general associated with a worse prognosis, it is possible that some of the improvement in the prognosis of ARF has been obscured. Moreover, it is difficult to ascribe the cause of death with any degree of certainty to any one of the many concurrent medical and/or surgical disease processes that are present in a patient with ARF. Most patients die with ARF and not of ARF. The impact of such factors is underscored by the fact that in one series the mortality of patients less than 25 years old was dramatically lower than that of patients over 40 years old (10.5% vs. 67%). Similarly, mortality for ARF in the younger pregnant population generally has averaged about 17%. Similar, although less striking, differences have been noted in other series with advancing age and an increase in associated illnesses. In addition to age and underlying illnesses as major prognostic factors, the nature of complications greatly influences the mortality. The complications that are most often associated with an adverse outcome are sepsis, cardiac or respiratory failure, and gastrointestinal bleeding.

Patients who survive the acute illnesses usually attain normal levels of serum creatinine, except for the patients with cortical necrosis in whom residual deficits are much more frequent. A normal serum creatinine level, however, may not be a totally valid index of complete recovery. A loss of 20% to 30% of the nephrons can be masked by compensatory hyperfunction of the remaining nephrons. The degree of loss seems variable depending upon the etiology but is more

likely to occur after ischemic injury. A morphological correlate may be a severe and extensive loss of basement membranes with widespread tubulorrhexis.

Most of the patients who recover completely or who show only mild residual impairment of renal function remain stable without further problems. However, in patients with cortical necrosis when significant amounts of functional renal mass may be permanently lost, proteinuria, hypertension, and progressive renal insufficiency have often ensued. Recent investigations have resulted in a great increase in understanding of the progression of renal disease and have suggested therapeutic interventions that ameliorate this process.^{114, 115} It is hoped that the ongoing investigations in the pathogenesis of ATN syndromes will result in a similar favorable outcome in the near future.

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