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NEPHROLOGY FORUM

Acute renal failure

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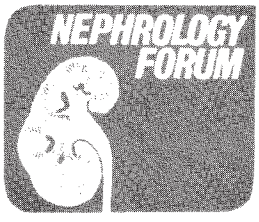
The *Nephrology Forum* is designed to relate the principles of basic science to clinical problems in nephrology.



Case presentation

An 85-yr-old woman was transferred to New England Medical Center Hospital (NEMCH) for management of acute renal failure (ARF). The patient was in apparent good health until 3.5 weeks earlier when she had a uterine prolapse and was admitted to another hospital. Her blood urea nitrogen (BUN) concentration, serum creatinine concentration, and results of urinalyses were normal. An electrocardiogram (EKG) revealed an old inferolateral myocardial infarction. The patient underwent a vaginal hysterectomy; in the immediate postoperative period she complained of chest pain. Over the week following the operation, EKG changes revealed the evolution of a new anterior myocardial infarction. During this same interval, several blood transfusions were required because of persistent vaginal bleeding. During one of these transfusions approximately 10 days prior to transfer to NEMCH, the patient developed a fever (41° C), shaking chills, and hemoglobinuria. She was treated with Benadryl and Solu-medrol. EKG revealed new Q waves in the inferior leads. Clindamycin, gentamicin, and nafcillin were also administered at this time. Over the next 10 days, urine output decreased, and the serum creatinine concentration increased. A Giovanetti diet and fluid restriction were instituted; the antibiotics were continued but in reduced dosage. Urine output remained in the range of 200 to 300 ml/day. At the time of transfer to NEMCH, the serum creatinine concentration was 12 mg and the BUN concentration was 130 mg/100 ml.

On admission to NEMCH, physical examination revealed the following: blood pressure, 170/80 mm Hg; temperature, 38.5° C; pulse, 68/min; respirations, 20/min; the skin had an erythematous maculopapular rash over the trunk; head, ears, eyes, nose, and throat were within normal limits; no jugular venous distention; the lungs had bibasilar dry rales and decreased breath sounds bilaterally with diffuse expiratory wheezes. Cardiac examination revealed a diffuse point of maximal impulse in the midclavicular line with no heave; normal S1 and S2; a grade II/VI systolic ejection murmur along the lower left sternal border; and no thrills rubs, or gallops. Abdominal and neurologic examinations were unremarkable. Pelvic examination revealed no masses or tenderness. There was no peripheral edema. Laboratory findings disclosed the following data: hemoglobin, 10.5 g/100 ml; hematocrit, 30%; white blood cell (WBC) count, 7,200 mm^3 with a normal differential; serum sodium, 129 mEq; serum potassium, 5.6 mEq; serum chloride, 95 mEq; total carbon dioxide, 14 mEq/liter; BUN, 132 mg; serum creatinine, 12.9 mg; serum calcium, 7.8 mg; serum glucose, 82 mg/100 ml; arterial oxygen tension, 81 mm Hg; arterial carbon dioxide tension, 28 mm Hg; arterial pH, 7.29. EKG revealed a normal sinus rhythm at the rate of 70/min; a prominent Q wave in lead 3; and biphasic Q waves in AVL, V3, and V4. Results of urinalyses revealed the following: pH, 5; many red blood cells (RBC); a few WBC; and a few tubular epithelial cells. A radiograph of the chest revealed the trachea to be deviated slightly to the right and a few old calcified granulomas. Renal scan and abdominal echogram revealed bilateral kidneys of normal size and no evidence of obstruction.

For the first 36 hours of hospitalization, the patient underwent peritoneal dialysis (approximately 30 exchanges) during which the BUN concentration decreased to 59 mg and the serum creatinine concentration to 9.4 mg/100 ml. Following dialysis, the patient's serum creatinine concentration increased slightly to 10.1 mg/100 ml; it then decreased over the next 2 weeks to 1.9 mg/100 ml. The patient was discharged 17 days following admission.

Discussion

DR. R. W. SCHRIER: This 85-yr-old patient underwent a vaginal hysterectomy complicated by an anterior myocardial infarction and some postoperative bleeding, which required blood transfusions. One of these transfusions was accompanied by fever, chills, hemoglobinuria, and possibly another myocardial infarction. In addition to treatment of the presumed transfusion reaction with Benadryl and Solu-medrol, several antibiotics (clindamycin, gentamicin, and nafcillin) were started. Immediately after this transfusion episode, the patient's serum

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creatinine concentration began to rise progressively, as her urine output remained in an oliguric range (<400 ml/24 hr). Ten days after the transfusion reaction, the patient was transferred to NEMCH with a serum creatinine concentration of 12 mg/100 ml and a BUN concentration of 130 mg/100 ml. The positive findings of the physical examination were a maculopapular rash of the trunk, bibasilar dry rales, and a systolic murmur. The laboratory findings were compatible with uremic metabolic acidosis and also revealed hypocalcemia, hyponatremia, and hyperkalemia. Results of urinalysis demonstrated hematuria and pyuria.

Predisposing factors. This patient was predisposed to develop ARF for several reasons: *(1)* advanced age, *(2)* persistent bleeding with probable hypovolemia, *(3)* recent myocardial infarction, and *(4)* recent anesthesia.

