NEPHROTOXIC ACUTE RENAL FAILURE

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I. Pathogenesis of Acute Renal Failure

II. Antibiotic Nephrotoxicity

III. X-Ray Contrast Nephrotoxicity

IV. Anesthetic Nephrotoxicity

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Nephrotoxic acute renal failure is a serious clinical disorder. A recent prospective study of 92 patients with acute renal failure indicated that toxins caused 21% of the cases (1). These authors further noted that toxin-induced acute renal failure occurred in only 5% of those patients with oliguric acute renal failure but in non-oliguric acute renal failure the figure rose to 28%.

Several characteristics of the kidneys appear to make them especially susceptible to nephrotoxic injury. Although the kidneys represent only 0.4% of the body weight, they receive 20% of the cardiac output and 90% of this blood flows to the renal cortex. Through the process of filtration, reabsorption and secretion nephrotoxins may achieve very high concentrations within tubular cells, particularly those of the proximal tubule.

The list of agents that cause nephrotoxic acute renal failure is extensive (Table 1). The first three entries on this table currently account for most cases of toxic nephropathy. Following a discussion of the pathogenesis of acute renal failure, these areas will each be discussed in depth. Agents that manifested their nephrotoxicity as acute interstitial nephritis (AIN) are also listed on the table. While AIN may be associated with a reduction in renal function, it usually represents a hypersensitivity reaction rather than what is usually understand as acute renal failure and will not be discussed here. The other toxins on the list are clinically less common and will not be discussed except where experimental studies with them have added to our understanding of the pathogenesis of acute renal failure. The reader is referred to the references listed for additional information on these.

Pathogenesis of Acute Renal Failure

Acute renal failure may be defined as a syndrome characterized by acute impairment of renal function resulting in the accumulation of nitrogenous waste (urea, creatinine) in the body which cannot be reversed by altering extra renal factors (e.g., restoring blood volume, raising blood pressure, improving cardiac function). Note that the definition includes no reference to oliguria or polyuria

Table I

	Acute Renal Failure	Acute Interstitial Nephritis	References
Antibiotics			
penicillin		x	138-140
cephalosporins	x	x	138-140
aminoglycoside	x		See Text
polymyxins	x	x	138-140
colistin	x		" "
rifampin		x	" "
sulfonamide		x	" "
X-ray Contrast Agents	x		See Text
Anesthetic Agents			
methoxyflurane	x		See Text
enflurane	x		"
Drugs			
dephenylhydantoin		x	141
allopurinal		x	142
sulfonamide diuretics		x	143
furosemide		x	144
phenylbutazone		x	145
phenindione		x	146
Heavy Metals			
mercury	x		147
arsenic	x		148
platinum	x		149
Petroleum distillates	x		150
Organic Solvents			
carbon tetrachloride	x		147,151
trichloroethylene	x		152
Ethylene Glycol	x		153
Insecticides			
chlordane	x		154
DDT	x		155

and thus either may be compatible with acute renal failure. Also, the term acute tubular necrosis is avoided since this is a histological lesion not seen in all cases of acute renal failure. The precise pathogenic mechanism responsible for acute renal failure is unknown but the large list of clinical disorders associated with acute renal failure and the many laboratory models used to produce the syndrome suggest that more than one or possibly a sequence of events may be involved. Table II describes the current theories used to explain the pathogenesis of acute renal failure. While these theories have been applied to all forms of clinical and experimental acute renal failure, it is noteworthy that several of the theories have received their strongest support from models of acute renal failure using nephrotoxic agents. A brief review of these theories will serve as a background for discussing the clinically important nephrotoxic agents and their mode of renal injury.

Table II

THEORIES OF ACUTE RENAL FAILURE

1. Tubular obstruction
2. Backleak of filtrate
3. Vasomotor nephropathy
4. Tubuloglomerular feedback
5. Altered glomerular capillary permeability

Tubular Obstruction. The tubular obstruction theory of acute renal failure suggests that proteinaceous casts and cellular debris resulting from nephron damage obstruct the tubular lumen. These events raise intratubular pressure, oppose filtration pressure, and eventually glomerular filtration ceases (Figure 1). Several experi-

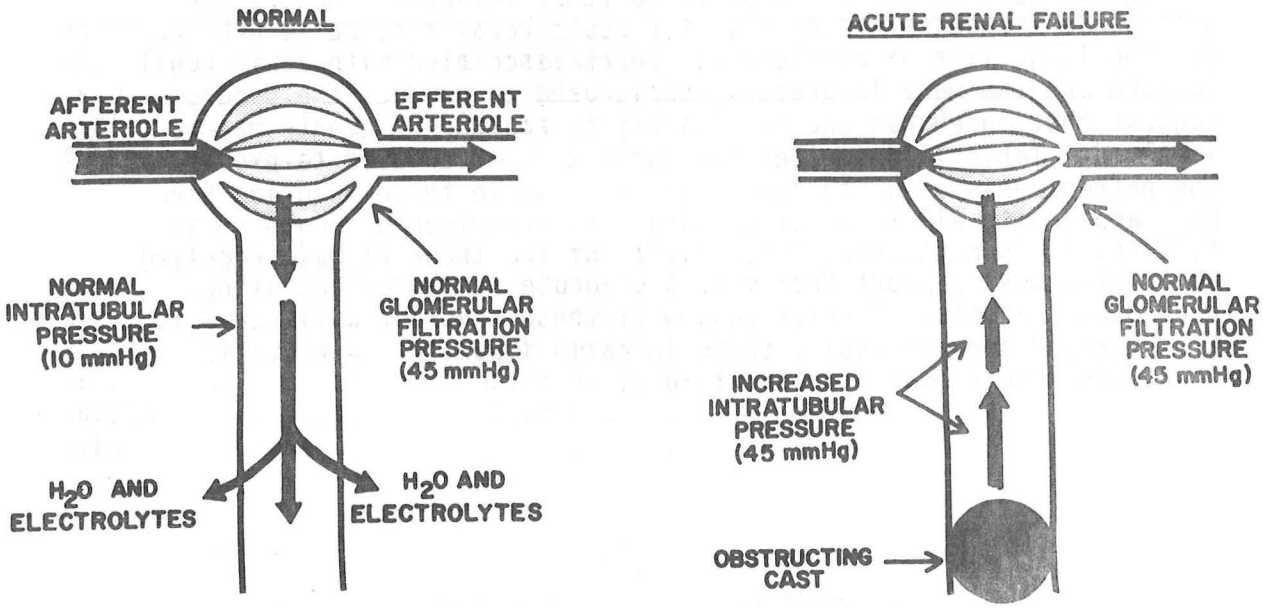


Figure 1

mental and clinical observations support this viewpoint (Table III). Dilated proximal tubules, intraluminal casts and debris, and interstitial edema are histological features of many clinical and experimental forms of acute renal failure. In addition, an increase in kidney volume averaging 140% of normal has been documented in patients with acute renal failure (2). When intratubular pressure measurements using micropuncture techniques were applied to several experimental models of acute renal failure the results were conflicting. In methemoglobin (3), glycerol (4), mercuric chloride (5,6), potassium dichromate (7), and uranyl nitrate (8), models of acute renal failure proximal intratubular pressure in early and late stages of acute renal failure in the rat were found to be normal (10-15 mm Hg) or low. In contrast, early post-ischemic acute renal failure, (1-8 hrs) in the rat (9,10) was associated with elevations of intratubular pressure (40-48 mm Hg) that after a period of time (24 hrs) fell towards and

Table III

TUBULAR OBSTRUCTION THEORY

SUPPORT	AGAINST
1. Increased kidney weight, dilatation of proximal tubules, casts in distal tubules and marked interstitial edema are all findings compatible with tubular obstruction.	1. Renal vein wedge pressures are normal in human ARF indicating that interstitial pressures are not elevated.
2. Increased intratubular pressure has been noted in some but not all nephrotoxic and ischemic models of ARF.	2. Edematous enlargement of kidneys in ARF may persist or increase at a time when function is recovering.
3. In ischemic ARF high intratubular pressures and reduced dye transit times have been returned to normal after "flushing" an isotonic solution through the nephron.	
4. Mannitol and furosemide, substances that strikingly increase tubular pressures can prevent certain forms of ARF.	

sometimes below normal even though the acute renal failure persisted. Also, in one ischemic model of acute renal failure, initially high intratubular pressures and reduced dye transit times have been returned to normal after "flushing" isotonic solutions through the nephrons with a micropipet (11). Lastly, mannitol and furosemide, substances that can strikingly increase intratubular pressure experimentally (12, 13) appear to prevent certain experimental (14) and possibly clinical forms of acute renal failure.

Several pieces of information speak against an important role for tubular obstruction in acute renal failure. Intrarenal as well as renal vein wedge pressures in patients with acute renal failure are normal indicating that interstitial pressures are not elevated despite renal edema (15,16). Also, enlargement of the kidneys in acute renal failure may persist or increase at a time when renal function is recovering.

Backleak Theory. The backleak theory proposes that urine is normally filtered at the glomerulus and leaks back into the peritubular capillaries through damaged and abnormally permeable tubules (Figure 2). Laboratory measurements of glomerular filtration rate which depend on urinary concentration of filtered but non-reabsorbable substances (creatinine, inulin) would thus be invalid since the "leaky" tubular epithelium would no longer be a barrier to reabsorption of

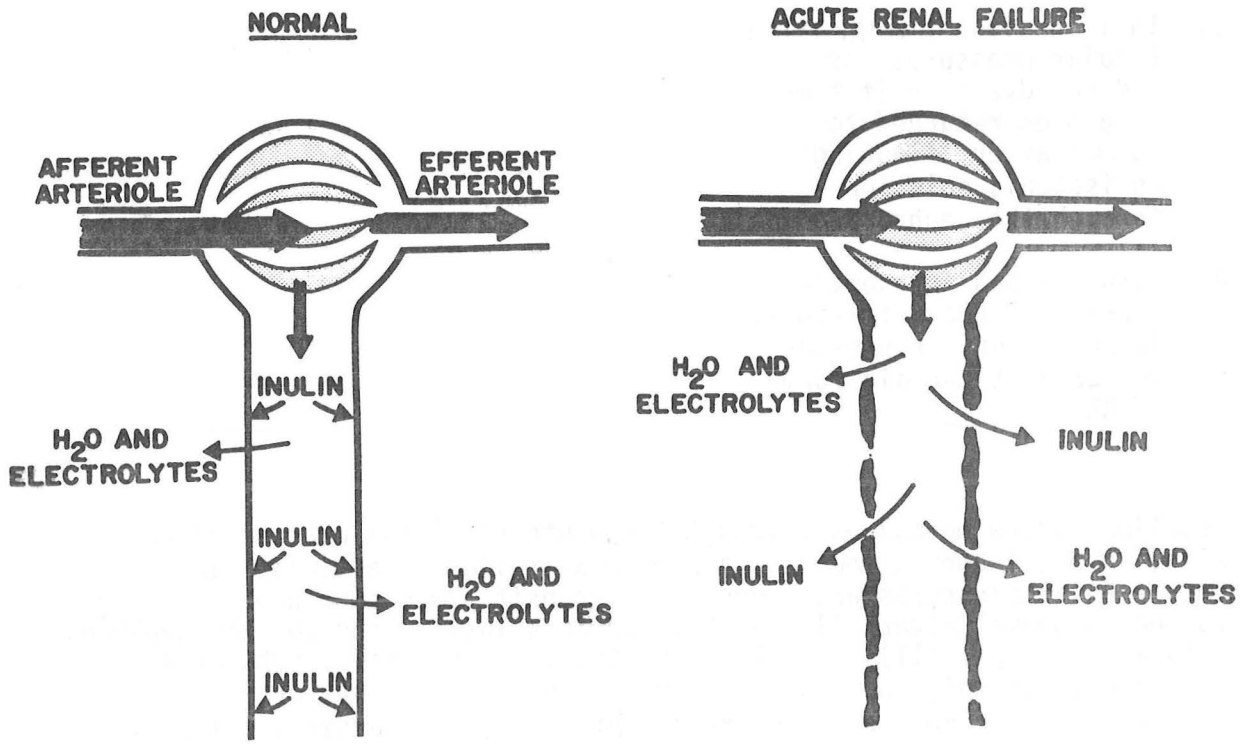


Figure 2

these substances. Thus while glomerular filtration rate if measured at the glomerulus would be normal, due to tubular backleak, inulin or creatinine clearance measurements using bladder urine would lead one to conclude that the glomerular filtration rate was very low or absent. Supporting this viewpoint is the finding of proximal tubular necrosis in some clinical as well as most experimental forms of acute renal failure (Table IV).

Table IV

BACKLEAK THEORY

1. Proximal tubular necrosis is compatible with back-leak of filtrate.	1. Severe tubular necrosis is not a consistently prominent feature of either ischemic or nephrotoxic induced acute renal failure in man.
2. Lissamine green and inulin may not be progressively concentrated alone the nephron in some nephro-toxic models of ARF.	2. The decrease in filtration rate in uranyl nitrate-induced acute renal failure occurs prior to any evidence of tubular necrosis.
3. SNGFR measured in the proximal tubules in some forms of mercuric chloride, uranyl nitrate, and ischemia-induced ARF has been shown to be near normal while whole kidney GFR is severely reduced.	3. Saline infusions prevent mercuric chloride-induced acute renal failure despite continued evidence of severe tubular necrosis.
4. Radiolabeled inulin injected into proximal tubules after ischemia or uranyl nitrate induced ARF is no longer completely recoverable in the ipsilateral kidney.	

Also, lissamine green and inulin in several experiment models have not undergone the expected increases in concentration along the nephron that would be expected if fluid but not these impermeable substances were being reabsorbed (5). The single nephron glomerular filtration rate (SNGFR) when measured in the proximal tubules in some forms of mercuric chloride, uranyl nitrate, and ischemia induced acute renal failure has been shown to be near normal while whole kidney glomerular filtration rate is severely reduced (5,9,17). This discrepancy between the SNGFR and whole kidney GFR suggests that the clearance marker was reabsorbed as it traveled along the nephron. Lastly, radiolabeled inulin injected into the proximal tubule after ischemia or uranyl nitrate induced acute renal failure is no longer completely recoverable in the urine of that kidney, indicating that the reabsorption of the inulin must have occurred somewhere along that nephron (9,17). Against a major role for backleak in the pathogenesis of acute renal failure is the observation that severe tubular necrosis in most forms of acute renal failure is not prominent. In addition, saline infusions prevent the reduction in inulin clearance following mercuric chloride administration but not the severe tubular necrosis (18).