It is known that ARF occurs more frequently in older individuals, and that the mortality rate associated with ARF is higher than in other age groups [1]. Renal function is known to deteriorate with age, so that an 85-yr-old person is normally expected to have a creatinine clearance of only some 45 ml/min [2]. It also is possible that advancing age impairs the protective mechanisms of renal autoregulation and renal prostaglandin release, which are evoked during vasoconstrictive insults, but this speculation remains to be studied. Moreover, it is important to recall that the presence of inhibitors of prostaglandin synthesis (e.g., aspirin, indomethacin, phenylbutazone, ibuprofen, and naproxen), which are widely used for treatment of arthritis in the aged, may predispose the kidney to more severe ischemia whenever a hemodynamic insult occurs [3, 4].

The patient described here had continued bleeding prior to the episode of hemoglobinemia and hemoglobinuria. Experimental evidence in AFR models indicates that fluid deprivation and volume depletion potentiate the development of pigment-induced (hemoglobin, myoglobin) ARF [5].

The postoperative complication of myocardial infarction must be considered in this patient's course toward ARF. A myocardial infarction can result in renal ischemia if the degree of myocardial dysfunction and decrease in cardiac output is sufficiently great. If cardiac failure occurs, however, the concomitant increase in left atrial pressure may exert an early protective effect on renal function. An increase in left atrial pressure initiates a reflex that decreases renal sympathetic tone and tends to vasodilate the kidney [6]. This phenomenon may account for the clinical aphorism that patients with an acute myocardial infarction do not develop ARF. This is of course not an absolute dictum; it is true, however, that for a given decrement in blood pressure, the degree of renal ischemia is less during cardiac failure (increase in left atrial pressure) than it is during hemorrhage (decrease in left atrial pressure) [7]. Finally, the occurrence of hematuria and renal functional deterioration in association with a recent myocardial infarction should always alert the clinician to the possibility of a mural thrombus with emboli to the kidney. Cardiac ultrasound and a renal scan are valuable tools for the detection of this disorder.

Whenever renal failure follows a recent operative procedure, it is important to discern whether the anesthetic used might be contributing to renal difficulty. Halothane and methoxyflurane are the anesthetics most frequently mentioned as potential etiologic factors in causing renal deterioration [8, 9]. The renal toxicity of halothane is generally associated with hepatic damage and with the consequent release of tissue thromboplastin, which is then followed by intravascular coagulation and renal cortical necrosis. The renal toxicity of methoxyflurane appears to relate more closely to the resulting increase in plasma fluoride concentration than to the increase in oxalate excretion [9]. If microsomal enzymes in the liver have been induced by previous use of the anesthetic or by phenobarbital administration, then repeat exposure to methoxyflurane may result in more rapid metabolism of the drug and a higher concentration of plasma fluoride. Enflurane, a fluoride-containing anesthetic, releases less fluoride on metabolism than methoxyflurane; this probably explains the agent's lower renal toxicity [10]. It is interesting, however, that renal toxicity with enflurane has been described in the setting of prior use of the anesthetic and a high plasma fluoride concentration [11]. In the patient we are discussing here, although we are not told the nature of the anesthetic used, the length of time between the operation and the onset of renal failure would dismiss the anesthetic as a primary cause of renal failure. If reoperation for continued vaginal bleeding had become necessary, however, it would be important to know if a fluoride-containing anesthetic had been used in the earlier operation. An elevated serum fluoride concentration may persist for a week after methoxyflurane administration [10]; whether such elevation predisposes the kidney to toxicity with other nephrotoxic agents remains to be studied.

Etiologic factors. As is often the case, this patient

not only had several factors predisposing her to develop ARF, she also encountered multiple agents and conditions of potential importance in the etiology of ARF; these include *(1)* nephrotoxic aminoglycosides, *(2)* penicillin homologues capable of triggering acute interstitial nephritis, *(3)* recurrent acute myocardial infarction, *(4)* septicemia, and *(5)* transfusion reaction with hemoglobinuria.

The aminoglycosides have become the most relied on antibiotics in the treatment of gram-negative bacterial infections. The aminoglycoside introduced first, neomycin, has been restricted to oral or topical use because of its nephrotoxic potential. The aminoglycosides now used are less nephrotoxic but all of them, including kanamycin, gentamicin, amikacin, sisomicin, and tobramycin, can cause impairment in renal function. One of the newest aminoglycosides, netilmicin, may offer the hope of a comparable antimicrobial spectrum with less nephrotoxicity [12]. The nephrotoxicity of the aminoglycosides probably relates to tissue-binding of the drug in the renal cortex [13], and the degree of tissue-binding appears to correlate with the number of free amino groups contained in a given agent [14]. Strikingly, the most nephrotoxic aminoglycoside, neomycin, has six free amino groups, and the least nephrotoxic, streptomycin, has only two free amino groups. Aminoglycosides remain bound to renal tissue long after the antibiotic has disappeared from the circulation; the half-life of aminoglycosides in serum is 30 min, but in renal tissue it is 109 hours [15]. Four weeks after a single injection of gentamicin in the rat, a therapeutic tissue concentration of 6 μg/g of tissue may persist [16]. This long tissue half-life no doubt explains why the onset of renal failure secondary to aminoglycosides has been reported to occur as late as several days after administration of the antibiotics has been discontinued. Cytosomes containing altered cell organelles (lysosomal cytosegrosomes) and lysosomal ingestion of phospholipid membranes (myeloid bodies) are characteristically found in the proximal tubular epithelium of patients treated with aminoglycosides; these anatomical changes, however, do not necessarily correlate with the degree of renal functional impairment [17].

Several factors are known to predispose patients to the development of aminoglycoside nephrotoxicity: *(1)* advancing age, *(2)* preexistant renal dysfunction, *(3)* volume depletion, *(4)* recent exposure to aminoglycoside or another nephrotoxic agent. The older the patient is, the greater the likelihood that aminoglycoside toxicity will occur [18]. This effect may be partially explained by the failure of clinicians to decrease the drug dosage in proportion to the decrease in glomerular filtration rate (GFR) that occurs with age. Preexisting renal dysfunction is another factor that predisposes patients to aminoglycoside nephrotoxicity [18]. Sodium restriction and volume depletion increase the incidence of aminoglycoside nephrotoxicity presumably because they serve to increase the cortical concentrations of the drug [19]. In one study, the incidence of aminoglycoside nephrotoxicity increased from 7 to 22% in patients who had recent exposure either to aminoglycosides or to other potentially nephrotoxic agents [18]. The patient described here was elderly, probably was somewhat volume depleted because of continued bleeding, may have been recently exposed to a nephrotoxic anesthetic, and was treated with the combination of gentamicin and clindamycin. It has been suggested that the latter agent may increase the nephrotoxic effect of aminoglycosides [20]. Furosemide administration frequently potentiates aminoglycoside nephrotoxicity probably because of the diuretic's potent volume-depleting effect [21]. The ability of cephalosporins to increase aminoglycoside renal toxicity is not as well established; in fact, the results of one experimental study even suggest that cephalosporins decrease renal cortical tissue concentrations of aminoglycosides and thus protect against nephrotoxicity [22].

The clinical course of aminoglycoside nephrotoxicity is, however, quite different from that observed in this patient. The nephrotoxic effect of aminoglycosides is generally gradual in onset and related to the dose and duration of drug administration [23]. A nonoliguric, self-limited form of ARF with a low mortality is most common with aminoglycoside nephrotoxicity [24]. It would be extremely rare for one to two doses of the drug to cause acute onset of oliguria and azotemia, as was observed in the patient presented here. In general, proteinuria, lysozymuria, and a renal concentrating defect with polyuria precede any decrease in GFR with aminoglycoside toxicity [13]; azotemia and glucosuria are later consequences of toxicity [25]. Since aminoglycosides are eliminated primarily by glomerular filtration, whenever serum creatinine concentration increases, the "trough" concentration of the antibiotic will also increase unless the dose has been altered. Thus, the serum creatinine concentration can be used to gauge the "trough" concentration of serum aminoglycoside when the latter measurement is unavailable.

Acute interstitial nephritis has become a more

frequently recognized cause of ARF. The drugs associated with this renal hypersensitivity reaction include sulfonamides, sulfonamide diuretics, furosemide, diphenylhydantoin, cephalosporins, phenylbutazone, allopurinol, phenindione, rifampin, penicillin and penicillin-homologues [26–32]. These reactions are generally associated with increased eosinophils in blood and urine: A Wright's stain of the urine is useful in detecting the eosinophiluria. Fever and skin rash are also frequent findings. This elderly woman received nafcillin and had a skin rash, thus suggesting the possibility of interstitial nephritis. The patient's fever, however, preceded the occurrence of the ARF. The immediate onset of the oliguria on the first day of penicillin homologue administration would be rare unless an amnestic reaction had occurred. No previous history of penicillin allergy, however, was noted. The patient's pyuria and hematuria are compatible with the diagnosis of acute interstitial nephritis.

The possible occurrence of another myocardial infarction, as evidenced by the finding of new Q waves, and septicemia also may have contributed to the ARF. Although fever and shaking chills occurred during the administration of a blood transfusion, other causes of fever must be considered. Culture of both the patient's blood and the transfused blood would have been helpful. ARF associated with septicemia is more common in the older age group. Immune complex glomerular disease associated with bacterial endocarditis [33] and abdominal abscesses [34] also might be considered, but again the rapidity of the onset of ARF in this patient makes both of these possibilities unlikely. A decrease in serum complement concentration, RBC casts in the urine, and positive blood cultures are important diagnostic features of diffuse proliferative glomerulonephritis associated with bacterial endocarditis [33]; none of these were noted in this patient. In patients with abdominal abscesses, however, neither positive blood cultures nor decreased serum complement concentrations are consistent findings [34].