Vasomotor Nephropathy. While backleak of filtrate and tubular obstruction have been shown to participate in some varieties of experimental acute renal failure, there is no direct evidence for participation of these mechanisms in human acute renal failure. In contrast, a marked decrease in renal blood flow is unequivocally present in human acute renal failure. The vasomotor nephropathy concept proposes that increased pre-glomerular vascular resistance and possibly postglomerular vasodilitation reduces effective filtration pressure and thereby causes cessation of glomerular filtration (Figure 3). A homogenous reduction in renal cortical perfusion is seen in all varieties of human and experimental forms of acute renal failure suggesting that a vascular mechanism may be the final common pathway (Table V). Moreover, clinical situations associated with increases in adrenergic nerve activities, catecholamines, and plasma renin activity (e.g., shock, surgery, anesthesia) are frequent forerunners of acute renal failure. Chemical and surgical renal nerve ablation may prevent ischemic acute renal renal failure from occuring in experimental animals (19,20) and man (21). Indomethacin enhanced glycerol-induced acute renal failure (considered a "vascular" form of acute renal failure) presumably by removing the protective vasodilating effect of prostaglandins (22,23). The "no reflow" phenomenon, i.e., failure of renal blood flow to return following a period of total ischemia, seen in rats immediately

after total renal ischemia initially appeared to be mediated by endothelial cell swelling induced by hypoxia (24).

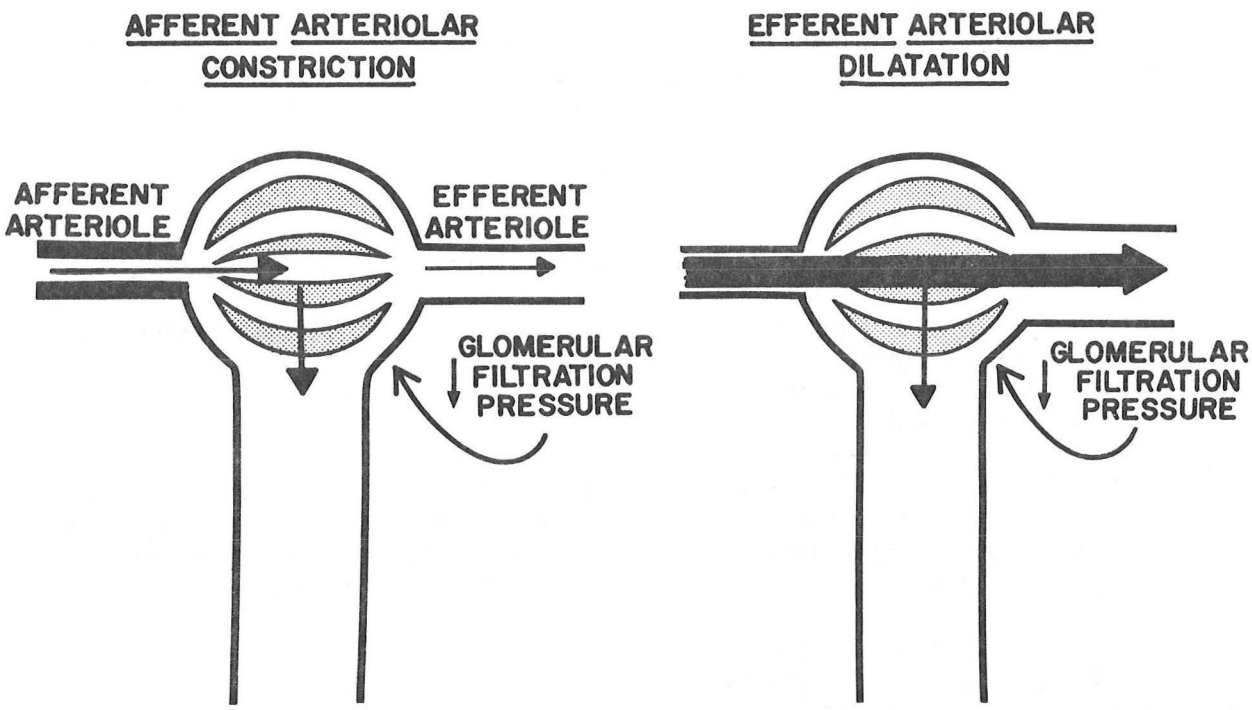


Figure 3

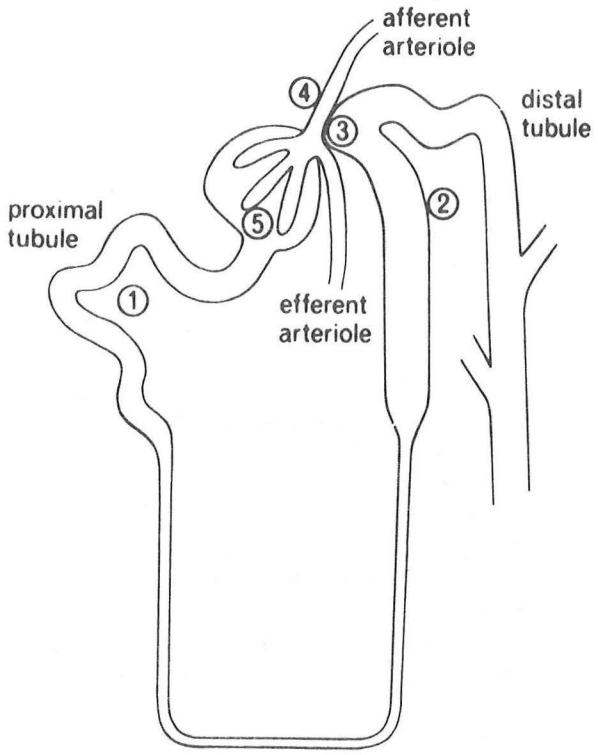
Several experimental observations, however, are not compatible with a vascular theory. The increase in proximal tubular pressure seen in post-ischemic acute renal failure (9,10) suggest on the contrary that glomerular capillary pressure is well maintained. Also, prostaglandins and most other vasodialators given during established acute renal failure can usually increase renal blood flow to normal levels without improving the renal excretory function (25-27). And lastly, "no reflow" and cell swelling are not seen in the dog after ischemia (28) and appear to be only transient finding after ischemia in the rat (29).

Table V

VASCULAR THEORIES

1. A homogeneous reduction in renal cortical perfusion is seen in virtually all types of human and experimental ARF	1. The increase in proximal tubular pressure seen in post-ischemic ARF suggests that glomerular capillary pressure is well maintained.
2. Clinical situations associated with increases in adrenergic nerve activity, catecholamines, and renin (e.g. shock, surgery, anesthesia) are frequent forerunners of ARF.	2. Prostaglandins and most other vasodilators can usually increase renal blood flow to normal levels without improving renal excretory function.
3. Chemical and surgical renal nerve ablation may prevent ischemic ARF in experimental animals and man.	3. "No reflow" and cell swelling are not seen in the dog after ischemia and appear to be only transient findings after ischemia in the rat.
4. Indomethacin enhances glycerol-induced ARF presumably by removing the protective vasodilating effect of prostaglandins.	
5. The "no reflow" phenomenon seen in rats immediately after renal ischemia appears to be mediated by cell swelling.	

Tubuloglomerular Feedback. While vasoconstriction unquestionably occurs in acute renal failure, both human and experimental, it is unclear that it has a causal association with the renal excretory defect. Thurau (30) has promoted the idea that vascular mechanisms dependent on the renin-angiotensin system are central to the pathogenesis of acute renal failure through a process known as tubuloglomerular feedback (Figure 4).



1. Ischemic or nephrotoxic insult leads to proximal tubular damage and incomplete sodium reabsorption.
2. Sodium delivery to distal tubule increases.
3. Juxtaglomerular cells sense high intratubular sodium concentration and release renin.
4. Afferent arteriole vasoconstricts in response to locally generated angiotensin (AII).
5. Fall in filtration pressure leads to reduction in GFR.

Figure 4

In this formulation, an ischemic or nephrotoxic renal insult leads to proximal tubular damage and incomplete sodium reabsorption. Thus, sodium delivery to the distal tubule increases. The juxtaglomerular cells in the distal tubules sense a high intratubular

sodium concentration and release renin locally. The nearby afferent arteriole vasoconstricts in response to locally generated angiotensin (AII). Thus, vasoconstriction of the afferent arteriole leads to a fall in filtration pressure and a reduction in glomerular filtration rate. Support for this hypothesis is as yet still somewhat circumstantial (Table VI).

Table VI

TUBULOGLOMERULAR FEEDBACK THEORY

SUPPORT	AGAINST
1. Presence of juxtaglomular hypertrophy in kidneys from patients with ARF.	1. Tachyphylaxis to the vasoconstrictor action of angiotensin II occurs rapidly in experimental animals.
2. Renin concentration is highest in the superficial cortex of the kidney, the site of most profound ischemia with ARF.	2. Active and passive immunizations to renin, competitive angiotensin antagonists, and angiotensin II converting enzyme inhibitor do not prevent experimental ARF.
3. Plasma renin activity is elevated in clinical and experimental acute renal failure.	3. Micropuncture studies in rats showed that angiotensin II vasoconstricts both afferent and efferent arterioles resulting in a decrease in renal blood flow without a reduction in GFR.
4. Prevention of experimental renal failure occurs with chronic but not acute renin suppression. Intrarenal (JGA renin) is only suppressed by the former.	4. Uranyl nitrate ARF can decrease GFR without decreasing renal plasma flow, a finding contrary to what should prevail if tubuloglomerular feedback is operative.
5. Dehydration stimulates renin activity and predisposes to clinical and experimental acute renal failure.	5. Plasma renin activity may return to normal levels within 24-48 hours of insult in spite of persistence of experimental acute renal failure.
6. Angiotensin inhibitor increases superficial cortical blood flow in experimental ARF.	

Plasma renin levels are invariably elevated early in clinical and experimental acute renal failure (31,32). Also, juxtaglomerular renin activity increased promptly after initiation of experimental acute renal failure in the rat (33). Prevention of experimental acute renal failure occurs with chronic but not acute renin suppression (18); intrarenal renin (juxtaglomerular apparatus renin) is only suppressed by the former (34). And lastly, volume depletion stimulates renin activity and also predisposes to clinical and experimental acute renal failure. However, equally forceful arguments can be marshaled against a role of the renin-angiotensin system in the pathogenesis of acute renal failure. Tachyphylaxis to the vasoconstrictor action of angiotensin II occurs rapidly in experimental animals (35,36). Active and passive immunization to renin, competitive angiotensin antagonists, and angiotensin II converting enzyme inhibitors do not prevent experimental acute renal failure (37,38). Micropuncture studies in rats show that angiotensin II vasoconstricts both afferent and efferent arterioles resulting in a decrease in renal blood flow without a reduction in glomerular filtration rate (39).

Altered Glomerular Permeability. This theory of acute renal failure proposes that chemical or morphologic alterations, or both, in the basement membrane of the glomerular capillaries results in a decrease in, or possibly, total cessation of glomerular filtration (Figure 5).

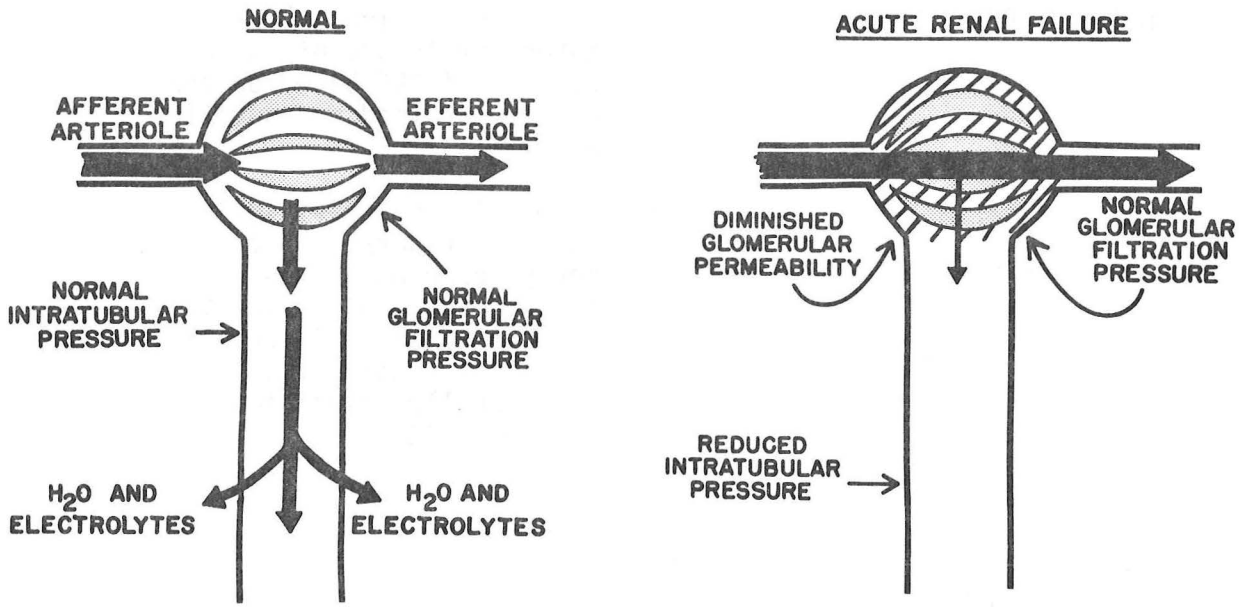


Figure 5

Supporting this theory are electron microscopic abnormalities in epithelial cell foot processes seen after uranyl nitrate (17), mercuric chloride (40), and norepinephrine (41) induced acute renal failure (Table VII).

Table VII

ALTERED GLOMERULAR PERMEABILITY THEORY

1. Electron microscopic alterations in epithelial cell foot processes after uranyl nitrate and norepinephrine (2 hour) induced ARF. When renal blood flow was elevated to normal levels in norepinephrine ARF, proximal tubules did not reexpand indicating filtration failure.	1. In clinical acute renal failure light and electron microscopic studies show little if any glomerular abnormality.
2. Reduction in total glomerular permeability (LpA) after uranyl nitrate induced ARF.	2. Chronic studies with the 2 hour norepinephrine infusion indicate that this is an irreversible lesion. This makes any theory of the pathogenesis of ARF based on the glomerular findings questionable.
	3. Glomerular changes similar to those reported after norepinephrine (2 hours) induced ARF are regularly seen in cases of idiopathic nephrotic syndrome, a condition usually associated with a normal GFR.