Despite the profusion of potential predisposing and etiologic factors, the temporal association between the transfusion reaction with hemoglobinuria and the onset of oliguria provides the most likely explanation for the ARF in this patient. It is noteworthy that hemoglobin infusion alone has not provided a reproducible model of ARF; it appears that the addition of RBC stroma, or prior volume depletion, or both may play a critical role [35]. It is also important to emphasize that the presence of a benzidine positive pigment in the RBC-free supernatant of the urine does not distinguish between hemoglobinuria and myoglobinuria. Myoglobinuria has come to be recognized more frequently as a cause of ARF [36]; as with hemoglobinuria, however, predisposing factors are important. Since myoglobin (mol wt, 17,000 daltons) is much smaller than hemoglobin (mol wt, 69,000 daltons) and since only hemoglobin has a plasma binding protein (haptoglobin), the plasma is generally pink with hemoglobinemia and its normal straw color with myoglobinemia. Muscle damage secondary to pressure or trauma, viral infections (e.g., influenza), acute hypophosphatemia, hypokalemia, alcoholism, and heroin abuse are examples of important clinical settings in which myoglobinuria may occur. A substantial elevation in the activity of the muscle enzymes (aldolase, creatinine phosphokinase) is a hallmark of this condition. Unless a sensitive immunologic test is available, it may be very difficult to establish the presence of myoglobinuria with certainty; therefore, the diagnosis is generally inferred by the presence of a benzidine-positive pigment in the urine in the face of normal appearing serum, elevated muscle enzyme activity in the plasma, and a proper clinical setting.

Pathophysiology of ARF. In keeping with the many predisposing and etiologic factors in ARF, the pathophysiology of this condition also appears to be multifactoral. This may be the reason why the pathophysiology of ARF has escaped clear delineation despite vigorous investigative efforts by many researchers over the past two decades. Some advances in our understanding of ARF, however, have been made. As implied, it now seems unlikely that any single pathogenetic sequence will account for all varieties of ARF. In addition, it is important to distinguish between initiating and maintenance factors in considering the pathogenesis of ARF. Until recently, the apparent absence of elevated intratubular pressures in a variety of experimental models of ARF and the presence of decreased renal blood flow (RBF) led many investigators to use the term "vasomotor nephropathy" to highlight the vascular role in the pathogenesis of ARF [37]. While vascular events are no doubt involved in the initiation of ARF, the maintenance of ARF probably cannot be explained solely by ischemic events. This tentative conclusion is based primarily on the finding that neither spontaneous nor pharmacologic restoration of normal RBF in man [38] or experimental animals [39, 40] is capable of reversing the ARF. It is possible, however, that persistent af-

ferent arteriolar constriction and efferent arteriolar dilatation obviates restoration of glomerular filtration pressure despite such restoration of RBF, and thus maintains the near absence of GFR.

Two recent findings have breathed new life into the theory that ARF is dependent on intratubular obstruction. *First,* the experimental model of ARF produced by renal artery-clamping in the rat has been found to be associated consistently with elevated intratubular pressures [41, 42]. *Second,* and perhaps most important, when RBF is restored in experimental models of ARF, elevations in intratubular pressures are uncovered that were not detectable in the presence of continued renal ischemia [43, 44]. These findings are compatible with the notion that relative tubular obstruction is an important factor in the maintenance of ARF.

The possibility that a decrease in glomerular permeability may contribute to the pathogenesis of ARF has been raised by the finding on scanning electron microscopy of "smudging" of glomerular epithelial podocytes in a model of ARF produced by high-dose norepinephrine [45]. The high doses of norepinephrine used in these studies however caused *irreversible* renal failure. When the dose of norepinephrine is decreased to produce a reversible form of ARF, there are no detectable changes in the ultrastructural appearance of the glomerular epithelium [46, 47]. Recent studies by scanning electron microscopy of kidneys from patients with ARF have also failed to demonstrate any consistent glomerular abnormalities [48]. Although some direct micropuncture studies have found modest changes in glomerular permeability in experimental ARF [44, 49], it seems unlikely that this factor is of primary importance in the pathogenesis of ARF.

It has become common practice to use the histologic term, acute tubular necrosis (ATN), and the clinical term, ARF, synonymously. Histologic studies, however, suggest that actual necrosis of tubular cells may, in fact, be present in only 10 to 20% of patients with clincial ARF [50]. The assumption that tubular necrosis was more common may have prompted the suggestion that excessive "back-leak" of glomerular filtrate across damaged tubular epithelium contributes importantly to the pathogenesis of the oliguria of ARF. Such "back-leak" has been documented in a few instances in experimental models of ARF, but generally only when severe tubular necrosis is produced [51–53]. Such a degree of tubular necrosis, however, does not occur in clinical ARF in man even when caused by nephrotoxic agents. Moreover, chronic saline loading [54] and the administration of mannitol [46] or furosemide [55] respectively can prevent the experimental ARF ordinarily induced by either mercuric chloride or norepinephrine, but do not prevent the associated tubular necrosis.

In summary, an interaction between vascular and tubular factors seems likely to be involved in the pathogenesis of ARF. An initial vascular insult may lead to events that cause relative tubular obstruction, perhaps secondary to impacted cytoplasmic blebs [56], and thereby maintain ARF. Changes in glomerular permeability and excessive "back-leak" across damaged tubular epithelium also may be contributing mechanisms, particularly when accompanied by severe ischemic insults. In this regard, the degree of involvement of any of these potential pathogenetic factors of ARF varies depending on the nature, severity, and duration of the initial insult.

Clinical diagnosis of ARF. The clinical approach to the diagnosis of ARF must focus primarily on the exclusion of immediately reversible prerenal or postrenal factors [57]. Thus, ARF is a diagnosis of exclusion. Volume depletion, cardiac failure, and peripheral vasodilatation are the principal factors that may cause renal hypoperfusion and thus prerenal azotemia. Prolonged prerenal azotemia is probably the most common cause of ARF. Next, postrenal or obstructive factors must be excluded as a cause of azotemia. A postvoid urethral catheterization to assess residual bladder urine volume is used to exclude bladder neck or urethral obstruction. A flat plate radiograph of the abdomen can detect the 90% of renal calculi that are radiopaque. As used in the patient described here, renal ultrasonography and renal scan are noninvasive procedures, which are useful in assessing the presence of upper urinary tract obstruction. Since the infusion of radiopaque contrast media has been reported with increasing frequency to cause or worsen ARF, high-dose i.v. pyelography must be used with caution to exclude urinary tract obstruction [58]. Patients with diabetes [59], and those with hyperuricemia or multiple myeloma [60] are particularly prone to develop ARF following administration of radiographic contrast media. The factors that predispose the diabetic patient to ARF following the use of radiocontrast media are (*1*) age greater than 55 years, (*2*) presence of renal insufficiency, (*3*) the presence of diabetes for more than 10 years with vascular complications, neuropathy, and retinopathy, (*4*) proteinuria, (*5*) dehydration, and (*6*) recent administration of nephrotoxic drugs. Many of these factors are simi-

Table 1. Urinary diagnostic indices for prerenal azotemia (PA), acute oliguric renal failure (AORF), acute nonoliguric renal failure (ANRF), acute obstructive uropathy (AOU), and acute glomerulonephritis (AG)[a]

	PA	AORF	ANRF	AOU	AG
Urine osmolality, *mOsm/kg of water*	518 ± 35	369 ± 20	343 ± 17	393 ± 39	385 ± 61
Urine sodium, *mEq/liter*	18 ± 3	68 ± 5	50 ± 5	68 ± 10	22 ± 6
Urine/plasma urea nitrogen ratio	18 ± 7	3.0 ± 0.5	7 ± 1	8 ± 4	11 ± 4
Urine/plasma creatinine ratio	45 ± 6	17 ± 2	17 ± 2	16 ± 4	43 ± 7
Renal failure index (see text)	0.6 ± 0.1	10 ± 2	4 ± 0.6	8 ± 3	0.4 ± 0.1
Fractional excretion of filtered sodium (%)	0.4 ± 0.1	7.0 ± 1.4	3.0 ± 0.5	6 ± 2	0.6 ± 0.2

[a] Values are expressed as Mean ± 1 SEM. Data taken from Ref. 63 reproduced with permission of Annals of Internal Medicine.

lar to those that predispose patients to aminoglycoside nephrotoxicity. It should also be emphasized that nondiabetic patients without myeloma or hyperuricemia may be predisposed to ARF from contrast media studies [61]. Preexisting renal disease and advanced age are probably the most important factors in these patients. Contrast media-induced ARF is characterized by a rapid onset of oliguria, with a peak serum creatinine concentration reached within 3 to 6 days, followed by gradual recovery. Those patients with markedly elevated serum creatinine concentrations (>3 to 6 mg/100 ml), however, may develop irreversible ARF [62].

Careful examination of the urine sediment and analysis of the biochemical composition of the urine are very important in the diagnosis of ARF. As already emphasized, urinary eosinophils suggest interstitial nephritis, whereas RBC casts suggest vasculitis or glomerulonephritis. A normal urine sediment suggests the presence of prerenal or post renal azotemia.

In a recent prospective study from our laboratory, several urinary findings were evaluated to assess their diagnostic value in patients with azotemia [63]. The results of this study are shown in Table 1. In those patients whose azotemia was reversible by correction of a prerenal factor (e.g., volume depletion) within 24 hours, the urinary indices were generally as follows: urinary osmolality >500 mOsm/kg of water, urinary sodium <20 mEq/liter, urine to plasma urea nitrogen ratio >8, and urine to plasma creatinine ratio >40. By contrast in those patients who followed a course of oliguric renal failure, the urinary indices were generally: Urinary osmolality <350 mOsm/kg of water, urinary sodium >40 mEq/liter, urine to plasma urea nitrogen ratio <3, and urine to plasma creatinine ratio <20. In general, patients with acute glomerulonephritis had urinary indices similar to those observed with prerenal azotemia, and patients with azotemia secondary to urinary tract obstruction had urinary indices similar to oliguric ARF. The urinary indices of patients with nonoliguric (>800 ml/day) renal failure were similar to oliguric renal failure except the mean urinary sodium concentration was somewhat lower. Urinary sodium concentrations (<20 mEq/liter) in our nonoliguric patients were however not as low as those observed by Vertel and Knochel [64] in burn patients; perhaps the large volumes of crystalloid-free solutions administered to burn patients with nonoliguric renal failure account for their much lower urinary sodium concentrations. Although these urinary indices were discriminating in 80% of patients, approximately 20% of patients had indices in an intermediate, nondiagnostic zone (e.g., urinary osmolality, 350 to 500 mOsm/kg; urinary sodium, 20 to 40 mEq/liter; urine to plasma urea nitrogen ratio, 3 to 8; and urine to plasma creatinine ratio, 20 to 40). This nondiagnostic zone could be narrowed, however, by the use of such derived indices as the "renal failure index" [(urinary sodium, mEq/liter)/(urine to plasma creatinine ratio)] and the fractional sodium excretion index [(urine to plasma sodium ratio)/(urine to plasma creatinine ratio) × 100]. These two measures tended to be <1 in prerenal azotemia and >1 in patients with oliguric or nonoliguric renal failure.