Also, when total glomerular permeability (LpA) was measured after uranyl nitrate induced acute renal failure in the rat (42), it was found to be reduced. When renal blood flow was elevated to preinsult levels 48 hrs after norepinephrine induced acute renal failure, proximal tubules did not reexpand indicating filtration failure (41). However, it is difficult to reconcile these experimental findings suggesting altered glomerular permeability in acute renal failure with the clinical findings that light and electron microscopic studies of the glomerulus in acute renal failure invariably have been normal (43,44). Also, chronic studies in our laboratory with the 2 hour norepinephrine infusion indicate that the lesion produced in the kidney was irreversible and the alterations in glomerular histology produced in this experimental model probably represented necrosis rather than reversible histological changes (45). Lastly, glomerular changes similar to those reported after norepinephrine induced acute renal failure, are regularly seen in cases of idiopathic nephrotic syndrome, a condition usually associated with a normal glomerular filtration rate. Unfortunately, no studies of glomerular permeability are available in human acute renal failure.

This brief review of the pathogenesis of acute renal failure is of necessity incomplete and no attempt has been made to resolve the inherent conflicts between the several proposed pathogenic mechanisms. Increased intratubular presence would not be expected in acute renal failure if either tubuloglomerular feedback or backleak of filtrate were occurring. Likewise, reduced glomerular permeability as the primary pathogenic event virtually precludes an important role for tubular obstruction, backleak of filtrate, or tubuloglomerular feedback.

Strict application of these findings from experimental models to human acute renal failure may be unwarranted since no experimental model truly mimics the human disease.

Antibiotics

Aminoglycoside antibiotics represent the clinician's strongest tool in combating serious gram negative infections and the number of these agents is proliferating rapidly. Also, the percentage of the serious bacterial infections due to resistant gram negative organisms is increasing, assuring the continued and probably increased use of these agents in the future. Unlike the penicillin and cephalosporin families of antibiotics, the use of the aminoglyco-

sides carries a substantial risk of nephrotoxicity. The earliest of the aminoglycosides, neomycin, proved too nephrotoxic for parenteral use and was quickly relegated to topical and oral use. Unfortunately, serious systemic absorption and toxicity may occur by these routes as well (46,47). The later aminoglycosides, kanamycin and gentamicin, were originally thought to have minimal nephrotoxic potential, but these estimates were later revised upwards, following realization that the original dosage recommendations were too low. The still newer aminoglycosides, tobramycin, sisomicin and amikacin while providing advantages in antibacterial spectrum over kanamycin and gentamicin do not seem to be less nephrotoxic (48). Despite recognition by clinicians that these drugs are potentially nephrotoxic and despite careful adjustment of dosage along guidelines established by manufacturers and clinical pharmacologists, nephrotoxicity remains a common and serious clinical problem (49). A recent prospective study of the incidence of acute renal failure in a general hospital indicated that nephrotoxic antibiotics appeared to be the primary cause in 16% of the cases (1).

Since the aminoglycoside antibiotics normally are reserved for hospitalized patients with serious gram negative infections, it is often difficult to decide which of the many nephrotoxic insults a patient is exposed to is responsible for an episode of acute renal failure. The following case illustrates this problem (Figure 6).

Case Report 1

A 41 year old white male was admitted to the Surgical Service at the VA Hospital, July 16, 1977, with leg pain. He had a history of severe bilateral atherosclerotic disease of the peripheral vasculature and two years earlier had undergone a left AK amputation. Following admission, an arteriogram demonstrated complete occlusion of the aorta below the renal arteries. An unsuccessful revascularization procedure under general anesthesia was followed in three days by a right BK amputation. Several revisions of the stump were required over the next two months. Because of a persistent purulent drainage from the stump following the initial

operation, parenteral and oral antibiotics were begun. Despite a combination of cephalothin and gentamicin, a fever of 100-103° persisted. On August 27, a wound culture grew acinetobacter resistant to gentamicin, ampicilin, and keflin, but sensitive to colistin and carbenicillin. The patient was begun on a 14 day course of colistin. On the 9th day of colistin therapy, azotemia was noted for the first time. Five weeks following discontinuation of all antibiotics, the patient's renal function had returned to baseline values.

In this patient, arteriography, multiple surgical procedures, general anesthesia, and three potentially nephrotoxic antibiotics all preceded development of non-oliguric acute renal failure. In retrospect the most likely cause of the patient's renal deterioration was the prolonged administration of gentamicin and colistin, two agents with substantial nephrotoxic potential.

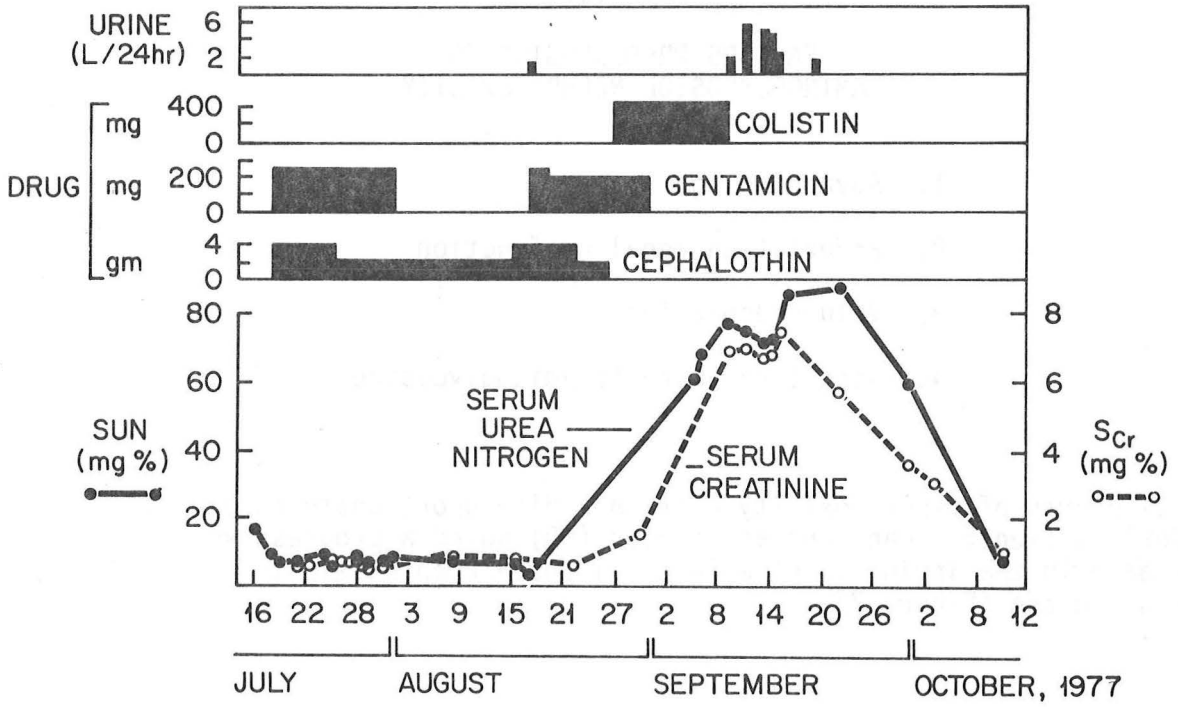


Figure 6

Clinical Patterns of Nephrotoxicity. Aminoglycoside nephrotoxicity is a dose and duration related phenomenon. Although aminoglycosides are said to produce acute renal failure (ARF), ARF as characterized by oliguria and an abrupt nearly total loss of renal excretory function probably occurs infrequently (50). In most cases, it is more precise to speak of aminoglycoside nephrotoxicity. The loss of renal excretory function is gradual rather than abrupt, rarely total and is followed by an equally gradual recovery. In severe cases recovery to the prior level of renal function may require weeks to months (51) and some cases may never return to normal.

Several lines of evidence suggest that aminoglycoside antibiotics cause nephrotoxicity as the result of accumulation of the drug in renal tissue and that some critical level must be reached before toxicity surfaces clinically (52-54). As demonstrated by Case 1, cessation of the aminoglycoside is not usually followed by prompt improvement in renal function.

Four major factors in the development of aminoglycoside nephrotoxicity are now apparent (Table VIII).

Table VIII

FACTORS PREDISPOSING TO
AMINOGLYCOSIDE NEPHROTOXICITY

1. Advancing age
2. Preexisting renal dysfunction
3. Volume depletion
4. Recent exposure to aminoglycosides

Most reports of nephrotoxicity contain a disproportionate number of elderly patients. Lane and associates (49) noted a progressive increase in the incidence of amikacin induced nephrotoxicity with advancing age (Figure 7).

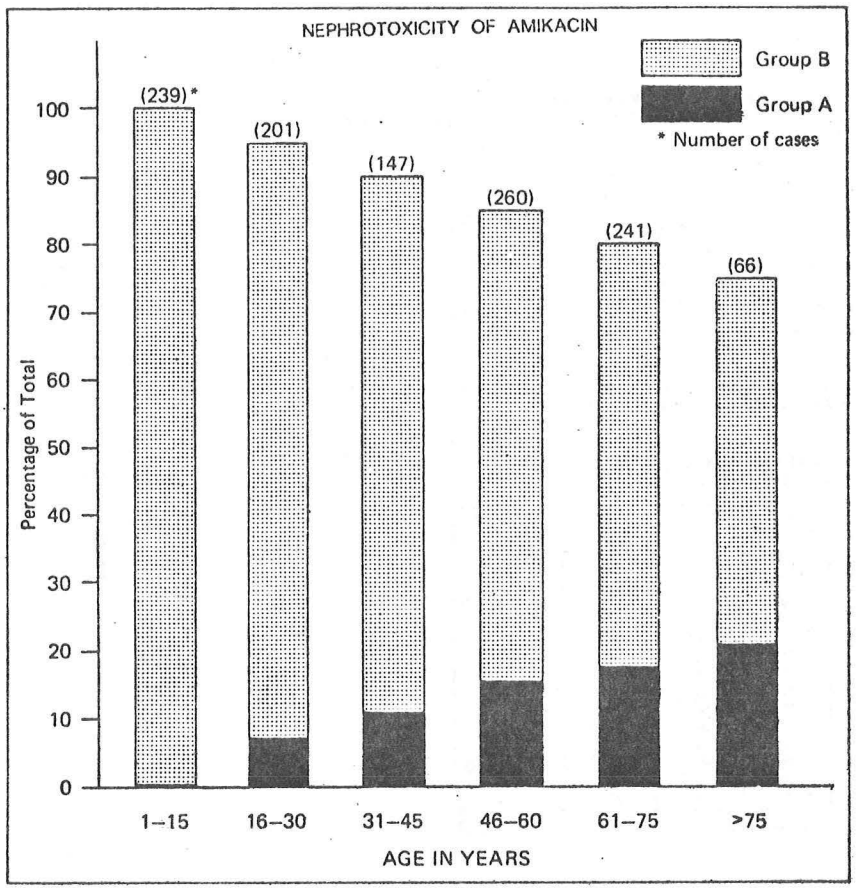
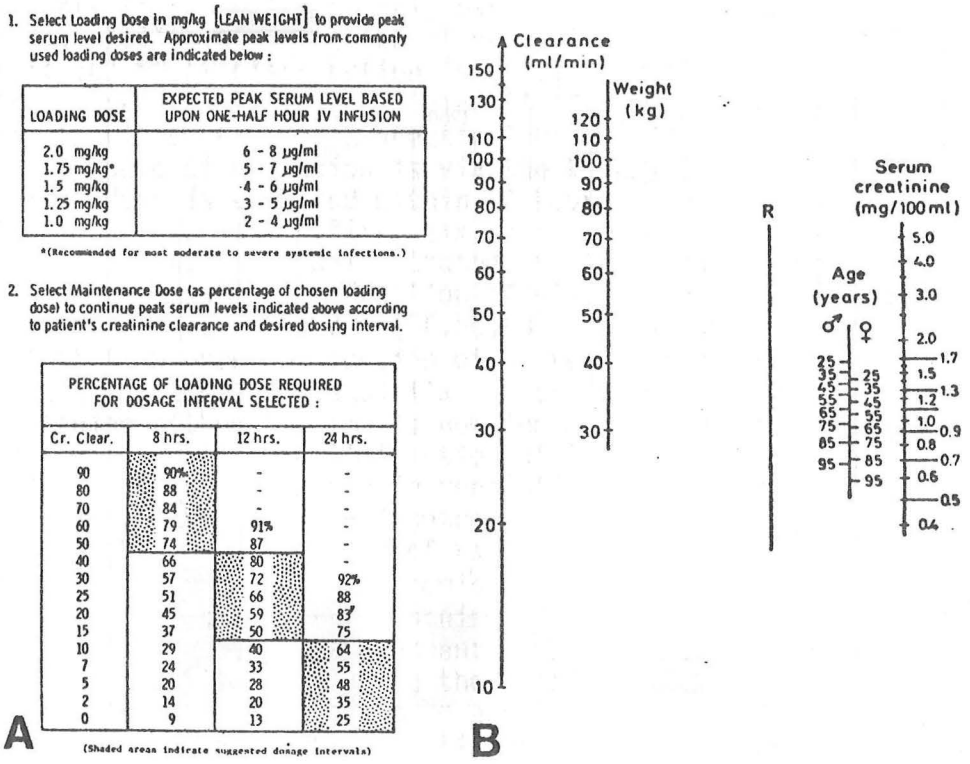


Figure 7. Percentage of each age bracket in which renal function deterioration developed (Group A) or in which no such deterioration was evident (Group B) (49).

The precise reason for this increased incidence of toxicity with age is not clear but probably includes dosing the drug on an overestimation of the true glomerular filtration rate (GFR). Dosing recommendations and nomograms for estimating GFR from serum creatinine, age, and weight are available that may improve dosing habits (Figure 8).