Those patients whose urinary indices fell within the nondiagnostic zone may well have been progressing from prerenal azotemia to ARF. It is tempting to suggest that it is this group of patients, in fact, who might benefit from prophylactic measures designed to prevent the development of ARF. In this regard, there is recent evidence suggesting that the efficacy of prophylactic measures relates to their ability to increase the rate of solute excretion; increased solute excretion, in turn, may exert its effect by attenuating secondary tubular obstruction [46, 65]. Although the renin-angiotensin system [66] and cell swelling [67] have been proposed as vascular mediators in the pathogenesis of ARF, prophylaxis in experimental ARF can be dissociated from renal tissue renin [68] and extracellular fluid osmolality [46]. Administration of isotonic or hyper-

tonic mannitol or furosemide with prompt replacement of urinary losses is most effective in increasing solute excretion rate and attenuating the ARF induced by low doses of norepinephrine [46, 55].

Those measures that increase solute excretion may also have the capacity to convert oliguric to nonoliguric renal failure. This effect on urine flow may be quite important in view of a recent study in patients with azotemia that demonstrated a lower mortality in nonoliguric versus oliguric renal failure (26% versus 50%, $P < .05$) [24]. Morbidity (e.g., infection, gastrointestinal bleeding, fluid overload) was also lower in patients with nonoliguric ARF, and only 28% of these patients required dialysis as compared to 84% of patients with oliguric ARF [24]. These beneficial effects associated with increased urine flow occurred whether the nonoliguric ARF was spontaneous or whether it had been converted from an oliguric ARF by furosemide administration. The results also provide some clues about which patients are more likely to convert from oliguric to nonoliguric ARF in response to furosemide therapy. Those patients who responded to furosemide by converting from oliguric to nonoliguric ARF had significantly lower mean serum creatinine concentrations (3.8 mg vs. 5.0 mg/100 ml), lower urinary sodium concentrations (47 mEq vs. 67 mEq/liter), and lower fractional sodium excretions (2.9 vs. 6.9) as compared to those who remained oliguric [24]. These results suggest that early diagnosis through appropriate assessment of urinary indices will be essential if furosemide is to improve morbidity and mortality in patients with ARF by inducing a nonoliguric state. As already suggested, it is conceivable that evolution to ARF may be prevented by furosemide or mannitol in those patients whose urinary indices are in the nondiagnostic transition zone between prerenal azotemia and ARF. Of course, the use of these agents for this purpose is no substitute for and should only follow correction of any prerenal factor that may be present, such as hypovolemia or congestive heart failure. Moreover, a prospective, randomized study remains to be performed to document the efficacy of furosemide or mannitol in preventing or attenuating ARF in man. In this regard, past failures to demonstrate any efficacy for furosemide in man [69] or in experimental animals [70] may reflect administration of the agent too late in the course of the ARF [69] or inadequate replacement of urinary water and electrolyte losses with consequent volume depletion [70]. In the patient discussed today, early assessment of urinary indices, restoration of blood volume, and a trial with furosemide might have converted an oliguric to a nonoliguric ARF.

Treatment. The use of hemodialysis in the Korean War diminished mortality of ARF from 95% to approximately 50 to 75% [71]; since then, however, the mortality among patients with traumatic ARF has not diminished further [72]. Certainly, much of the mortality in ARF is due to a complicating illness or illnesses. Nevertheless, since infection still remains the primary cause of death, it is possible that the uremic state predisposes to these infections [73]. Thus, more efficient and earlier dialysis might further diminish the mortality rate in ARF. In this regard, some studies suggest that early dialysis, prior to the onset of uremic symptoms may decrease mortality in ARF. This prophylactic approach involves using dialysis to maintain the serum creatinine concentration below 8 to 10 mg/100 ml and the BUN concentration below 100 mg/100 ml. This method, however, may still not be adequate to avoid some complications of uremia, such as the increased frequency and severity of infections.

Some evidence in support of this possibility is derived from a small series of military casualties in Viet Nam [74]. Two groups of comparably traumatized casualties were studied. In one group in which the BUN concentration was maintained below 50 mg/100 ml and the serum creatinine concentration below 5 mg/100 ml, the mortality was 37% (three of eight patients died); whereas in another group in which the BUN concentration was maintained only below 120 mg/100 ml and the serum creatinine concentration below 10 mg/100 ml, the mortality was 80% (eight of ten patients died). Based on these limited findings, it would seem reasonable to explore further the possibility that a dialysis schedule more aggressive than presently used for "prophylaxis" might further decrease the mortality of ARF. With respect to the patient discussed here, arrangements to transfer her for dialysis at a time when the serum creatinine and BUN concentrations had already reached 12 mg and 130 mg/100 ml, respectively, were made somewhat late in her course. An earlier transfer would have allowed for earlier evaluation and dialysis.