1. Select Loading Dose in mg/kg [LEAN WEIGHT] to provide peak serum level desired. Approximate peak levels from commonly used loading doses are indicated below:

LOADING DOSE	EXPECTED PEAK SERUM LEVEL BASED UPON ONE-HALF HOUR IV INFUSION
2.0 mg/kg	6 - 8 µg/ml
1.75 mg/kg*	5 - 7 µg/ml
1.5 mg/kg	4 - 6 µg/ml
1.25 mg/kg	3 - 5 µg/ml
1.0 mg/kg	2 - 4 µg/ml

*(Recommended for most moderate to severe systemic infections.)

2. Select Maintenance Dose (as percentage of chosen loading dose) to continue peak serum levels indicated above according to patient's creatinine clearance and desired dosing interval.

PERCENTAGE OF LOADING DOSE REQUIRED FOR DOSAGE INTERVAL SELECTED:			
Cr. Clear.	8 hrs.	12 hrs.	24 hrs.
90	90%	-	-
80	88	-	-
70	84	-	-
60	79	91%	-
50	74	87	-
40	66	80	-
30	57	72	92%
25	51	66	88
20	45	59	83
15	37	50	75
10	29	40	64
7	24	33	55
5	20	28	48
2	14	20	35
0	9	13	25

(Shaded areas indicate suggested dosage intervals)

A

B

Figure 8. Gentamicin dosing chart. B. Nomogram for rapid evaluation of endogenous creatinine clearance. With a ruler, join weight to age. Keep ruler at crossing point of line marked "R." Then move the right-hand side of the ruler to the appropriate serum creatinine value and read the patient's clearance from the left side of the nomogram (55).

Lang et al. (49) also noted that prior renal dysfunction existed in many patients who developed toxicity (Figure 9).

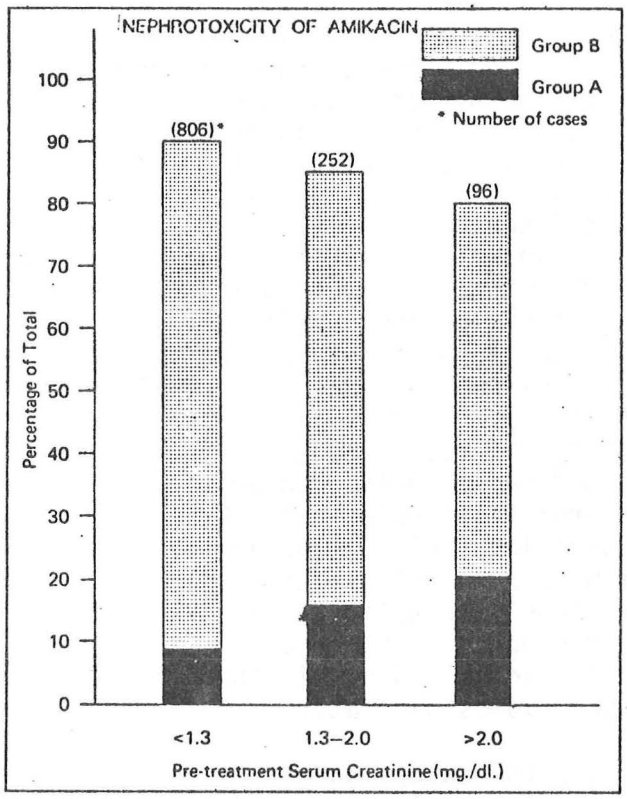


Figure 9. Percentage of patients, arranged by pretreatment serum creatinine, whose renal function either deteriorated (Group A) or showed no deterioration (Group B) (49).

Enhanced aminoglycoside nephrotoxicity during volume depletion is a clinical observation recently confirmed in the experimental animal (54). Two pathophysiologic factors are likely to be operative here: a) reduction of GFR and b) enhanced binding of the antibiotic in renal tissue. It is becoming clear that recent, prior therapy with an aminoglycoside predisposes to nephrotoxicity. Lane et al. (49) noted that prior aminoglycosides or other nephrotoxic antibiotics were given in 22% of patients developing amikacin toxicity while these agents were given to only 7% of patients not developing toxicity ($p<.0001$). These data suggest that aminoglycoside may cause toxicity by a common mechanism that depends upon the total accumulated dose of the antibiotics in renal tissue.

Pathophysiology of Aminoglycoside Nephrotoxicity. Aminoglycosides are highly polar organic bases containing 3-5 free amino radicals. Following injection of gentamicin into the body, the apparent volume of distribution is equal to that of inulin (56), and thus equal to the extracellular fluid compartment. Gentamicin is not protein bound at therapeutic levels (57) and its only important route of excretion is via the kidney (58). Eighty-90% of a given dose is excreted within 24 hours with the largest fraction excreted in the first six hours (59). Renal secretion of gentamicin has not been demonstrated and the renal clearance of gentamicin expressed as a fraction of glomerular filtration rate is reported between .8 and 1 (56,58,60). These observations suggest that the renal excretion of gentamicin occurs primarily via filtration and thus is similar to the excretion of inulin or creatinine although there is now increasing evidence from renal tissue studies that a small fraction of filtered gentamicin is reabsorbed, and concentrated in renal tissue (59,61,62). Jerrauld and Silverblatt (63) noted that radiolabeled gentamicin appeared in the apical portion of rat proximal tubular cells 2 minutes following intravenous administration. Also, blockade of the organic base secretory mechanism with N-methyl nicotinamide failed to reduce gentamicin concentrations in renal cortical homogenates. Lastly, following the loading dose, subsequent doses of aminoglycosides are more easily accounted for in the urine suggesting that the renal tissue becomes saturated.

The aminoglycoside antibiotics with the exception of streptomycin, concentrate to high levels in renal tissue (59,61,62), and this factor appears to correlate with toxicity. Luft and Kleit (61) measured the concentrations of gentamicin, tobramycin, kanamycin, and streptomycin in rat renal tissue after a single subcutaneous injection (Figure 10). Streptomycin disappeared rapidly from renal tissue in comparison to the other agents. Moreover, when renal cortex and medulla were examined for drug concentration, streptomycin in contrast to the other 3 was not preferentially concentrated by cortical tissue, but was present in concentrations similar to those found in urine at the same time. This indicates little or no tissue uptake of the streptomycin. It is difficult to escape the conclusion that the renal cortical concentration of aminoglycosides is a central factor in nephrotoxicity. In addition, the two most nephrotoxic families of antibiotics, aminoglycosides and polymyxins, are the only antibiotics that are concentrated to high levels in renal tissue. The normal renal cortex concentrates gentamicin 20:1 over serum with the value falling to 6:1 in the

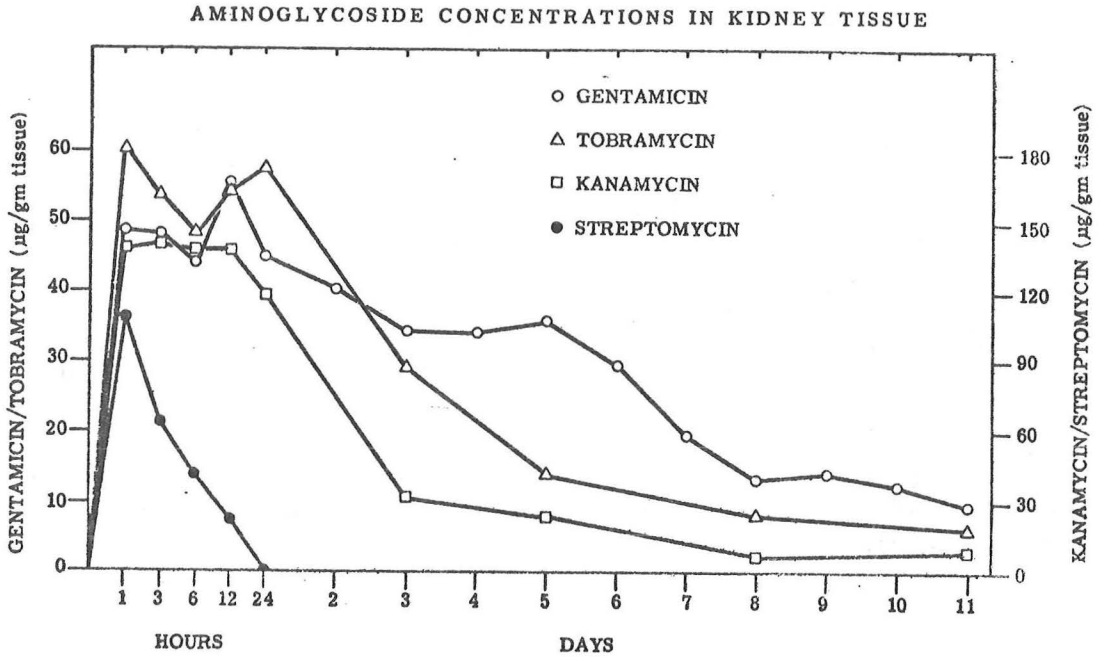


Figure 10. Comparison of concentrations of gentamicin, tobramycin, kanamycin, and streptomycin in renal tissue of rats after a single sc injection of 10 mg of gentamicin or tobramycin/kg or of 150 mg of kanamycin or streptomycin/kg (61).

medulla (62). Once concentrated in renal tissue, aminoglycoside excretion is very slow. Luft and Kleit (61) noted that the half life of gentamicin in serum was 30 minutes but was 109 hours in renal tissue. Fabre and associates (59) studied the decay of renal tissue concentrations of gentamicin and sisomicin in the rat following a single intraperitoneal injection (Figure 11). Within one hour of injection, the renal cortex concentrations of both drugs was 10 fold higher than simultaneous serum levels. The maximum concentrations in the cortex were not reached before the 6th hour post injection, a time when gentamicin and sisomicin were undetectable in the serum. Even 4 weeks following this single injection, renal cortical concentrations of both drugs were 6 µg/g tissue, higher than the minimum inhibitory concentration for susceptible organisms.

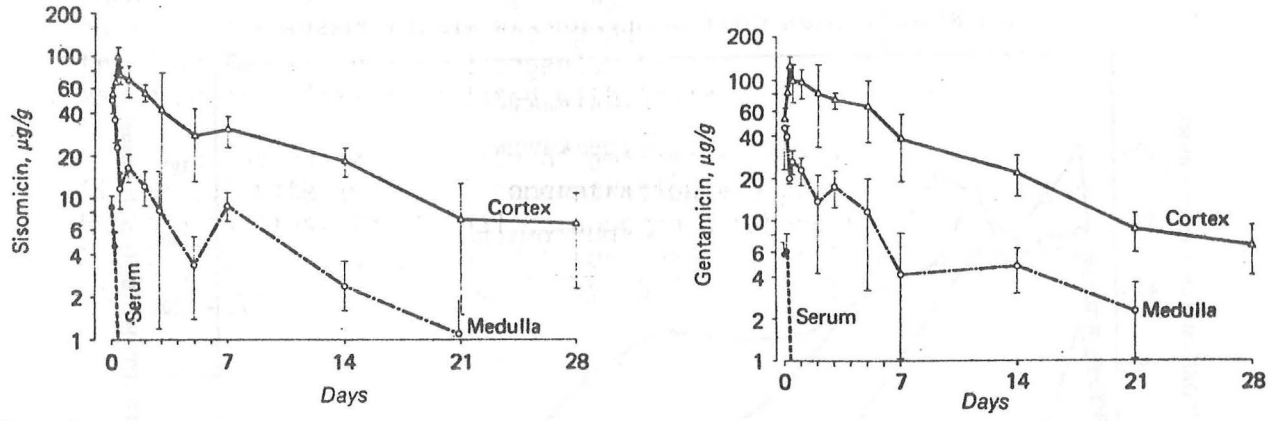


Figure 11. Concentrations of sisomicin and gentamicin in the renal cortex, renal medulla and serum after a single i.p. injection of 4 mg/kg. Values are the means of six rats ± SD (59).

The capacity of the kidney to accumulate aminoglycoside is quite large and repeated injections result in progressively higher tissue concentrations (59) (Table IX).

Table IX

RENAL TISSUE AMINOGLYCOSIDE

	Single Injection 4mg/Kg		Daily Injection 4 mg/Kg x 7 Days	
	Gentamicin	Sisomicin	Gentamicin	Sisomicin
Cortex	96 ±21	69 ±17	356 ±139	357 ±100
Medulla	23 ± 5	17 ± 4	48 ± 19	53 ± 15

From Ref. 59

Capacity values of 600-700 μg/g have been demonstrated in the dog (53). At these levels, severe renal dysfunction was always noted.

Recent work by Whelton and associates (64) indicates that competition for proximal tubular organic base or acid transport by quinine or cephalothin respectively does not influence tobramycin concentrations in renal cortex. Amino acid infusion, however, does reduce cortical tobramycin accumulation. Whether this effect is due to competition for a common carrier is unknown. In the presence of severe renal impairment, cortical concentration of aminoglycosides is almost totally abolished. Analysis of renal tissue gentamicin concentration following a single injection of the drug in patients being nephrectomized prior to renal transplantation indicated that severely diseased kidneys no longer concentrated the drug when compared to plasma (65) (Figure 12).

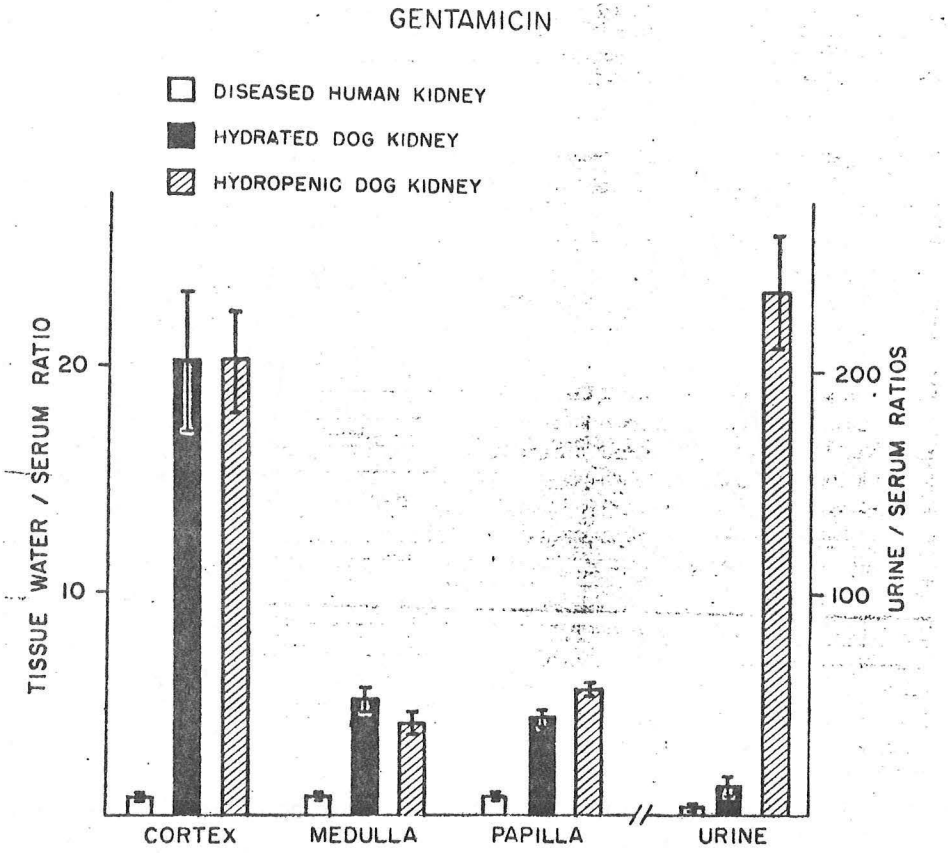


Figure 12. Comparison of gentamicin accumulation in diseased human kidneys versus that measured in healthy hydrated and hydropenic dogs. Striking decrease in tissue accumulation in diseased kidneys is apparent with most substantial reduction occurring in cortex (65).

Moreover, the likelihood that these drugs in usual therapeutic doses in renal insufficiency may not produce inhibitory gentamicin concentrations for an infecting organism in either renal tissue or urine may make the risks associated with their use unacceptable (66).

The nephrotoxic effects of aminoglycoside antibiotics on glomerular filtration rate and renal concentration are probably the best known, but the earliest functional derangements appear to occur in the proximal tubule. Enzymuria occurs in experimental animals after as few as three days of treatment and several days before any change in GFR (53,67) (Figure 13).

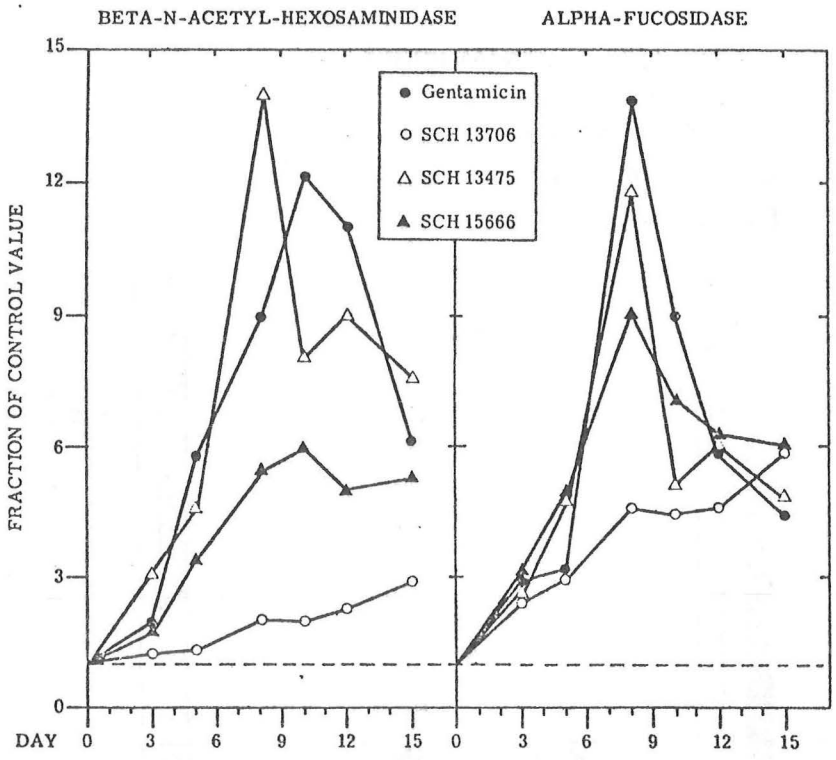


Figure 13. Urinary excretion of the lysosomal acid hydrolases beta-n-acetyl-hexosaminidase and alphafucosidase expressed as fractions of control value. Controls were 131.1 µg per day and 8.2 µg per day, respectively (53).

Low level proteinuria is an early indication of nephrotoxicity and is common to most aminoglycosides (53,68), even the newer, reportedly less nephrotoxic netilmicin (69). Aminoaciduria was reported following administration of neomycin in the rat (68) but does not occur with nephrotoxic doses of gentamicin in rabbits (70). Glycosuria developed following neomycin in rats (68) and following gentamicin in rabbits (70). We recently observed glycosuria following high dose gentamicin in the dog (Figure 14). Glycosuria was a late finding of gentamicin toxicity in our study and its onset paralleled the rise in serum creatinine and fall in GFR. This defect in tubular handling of glucose was reversible in surviving animals and was not associated with hyperglycemia. Several reports indicate that gentamicin has a suppressive effect on normal kidney cortical slice uptake of p-aminohippurate (PAH) (71,72) but others have reported normal PAH uptake as well as tetraethylammonium chloride (TEA) uptake in the presence of gentamicin (73). However, tissue slices from animals chronically treated with gentamicin and acidified with ammonium chloride do have a reduced uptake of both PAH and TEA (74).

Aminoglycosides are known to impair urinary concentrating ability. Although the mechanism is not completely understood, it is clear that urinary osmolality falls well before there is a significant reduction in glomerular filtration rate (53,69). Netilmicin, a semisynthetic aminoglycoside appears to impair renal concentration less than gentamicin (69). Since the onset of polyuria is temporally related to several proximal tubular disturbances (enzymuria, proteinuria), it may be that impaired proximal sodium reabsorption is at least in part responsible for this diuresis, although information on this point is incomplete. Thus, the characteristic features of aminoglycoside toxicity include proteinuria, polyuria, and a fall in urine osmolality occurring prior to a significant change in GFR (53). Studies by Luft and associates (53), using gentamicin and several experimental aminoglycosides demonstrated that proteinuria, enzymuria, azotemia, and reduction of GFR all closely paralleled the accumulation of this agent in renal cortical tissue. Further support of this point comes from Dellinger et al. (75) who noted that the protective effect of cephalothin against gentamicin nephrotoxicity in rats was associated with a significantly lower renal cortical gentamicin concentration than was achieved in animals given gentamicin alone. The only apparent exception to this rule appeared to be netilmicin, a semisynthetic aminoglycoside that when compared to gentamicin over a wide dosage range produced significantly less proteinuria, less reduction in urine osmolality, and virtually no impairment of GFR despite achieving renal tissue levels equal to

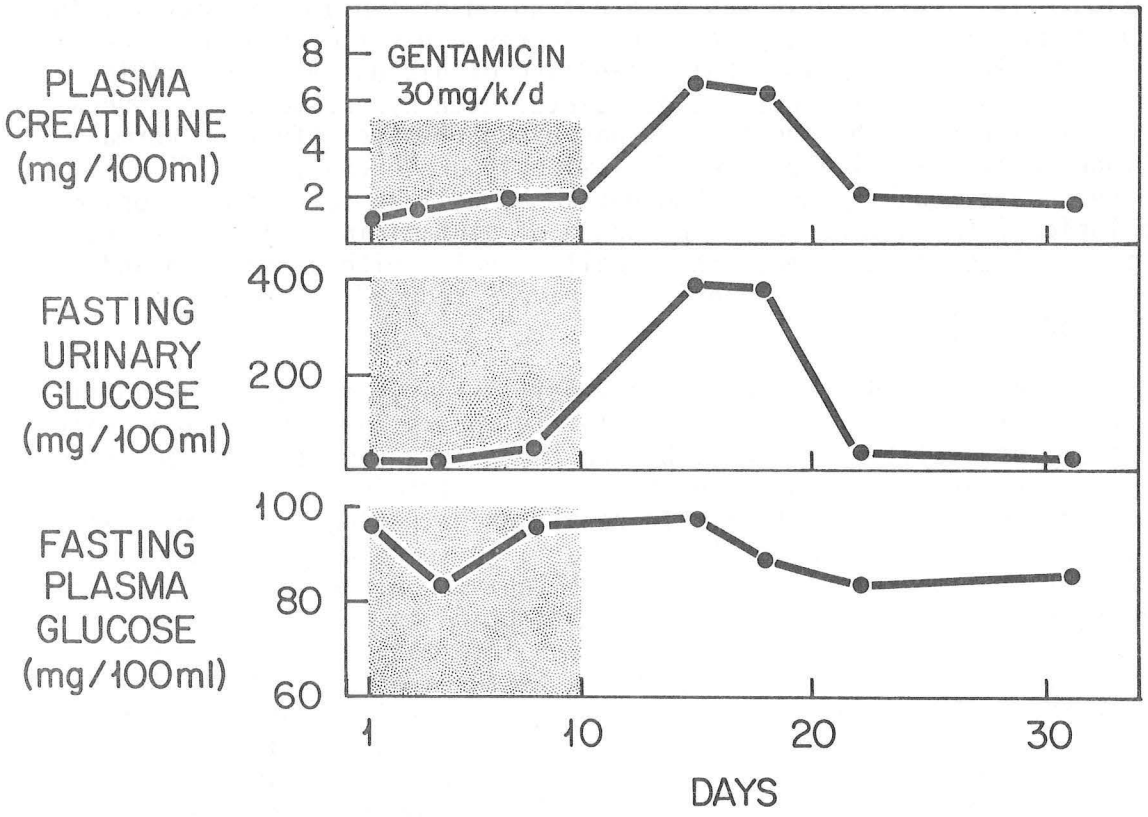


Figure 14. Experimental aminoglycoside nephrotoxicity in the dog (n=6). Effect of 10 day course of intramuscular gentamicin (30 mg/Kg/day) split into 2 doses on plasma creatinine, fasting urine glucose and fasting plasma glucose. Glucosuria is a late manifestation of nephrotoxicity.

gentamicin at each dosage tested (69). However, the number of animals used in this study was small and these results require confirmation.

The cellular mechanism by which aminoglycosides impair renal function is unknown. Aminoglycosides impair protein synthesis in susceptible bacteria (76) and this action is likely to be involved in their toxicity to renal tissue. Kunin (52) evaluated the in vitro binding of several antibiotics to various tissue homogenates and demonstrated aminoglycosides binding to particulate cell functions. Renal tissue binding was most marked with the more toxic aminoglycosides which were also those with the greatest number of free amino groups (Figure 15).

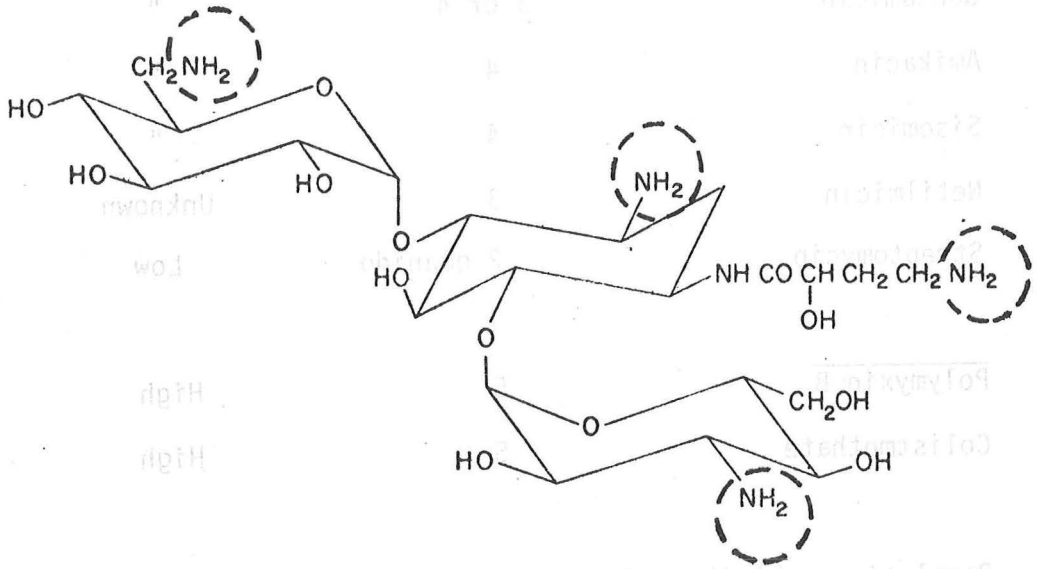


Figure 15. The structure of amikacin.

Clinical and experimental studies bear out this association between toxicity and the number of free amino groups on the molecule. Neomycin, the most toxic aminoglycoside has 6 free amino groups, while the least toxic of the series, streptomycin has two quanido groups (Table X). The aminoglycosides currently in use have 4-5 free amino groups. It is worth noting here that polymyxin-B and colistimethate, two antibiotics with a high potential for nephrotoxicity, each contain 5 free amino groups.

Table X

AMINOGLYCOSIDE NEPHROTOXICITY

	Free Amino Groups	Clinical Toxicity
Neomycin	6	High
Tobramycin	5	Intermediate
Kanamycin	4	"
Gentamicin	3 or 4	"
Amikacin	4	"
Sisomicin	4	"
Netilmicin	3	Unknown
Streptomycin	2 quanido	Low
Polymyxin B	5	High
Colistmethate	5	High

Renal tissue binding of aminoglycosides may be altered by several factors including expansion or contraction of ECF and concomitant administration of other drugs. Bennett and associates (54) studied the effects on aminoglycoside nephrotoxicity of saline expansion and sodium restriction. A low sodium diet potentiated the nephrotoxic effect of gentamicin as measured by mortality, renal histologic changes, azotemia and renal cortical drug concentration (Table XI). Also, renal cortical gentamicin concentrations were three fold higher in the low sodium group of rats that sustained severe renal injury.