Fluid restriction, as undertaken in this patient, is appropriate in patients with oliguric ARF. It should be remembered, however, that patients with nonoliguric renal failure must receive adequate fluid and electrolytes to replace urinary and insensible losses. Failure to provide such fluid and electrolyte replacement in this setting may convert nonoliguric ARF to oliguric ARF with its attendant higher mor-

Table 2. Biochemical parameters suggesting hypercatabolism in patients with acute renal failure

BUN	>30 mg/100 ml per day increase
Serum creatinine	>1 mg/100 ml per day increase
Serum potassium	>1 mEq/liter per day increase
Serum uric acid	>15 mg/100 ml[a]
Serum phosphate	>8 to 10 mg/100 ml, frequently with severe hypocalcemia <6 mg/100 ml
Serum bicarbonate	>2 mEq/liter per day decrease

[a] Urine uric acid to creatinine ratio >1 suggests hyperuricemia was cause rather than consequence of acute renal failure. Data taken from Ref. 77.

bidity and mortality. This elderly woman was treated with a low-protein Giovanetti diet prior to institution of hemodialysis. Although this diet may be of value in chronic renal failure, its use in ARF is probably not appropriate. Restriction of protein, albeit of high quality, may indeed retard the rate of development of azotemia and delay the need for hemodialysis. On the other hand, Abel, Beck, Abbott, et al [75] have demonstrated that hyperalimentation with glucose and amino acids—the so-called renal failure fluid—is associated with more rapid recovery of patients with ARF as well as with a lower mortality in those patients who required dialysis. Although this prospective study awaits confirmation, it seems appropriate, particularly in patients who are hypercatabolic because of fever, trauma, or rhabdomyolosis, to institute hyperalimentation using a similar type of parenteral fluid. Further support for this approach is provided by the observation that amino acid supplementation enhances recovery from experimental ARF [76].

The choice of either peritoneal dialysis or hemodialysis, depends on a number of factors including the availability of equipment and trained personnel for hemodialysis. Although hemodialysis has certain disadvantages, such as greater hemodynamic stress, the requirement for anticoagulation, a need for vascular access, and a higher incidence of the dysequilibrium syndrome, it is much more efficient and clearly the method of choice in the hypercatabolic patient. The state of catabolism in the patient with ARF is often apparent from the clinical history and can be gauged by the rate of biochemical changes. General biochemical guidelines for determining whether a patient is catabolic or noncatabolic are listed in Table 2. Peritoneal dialysis is a simpler and more economical means of dialysis and is quite acceptable in the noncatabolic patient, barring recent intraabdominal surgery or the presence of abdominal adhesions. A major disadvantage is the elevation of the diaphragm produced by the fluid in the peritoneal cavity; diaphramatic immobility may lead to pulmonary complications such as atelectasis and pneumonia and worsen chronic obstructive pulmonary disease, if present.

In closing, it is well to remember the quote by Smith [78], which highlights the importance of normal renal function in man: "Bones can break, muscles can atrophy, glands can loaf, even the brain can go to sleep, without immediately endangering our survival; but should the kidneys fail . . . not bone, muscle, gland, nor brain could carry on."

Questions and Answers

DR. J. T. HARRINGTON: What was the time course over which intratubular pressures were measured in the experimental model of ARF evoked by clamping of the renal artery [41, 43]?

DR. R. W. SCHRIER: At approximately 2 to 4 hours, intratubular pressures were increased, but at 24 hours they were normal. At 24 hours, however, if sufficient saline solution was administered to restore RBF to normal, intratubular pressures were found to be increased. Other studies using the experimental model of ARF produced by norepinephrine in low doses [44, 46] also have demonstrated that intratubular pressures are higher than normal when the RBF is returned to control levels.

DR. J. T. HARRINGTON: Do intratubular pressures in the low-dose norepinephrine model of ARF fall back to normal after a few days even though normal renal hemodynamics are maintained? If intratubular pressures are elevated sufficiently by tubular obstruction, filtration might well cease, allowing tubular pressure to return to normal.

DR. R. W. SCHRIER: To my knowledge there are insufficient data to answer your question, but your proposal seems likely. For example, complete ureteral ligation will increase intratubular pressures, which will eventually return to normal through one or more mechanisms that are not well understood such as tubular compliance, and reflex pathways. Thus, an element of tubular obstruction is difficult to exclude at almost every stage of ARF even though the absolute intratubular pressures are not found to be elevated at all times.