Numerous clinical reports suggest that cepholosporin antibiotics augment the toxicity of aminoglycoside antibiotics (77,78). However,

Table XI

GENTAMICIN NEPHROTOXICITY

	Normal Sodium	Saline Drinking	Low Sodium	
Mortality	0/9	1/9	4/9	
BUN (mg%)	31±3	28±2	276±19	*
Creatinine (mg%)	1.2±0.1	1.2±0.1	9.8±3	*
Renal Cortex Gentamicin (μ/g)	388±22	278±21	900±123	*

*P<.001

From Ref. 54

since this combination of antibiotics is rarely used in other than life threatening situations, it is difficult to evaluate the precise contribution of each agent in the observed toxicity. The Boston Collaborative Drug Suveillance Program failed to support synergism between cephalothin and gentamicin in renal toxicity (74b). Moreover, the use of a cephalosporin antibiotic in an animal model of aminoglycoside nephrotoxicity produced unexpected results. Several reports now confirm a protective effect of high dose cephalosporins against gentamicin nephrotoxicity in the rat (79,80). Luft and coworkers (79) found that high dose cefazolin and cephaloridine prevented a significant fall in GFR when compared to 1) low dose cephazolin and gentamicin, 2) low dose cephalothin and gentamicin and 3) gentamicin alone (Figure 16). However, all groups experienced similar increases in urinary protein excretion, enzymuria, and reduction in urine osmolality. This dissociation between proximal tubular dysfunction and the fall in GFR was not due to a difference in renal tissue accumulation since renal cortical gentamicin concentrations were similar in all groups. Animals receiving gentamicin in conjunction with high dose cephalothin experienced substantially less tubular necrosis and had reduced formation of giant cytosegresomes, a characteristic renal histologic feature of aminoglycosides (81).

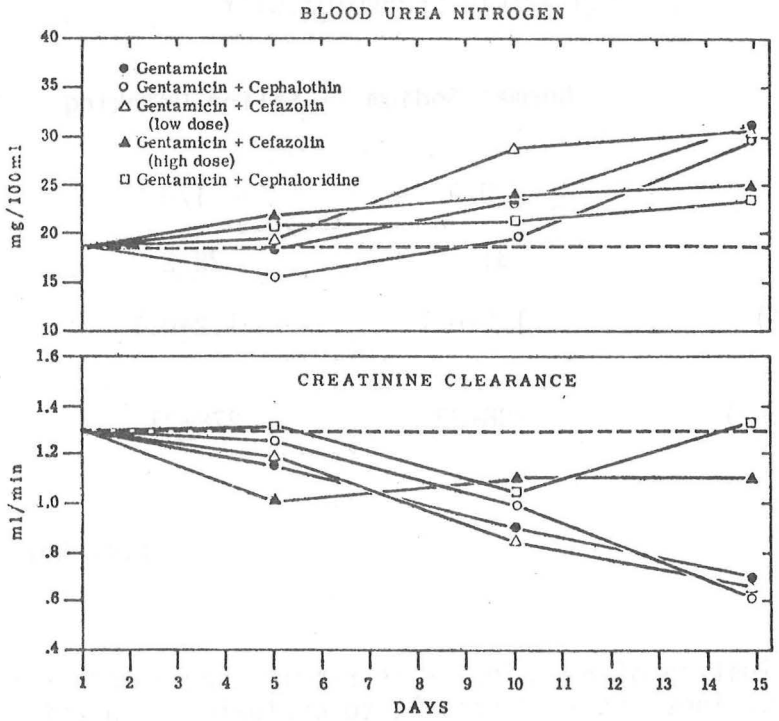


Figure 16. Protective effect on renal function of combination of gentamicin with cephaloridine or high dose cefazolin versus gentamicin alone or in combination with low dose cephalosporins (79).

Dellinger and associates also confirmed a protective effect of cepholathin on gentamicin nephrotoxicity in the rat (80) but in contrast to the study by Luft (79), they noted that this drug combination resulted in lower renal cortical gentamicin concentrations than occurred in animals treated with gentamicin alone (75) (Figure 17). The difference between these studies may reflect the strain of rats used in each. The Fisher F344 rats used in the latter study has a peculiar susceptibility to gentamicin as compared to the Sprague-Dawley rats used by Luft. The mechanism for the protective effect

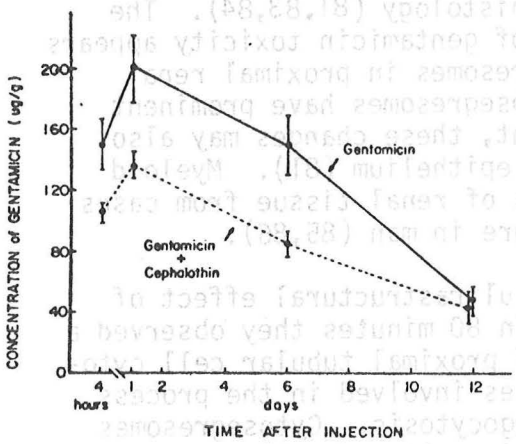


Figure 17. Concentrations of gentamicin in the renal cortex at various time intervals after the administration of gentamicin alone (12 mg/kg) or together with cephalothin (400 mg/kg) (75).

of the cephalosporin antibiotic on gentamicin toxicity is unclear but a recent study suggests that cephalothins block some toxic membrane effect of gentamicin (82).

This reduction in renal gentamicin binding and toxicity after volume expansion or cephalothin administration has several potential therapeutic implications. First volume expanded patients presumably would have decreased renal cortical tissue levels and thus be at less risk from aminoglycoside nephrotoxicity. Second, efforts to develop aminoglycosides with less avid renal cortical binding may expand their useful therapeutic range while minimizing their toxic potential.

Histology. Following gentamicin administration in the rat, dose dependent changes occur in renal histology (81,83,84). The earliest and most sensitive indicator of gentamicin toxicity appears to be an increase in lysosomal cytosegresomes in proximal renal tubular epithelium. Many of these cytosegresomes have prominent myeloid bodies (81). To a lesser extent, these changes may also occur in glomerular and distal tubular epithelium (81). Myeloid bodies have also been reported in cases of renal tissue from cases of gentamicin-induced acute renal failure in man (85,86).

Vera-Roman (83) studied the acute ultrastructural effect of single injections of gentamicin. Within 80 minutes they observed a prominent increase in the population of proximal tubular cell cytosomes and cytosegresomes, cell organelles involved in the process of exocytosis, endocytosis, and autophagocytosis. Cytosegresomes are felt to represent cytosomes containing altered cell organelles. It is likely that the characteristic myeloid body represents a lysosomal digestion product of phospholipid such as is present in internal and external cell membranes (87). However, these histologic changes are not specific for gentamicin as bacitracin will also increase the number of cytosegresomes in the proximal tubular cells (88). In addition, intralysosomal myeloid bodies may be seen in the kidneys of rats and dogs following administration of erythromycin and clindamycin (89). Kozek et al. (81) suggested that gentamicin might impair lysosomal degradation and in this manner form myeloid bodies. Since a number of renal injuries and toxins may stimulate formation of cytosegresomes, it is unclear whether the increase in cytosegresomes following gentamicin reflects a compensatory response to digest the antibiotic itself, or represents a form of sublethal cytoplasmic damage with removal of injured cell organelles.

The histologic changes occurring after gentamicin develop quickly but resolve slowly. The renal histologic abnormalities in rats sacrificed 8 days after discontinuing gentamicin differ very little for those obtained from animals sacrificed while still being treated. At intermediate toxic doses, mild to moderate functional changes plateau at a time when there is increased prominence of the Golgi apparatus and ribosomal material (81). These changes suggest a compensatory reaction. With more severe toxicity, portions of cells heavily ladened with myeloid bodies may fill tubular lumina. Histologic alterations following gentamicin occur preferentially in certain renal tubular cells.

Following intermediate nephrotoxic doses of gentamicin in the rat, tubules with minimally altered epithelium were found side by side with tubules having severely disrupted or sloughed epithelium (84). In addition, the early segment of the proximal tubule was more susceptible to injury than the late or pars recta segment. Even with severe functional damage and widespread histological alterations in the proximal tubules, the distal convoluted tubule and cortical collecting tubules were intact except for the presence of scattered cytosegresomes and myeloid bodies. In the damaged proximal tubular cells, regeneration of tubular epithelia was evident at 10 days and was progressing at 14 days despite continued administration of gentamicin. This suggests that the immaturity of the regenerating cells may afford some protection against gentamicin toxicity. The preferential damage to proximal tubular structures with the almost total sparing of distal nephron segments despite the much higher intraluminal gentamicin concentrations suggests that aminoglycoside toxicity depends upon transport of the drug to an intracellular location, and that significant transport occurs only in proximal tubular cells. The recent study by Jerrauld and Silverblatt (82) suggests that transport of gentamicin into proximal tubular cells occurs from the luminal side of the cell and not via the organic base secretory pathway.

In summary, gentamicin appears to induce focal cytoplasmic injury and thereby increases the rate of autophagic activity in proximal tubular cells as evidenced by increased numbers of cytosomes and cytosegresomes. The myeloid bodies seen within these lysosomal structures are characteristic of but not specific for gentamicin toxicity and probably represent digestion products of membrane phospholipids. For the present myeloid bodies should be considered a histologic marker of drug administration and tissue uptake but they do not necessarily indicate toxicity (90). All of these histologic changes are reversible with time. Cells of the distal tubule and collecting duct appear to be protected against gentamicin toxicity and this presumably reflects an inability to transport the drug to an intracellular location.

Conclusions. Until safer antibiotics can be produced, the important clinical question for the present is how can the currently available aminoglycosides be used to their full therapeutic potential while minimizing the risk of serious nephrotoxicity. Unfortunately, there is no good clinical marker to predict impending toxicity from aminoglycosides. The relationship of blood level of aminoglycoside to toxicity continues to be a confusing area. A rising trough level

of aminoglycoside, i.e., the serum level of aminoglycoside present immediately prior to the next dose of drug, is said to indicate drug accumulation and impending nephrotoxicity (91,92). These authors suggest that trough levels rise before nephrotoxicity and further that careful monitoring of the trough level may prevent nephrotoxicity. However, the physiology of gentamicin excretion reviewed above, namely that the ratio of gentamicin clearance to inulin clearance is nearly 1.0, does not support this viewpoint. Since the kidneys excrete gentamicin in a manner similar to that of inulin or creatinine, a rising trough level of gentamicin must hold the same significance as a rising serum creatinine, i.e., glomerular filtration has already fallen. Since the serum creatinine is more readily available there seems to be little reason to monitor trough antibiotic levels to detect nephrotoxicity. A more important use for peak and trough antibiotic levels is to assure maintenance of effective but not excessive blood levels for the infection under treatment. The data of Dalhgren et al. (91) suggests that subtle reductions of GFR occur in all patients with normal renal function receiving 4.5 mg/Kg/d of gentamicin (Figure 18).

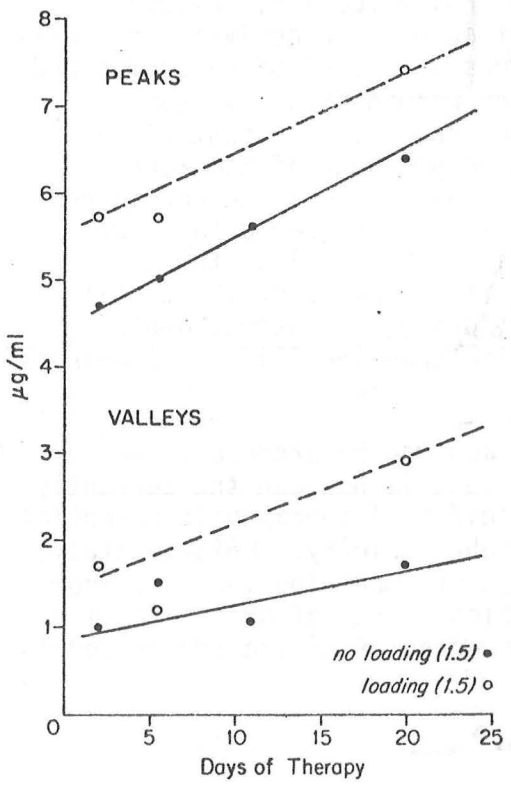


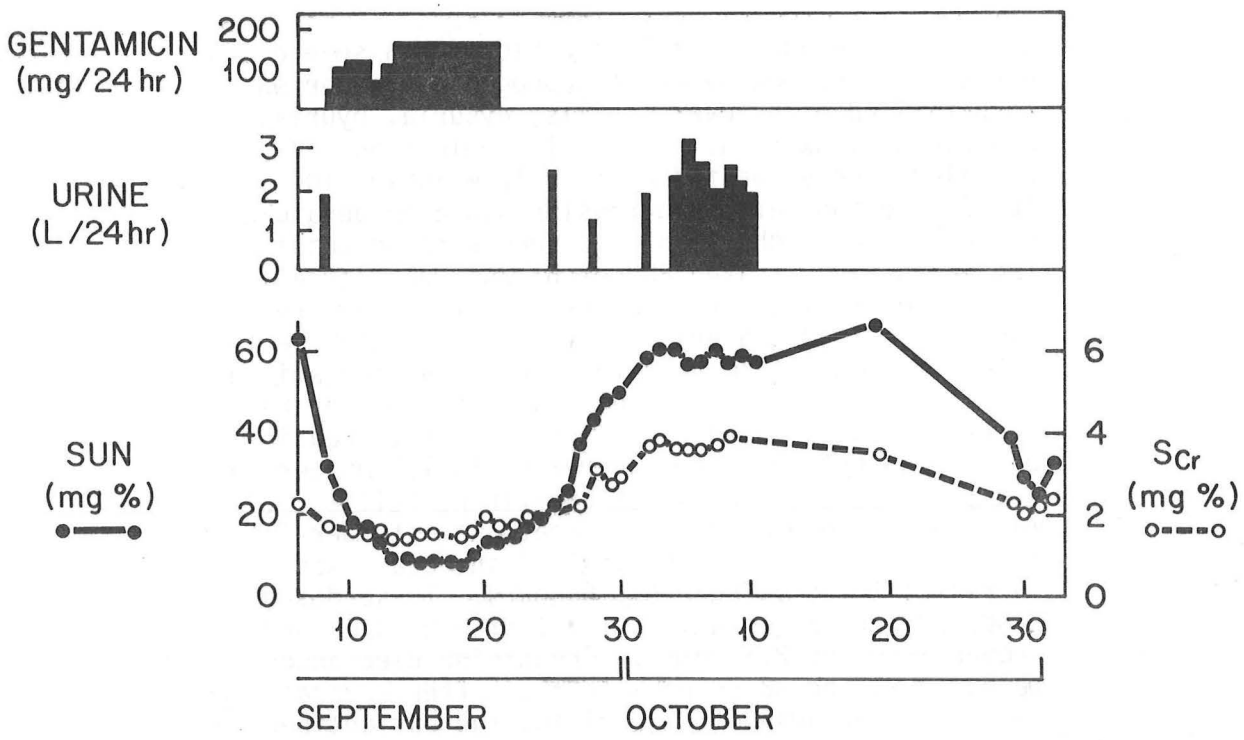
Figure 18. Relation of mean peak and valley serum concentrations in patients with normal serum creatinine receiving 1.5 mpk eight hourly to duration of therapy. Loading dose refers to an initial dose of 2 mpk (91).