DR. F. J. GENNARI (*NEMCH*): I would like to sound a note of caution in the use of a single overall mortality figure of 50 to 60% for ARF. It is well recognized that ARF can be divided into subgroups with widely divergent mortality rates. For example, mortality may be near zero in young patients with ARF induced by a nephtrotoxin or an incompatible

blood transfusion; by contrast, patients with ARF and severe trauma or extensive burns may have a mortality rate of 80 to 100%. In order for a prospective study to provide truly useful information concerning the value of a particular treatment in patients with ARF, the patients in each study group should be paired according to the illness on which the ARF is superimposed.

DR. R. W. SCHRIER: These are good points. A related question is whether the failure to reduce the mortality in ARF over the last 30-odd years is explained by the fact that we are dealing with sicker patients. That is to say, if we could go back two to three decades and apply our modern techniques, could we bring the mortality rate down to 20%? This contention can be neither proved nor disproved. It could be argued that some of the changes in the mix of patients with ARF over the past 30 years should actually have improved the mortality figures. For example, the mortality rate of patients with aminoglycoside-induced ARF may be as low as 18% [24]. There is no question that any study of a randomized large group of patients with ATN containing comparable numbers of good-risk and poor-risk subgroups, would be most helpful. Granted, to pair patients may be even better, but it is very hard to obtain adequate numbers of patients using this approach.

DR. J. P. KASSIRER: How do you interpret the recent micropuncture study of ARF by Bayliss et al [79] on glomerular permeability with aminoglycosides? As I recall, these investigators suggested that the reduction in filtration coefficient (Kf) might be responsible for the decrease in glomerular function, at least in their particular rat model.

DR. R. W. SCHRIER: That study demonstrated that rats given 4 mg/kg of gentamicin had a measurable reduction in GFR, which could be explained largely on the basis of a diminished Kf. The magnitude of the fall in GFR was not sufficient to cause azotemia, but it certainly could be a potential contributing pathogenetic mechanism.

DR. J. P. KASSIRER: Might a larger dose of an aminoglycoside produce a greater diminution in Kf and GFR?

DR. R. W. SCHRIER: In the study by Bayliss et al [79] the decrease in Kf in the group of rats receiving 40 mg/kg was not greater than a group of rats receiving 4 mg/kg. The decrease in GFR was greater in the group receiving 40 mg of gentamicin, thus demonstrating the importance of other glomerular factors. Of course, it is always possible that results obtained using these very large doses of aminoglycosides in rats may not be directly applicable to man.

DR. J. J. COHEN: Your comments suggested that gentamicin-induced ATN may be slowly progressive and may continue to worsen after administration of the agent is discontinued. In your experience, how long can the serum creatinine concentration continue to increase once the drug is stopped?

DR. R. W. SCHRIER: Because aminoglycosides accumulate and persist in the renal cortex, discontinuation of the drug will not rapidly reverse the azotemia and improvement may take several days to weeks.

RENAL FELLOW: In evaluating a patient suspected of having ATN, do you think it is necessary to obtain a urine to plasma creatinine ratio as well as a urinary sodium concentration?

DR. R. W. SCHRIER: As mentioned earlier, I think there is some evidence for a nondiagnostic zone in which patients who are evolving from prerenal failure to ATN may fall [63]. This area of overlap between prerenal failure and ATN seems to be smaller when the renal failure index (urinary sodium/urine to plasma creatinine) is used. Before we performed our study, my bias was that the urine to plasma creatinine ratio would be more valuable than the urinary sodium concentration; this possibility was not substantiated. We had a 20% overlap of patients whether the urinary sodium concentration or urine to plasma creatine concentration was used. Combining this information in the renal failure index was helpful, however. Even so, a significant percentage of patients still fall into a nondiagnostic zone.

DR. J. J. COHEN: In your study [24], what criteria were used to assign patients into the ATN group?

DR. R. W. SCHRIER: This categorization was done by correcting all prerenal factors that could be identified; those patients in whom azotemia was reversed within 24 hour by correction of prerenal factors were considered to have had prerenal failure. We also excluded urinary tract obstruction, which occurred in 8% of the patients with azotemia. This latter exclusion was important, since the urinary indices with obstruction were similar to those in ATN. Thus, a diagnosis of ATN was made by excluding prerenal and postrenal (obstructive) causes of azotemia.

DR. N. E. MADIAS (*NEMCH*): What constitutes an adequate trial with furosemide?

DR. R. W. SCHRIER: It is known that furosemide may induce a significant diuresis when the GFR is less than 10 ml/min. A dose of 300 to 600 mg of furosemide may be necessary, however, to induce a

diuresis in the presence of either advanced acute or chronic renal impairment.

DR. J. J. COHEN: Some have argued that administration of mannitol is a useful prophylactic maneuver, for example in patients undergoing abdominal aortic aneurysm surgery. Considering the information you now have, do you think pretreatment of high-risk patients with furosemide would be worthwhile?

DR. R. W. SCHRIER: On the basis of our experimental studies in low-dose norepinephrine-induced ARF [46, 47, 55, 65], the common parameter of prophylaxis seemed to be increased solute excretion, not the particular agent used. Thus, furosemide administration should theoretically be as effective as mannitol if volume depletion is avoided. In the absence of volume depletion, the large volumes of administered saline necessary to achieve solute excretion rates comparable to those obtained following mannitol or furosemide administration makes saline a less desirable prophylactic agent.

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