They noted that all patients receiving these doses experienced a rise in both peak and trough drug levels with continued therapy. Patients who received a loading dose of 2 mg/kg had an even steeper rise in the trough level. These rising trough levels, even in patients with clinically normal renal function, suggest subtle renal impairment and resultant drug accumulation. Most patients complete their course of gentamicin without experiencing clinical evidence of nephrotoxicity, but recent data suggests that nephrotoxicity in some cases may be missed because it occurs following what is thought to be an uneventful and non-toxic course of the drug. Gary, et al. (51) recently reported on renal functional impairment occurring in five patients who developed clear evidence of renal toxicity only after completion of the course of gentamicin. We have recently observed the same phenomenon in a diabetic patient (see figure below).

Case Report 2

A 45 year old adult onset diabetic with a severe peripheral neuropathy and a neurogenic bladder was hospitalized with fever, chills, dysuria, pyuria, and right flank pain. Physical examination revealed a pale, wasted white male weighing 104 lbs with orthostatic hypotension and a temperature of 102^{0}. The right flank was tender to percussion. The initially elevated BUN of 63 and serum creatinine of 2.3 mg% fell quickly in response to volume repletion. Blood and urine cultures grew Enterobacter aerogenes and treatment with intravenous gentamicin was instituted. The initial dose was 1 mg per Kg every 24 hours, based on an initial serum creatinine of 2.3 mg% but was later increased to 1.5 mg per Kg every 16 hours as the serum creatinine fell to 1.5 mg%. After several days of treatment with persistent fever spikes to 102^{0}, the gentamicin dosage was increased to 55 mg/Kg every 8 hours. These dosages produced a peak gentamicin level of 3.9 µg/ml and a trough level of 2.2 µg/ml. Creatinine clearances measured 21 and 36 cc per minute. After several days on the higher dose of gentamicin, the patient became afebrile, asymptomatic, and urine cultures were negative. At the time the gentamicin was discontinued on September 21, the serum creatinine was

1.7 mg%. Following discontinuation of the gentamicin, the serum creatinine rose steadily to 3.9 mg% by October 8th but was not accompanied by oliguria. Volume expansion with intravenous saline failed to improve renal function and no other nephrotoxins could be implicated. Over the next several weeks serum creatinine gradually returned toward pregentamicin levels.



Case Report 2

Thus, patients who appear to have received a full course of an aminoglycoside antibiotic without nephrotoxicity, if followed for longer periods, may have a reduction in glomerular filtration rate as estimated from changes in serum creatinine.

The most realistic interpretation of both experimental and clinical data now seems to be that some degree of renal toxicity should be assumed to occur in all patients treated with aminoglycosides. However, the clinical expression of toxicity may vary from subtle alterations in proximal tubular handling of enzymes and small molecular weight proteins to oliguric acute renal failure. The clinical and experimental studies outlined above suggest that the following guidelines may maximize the therapeutic benefit of these important drugs while minimizing their nephrotoxic potential (Table XII).

Table XII

GUIDELINES FOR AMINOGLYCOSIDES ADMINISTRATION

1. Maintain an expanded extracellular fluid volume
2. Adjust dose to glomerular filtration rate, especially in elderly, before and during therapy.
3. Use with caution when an aminoglycoside has been given recently or in the presence of other nephrotoxins (antibiotics, anesthetics, x-ray contrast).
4. Using culture results, establish clear guidelines for continuation or discontinuation of aminoglycoside when therapy was begun empirically.

The volume status of the patient must be maximized within the limits of the clinical situation in each patient prior to receiving an aminoglycoside. Preexisting renal insufficiency, especially in the elderly, must be recognized and the dose of drug reduced accordingly. A serum creatinine within the "normal range" is no substitute for carefully performed 6, 12, or 24 hour creatinine clearance, since the former measurement bears only a rough correlation to the glomerular filtration rate in any given patient. Serum levels of the drug may help in main-

taining therapeutic blood levels. Since cortical aminoglycoside concentrations may take several months to dissipate, aminoglycosides must be used with caution following a recent course to the same or another aminoglycoside. Since gram negative sepsis may lead to death within 24 hours of onset, aminoglycoside antibiotics are often begun empirically in these seriously ill patients. To minimize nephrotoxic reactions in these patients who are especially at risk, a clear plan of action should be formulated in advance regarding continuation or discontinuation of aminoglycoside therapy based upon the results of the cultures and antibiotic sensitivities.

X-ray Contrast

From the renal point of view, x-ray contrast administration is generally regarded as a safe procedure, even in the presence of chronic renal failure (93-95). Moreover, the use of excretory urography in cases of unexplained renal failure may be crucial in uncovering reversible factors, e.g. urinary tract obstruction. However, renal failure may complicate several x-ray contrast procedures including cholecystography (96-99), excretory urography (100-107) and arteriography (108,109). The oral cholecystographic agents implicated in acute renal failure include iopanoic acid (Telepaque), bunamiodyl sodium (Orabilex), ipodate sodium (Oragrafin) and tyropanoate sodium (Bilopaque) and renal toxicity appears to be favored in the presence of liver disease or excessive dosages (99). Since the liver and kidney represent major excretory pathways for these agents, reduced hepatic conjugation and excretion obligates a larger fraction to renal excretion.

Performance of excretory urography in patients with multiple myeloma may lead to acute renal failure (110) and the most important predisposing factor in these patients appears to be dehydration (102). Despite numerous case reports documenting this complication in multiple myeloma, the overall risk of developing acute renal failure for these patients is still small. Several retrospective studies of the incidence of ARF in multiple myeloma revealed only 2 cases of ARF developing after 376 examinations (102,111,112). These figures are presented not as an endorsement to use excretory urography in multiple myeloma but rather to indicate that excretory urography is not contraindicated in multiple myeloma. Excretory urography may be performed in multiple myeloma if 1) the information is critical to patient care and cannot be gained by a technique carrying less risk (e.g., renal ultrasonography, renal scan) and 2) dehydration is avoided. Also, any patient with unexplained renal disease undergoing excretory urography should have the urine screened for Bence-Jones proteins with the TSA test or if unavailable, the dipstix and sulfosalicylic acid (SSA) test. A negative dipstix (albumin) and positive SSA (all urinary proteins) may be considered presumptive evidence of Bence-Jones proteinuria.

Patients with diabetes mellitus represent another group particularly prone to developing ARF after excretory urography

(100,101,104-107). Kamdar et al. (107) analyzed all the cases of ARF following intravenous x-ray contrast studies in diabetes mellitus reported at the time of their publication and made the following observations (Figure 19).

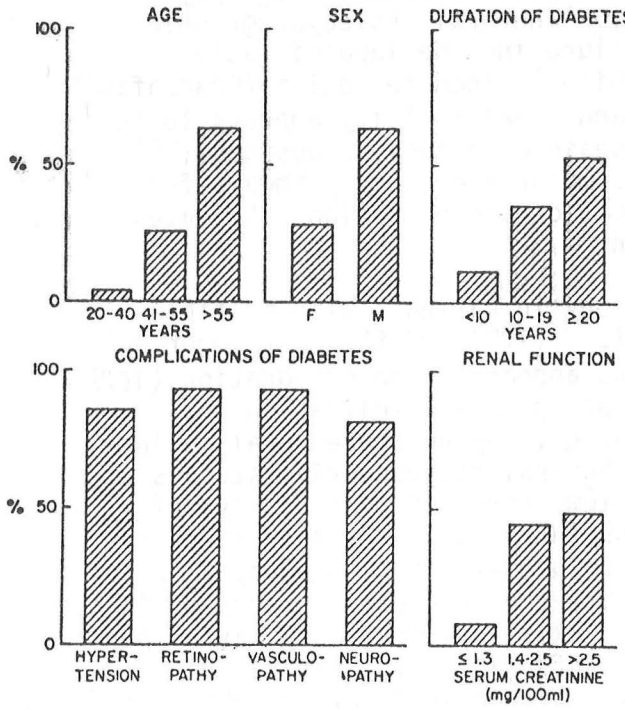


Figure 19. Clinical features in patients with diabetes mellitus and dye-induced acute renal failure (107).

The diabetic patient most likely to develop ARF after x-ray contrast was over 55 years and 90% of the patients were older than 40. The duration of diabetes mellitus in most patients was greater than 10 years. The majority had arterial hypertension, diabetic retinopathy, vascular complications, and neuropathy. Prior renal insufficiency was an almost unvariable finding in these patients.

Additional risk factors stressed in other publications include prior dehydration, proteinuria (often nephrotic range) and the recent

administration of nephrotoxic antibiotics (100,101,103,104).

The clinical picture in these patients is rather typical. Renal failure following contrast is rapid in onset and usually oliguric (Figure 20).

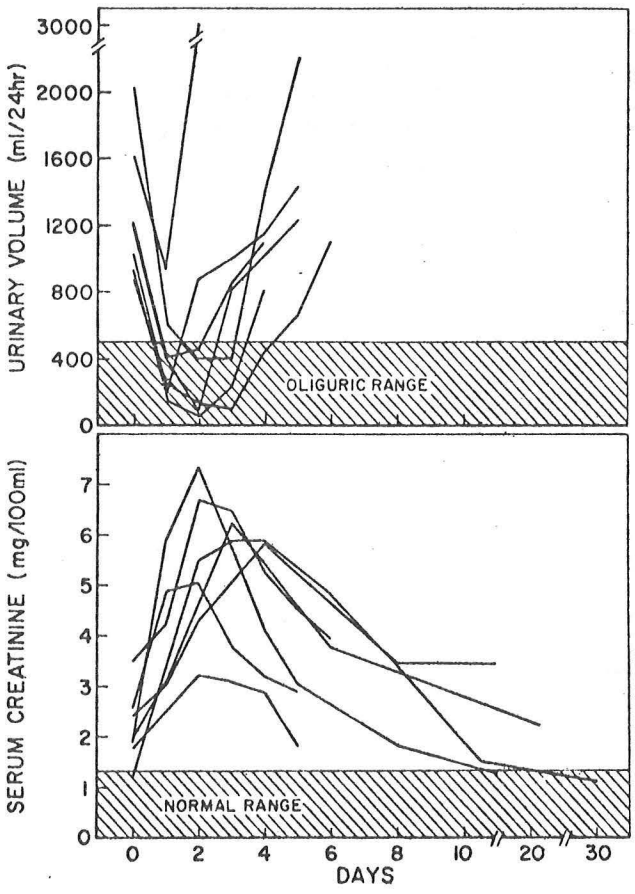


Figure 20. Urinary volume and serum creatinine levels before and after intravenous administration of contrast (107).

Kamdar and associates (107) also tabulated the combined experience of his and the previously reported cases regarding the time course of renal injury. The onset of acute renal failure was rapid and the duration of oliguria for most patients was 3-4 days (Figure 21).

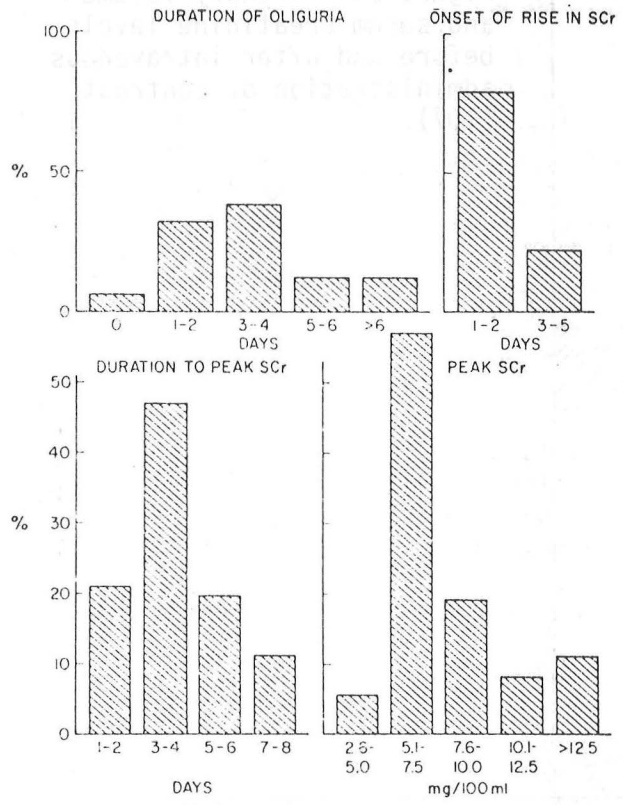


Figure 21. Course of dye-induced acute renal failure in patients with diabetes mellitus (107).

The peak serum creatinine of between 5 and 7.5 mg% was reached in the majority of patients between the 3rd and 6th day. While recovery of renal function to baseline levels is usually achieved after contrast-induced acute renal failure, temporary dialysis (104) and chronic hemodialysis (105) have been necessary in some patients. Patients with multiple myeloma and diabetes mellitus are not unique in their

susceptibility to developing ARF after excretory urography. Eight of 13 patients with acute renal failure reported by Ansari (106) had neither of these disorders. In this group of patients preexisting renal insufficiency seemed to have been the unifying factor explaining their susceptibility to toxicity.

Direct injection of x-ray contrast into the arterial circulation appears to be even more toxic to the kidneys than when given by the intravenous route. Diabetes was the underlying disease in 6 of 10 patients developing ARF after renal angiography in one series (106). Acute renal failure developed in four patients as a complication of cerebral angiography (108). All four patients were adult onset diabetics and 3 had mild renal impairment prior to the study. Weinrauch et al. (109) noted a 92% incidence of acute renal failure occurring in 13 azotemic juvenile diabetics undergoing coronary angiography. Although the mean serum creatinine of this group prior to angiography was 6.8 mg%, none was undergoing hemodialysis. Following the procedure 6 patients required chronic hemodialysis. Two of these subsequently received kidney transplants but four remained on chronic hemodialysis. Port and associates (113) reported 8 cases of acute renal failure after angiography. Five of 8 patients had an increased serum creatinine at the time of the study and only one patient was diabetic. Dehydration, shock and excessive contrast dose were not apparently present. Thus, non-diabetics with renal insufficiency are also at risk when undergoing angiography.

Several theories have been proposed to explain the renal toxicity of x-ray contrast agents (Table XIII).

Table XIII

THEORIES OF CONTRAST ASSOCIATED ARF

1. Tubular obstruction secondary to precipitated proteins
2. Contrast induced immune-complex disease
3. Slowing of microcirculation
4. Obstructive crystalluria (uric acid)
5. Direct nephrotoxic effect

The histology of myeloma kidney is characterized by intratubular casts and the associated renal functional impairment is felt to be at least partly due to tubular obstruction. Such observations have led to the theory that contrast agents may accelerate this precipitation of Bence-Jones proteins (114,115). In support of this position, Lasser and associates (116) demonstrated that two urographic contrast agents no longer in use because of their toxicity, iodopyracet (Diodrast) and sodium acetrizoate (Urokon), produced *in vitro* precipitates in the urine of myeloma patients in a pH range of 4.5 to 5.5. However, agents that have been in use for the past 15-20 years, meglumine diatrizoate (Renografin) and sodium diatrizoate (Hypaque) produced no precipitate in this pH range. It is clear, however, that even the latter two agents are capable of causing ARF in multiple myeloma (102), and other factors must be involved. McQueen and associates (117) demonstrated that Bence-Jones proteins readily cause Tamm-Horsfall proteins to sludge *in vitro*. Whether this same phenomenon occurs *in vitro* and causes tubular obstruction as proposed by Berdon et al. (118) is still conjectural. It is equally plausible to propose that ARF results from a primary reduction in glomerular filtration and that tubular precipitation of proteins represents a secondary phenomenon.

Kleinkneckt et al. (119) detected IgM Kappa type antibodies against contrast material in one patient who developed acute renal failure following her first exposure to x-ray contrast during excretion urography. The authors speculated that circulating immune complexes may have liberated vasoactive substances capable of inducing renal cortical ischemia and anuria.

Several observations point to contrast-induced vascular alterations as the common pathway for toxicity. Sobin and associates (120) observed that contrast material caused aggregation of erythrocytes, slowing of the microcirculation and vasoconstriction in human corneal-scleral blood vessels. Whether similar changes occur in the renal circulation is unknown. Transient decreases in renal plasma flow and glomerular filtration rate occur after large-dose excretory urography in man (121-123) and this may assume great importance in patients with preexisting renal disease or in the presence of dehydration.

Contrast materials are uricosuric (124,125). The oral cholecystographic agents (Telepaque, Oragrafin, and Cholografin) are the most likely agents to cause uricosuria but Hypaque to some

degree also shares this property (125). Based on these clinical observations, these latter two studies postulate that acute renal failure developing after radio contrast administration may represent a form of acute uric acid nephropathy. However, prior treatment with allopurinol was not effective in preventing this complication in one patient(126).

A direct nephrotoxic effect of these agents on the kidney is the most widely held theory of contrast induced nephrotoxicity. Changes of acute tubular necrosis in the dog (127) and man (128) were associated with toxicity from various radio contrast agents. Goldstein, et al. (129) noted the appearance of glutathione transferase, a proximal tubular enzyme in the urine of 5 of 16 patients following renal angiography. Although none of these patients experienced an increase in BUN or creatinine following the procedure, the data does suggest that the contrast agents produced early toxicity to the proximal tubular cells. It is worth recalling here that aminoglycoside antibiotics also cause proximal tubular enzymes spillage into the urine as one of the earliest signs of their nephrotoxicity (53). Lasser et al. (127) studied the histologic effect of several contrast agents injected directly into the dog kidney. The halogen portion of the molecule appeared to represent the toxic portion since injection of the basic non-halogenated molecule constructed with prosthetic groups in all positions on the benzene ring caused no renal histologic damage.

In summary, radio contrast administration is ordinarily a safe procedure, but patients with multiple myeloma and diabetes mellitus are at a somewhat higher risk, particularly when renal function is impaired. Contrast studies in these groups should be performed with strong indications and only when the potential benefits outweigh the risks. Procedures such as renal ultrasonography or renal scanning may be acceptable alternatives. The now routine use of high dose contrast injections has substantially improved urographic visualization of the kidneys and has eliminated the need for prior dehydration maneuvers. All patients about to undergo urographic or angiographic procedures should be encouraged to drink liberal amounts of fluids, especially those patients subjected to repeated enemas. In circumstances where fever, vomiting, and diarrhea complicate an illness, the procedure should be delayed until proper fluid balance has been restored. To prevent dehydration in diabetics and patients with multiple myeloma intravenous fluid administration prior to the study is also recommended. Although there is no correlation between the occurrence of

acute renal failure and the dose of contrast media or its iodide content (107), it seems prudent to use the smallest quantity of contrast compatible with a good study. Little is known regarding prevention of toxicity in high risk patients, but induction and maintenance of a mannitol diuresis might be warranted during renal angiography where contrast is delivered to the kidneys in high concentrations.

Anesthetics

The administration of the anesthetic methoxyflurane (Penthrane) has been associated with acute renal failure in man (130) and in some patients appears to be irreversible (131). The severity of renal functional and renal pathological changes is proportional to the dose of methoxyflurane administered (132). In clinical usage, toxicity appears to be enhanced when the anesthetic agent is administered without anesthetic adjuvants, i.e., more methoxyflurane is required to achieve the same depth of anesthesia (130). Several clinical as well as experimental studies now confirm that the fluoride ion is the most likely cause of the nephrotoxicity. Cousins and Mazze (132) studied dose related abnormalities in renal function in patients receiving either methoxyflurane or halothane (Fluothane). Methoxyflurane and halothane affected renal function and serum electrolytes in very different ways (Figure 22). Methoxyflurane was associated with a progressive rise in serum fluoride levels as the duration of anesthesia increased. In addition, serum urea nitrogen levels rose as did the serum sodium and serum osmolality. In contrast, halothane had no effect on these measured variables. In this study, the mean threshold of toxicity occurred at approximately 2.3 minimum alveolar concentration hours (MAC) corresponding to a peak serum inorganic fluoride concentration of 50-60 μM/L. In addition, methoxyflurane administration was associated with an increase in urinary inorganic fluoride excretion as well as an increase in the 24 hour oxalic acid excretion (Figure 23). Also, methoxyflurane resulted in increased urine flow rates during the postoperative period as well as a prolonged return to the preoperative maximum urinary osmolality. This impairment in urinary concentration following methoxyflurane administration was vasopressin-resistant (Figure 24).

Studies in man and animals indicate that fluoride administration causes polyuria. Whitford and Taves (133) administered sodium fluoride to four groups of rats and noted that polyuria correlated directly with the plasma fluoride level (Figure 25). These data suggested that the polyuria was directly related to plasma fluoride concentration up to about 300 μM/L, but at higher concentrations there was some loss of the effect.

Enflurane (Ethrane) is a newer fluorinated anesthetic similar to methoxyflurane in anesthetic characteristics but considerably less nephrotoxic. To determine the reason for this difference,

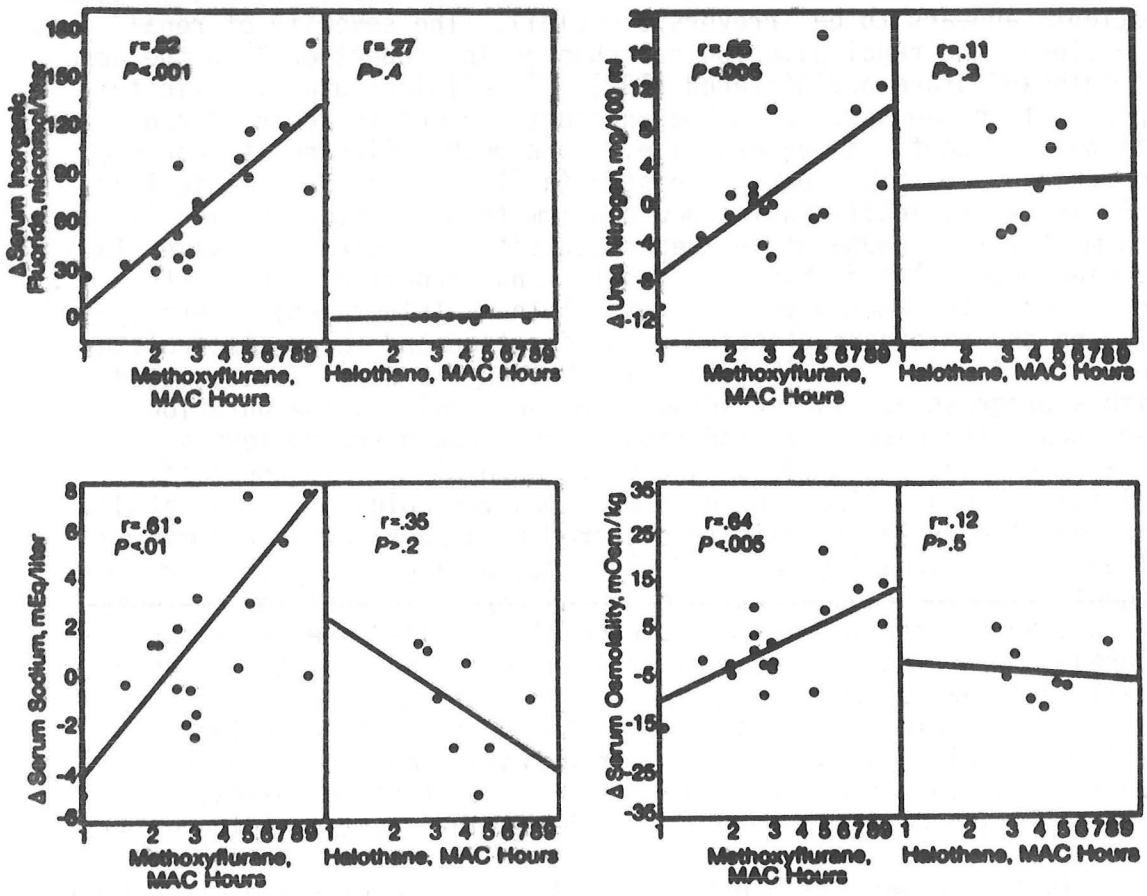


Figure 22. Dose-response curves for postoperative changes in serum variables measured 48 hours after surgery. Values are plotted at anesthetic dosage (MAC hours) for methoxyflurane and halothane. Patients anesthetized with methoxyflurane had dose-related increases in serum inorganic fluoride, blood urea nitrogen, sodium, and osmolality (132).

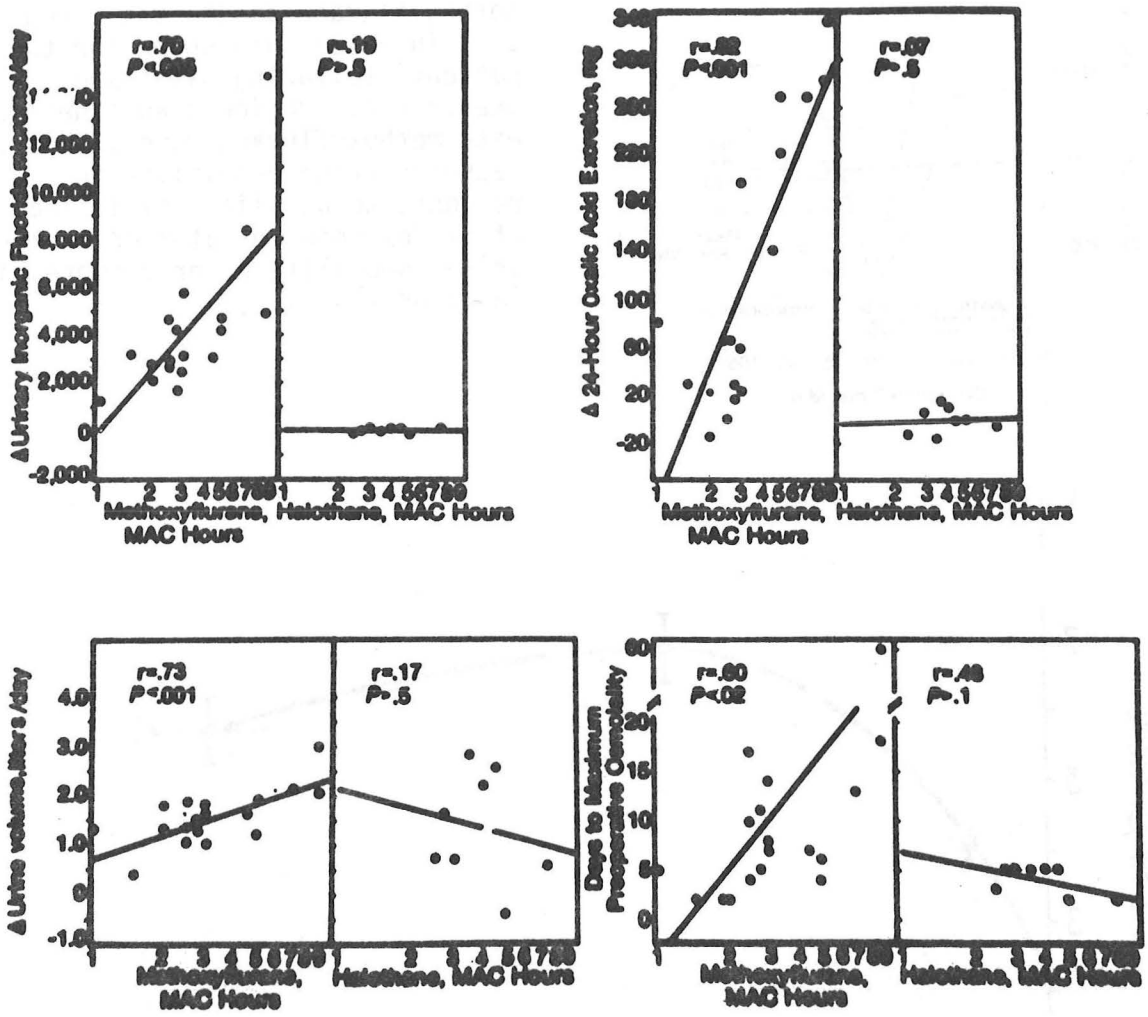


Figure 23. Dose-response curves for postoperative changes in urine variables 48 hours after surgery. Values are plotted at anesthetic dosage (MAC hours) for methoxyflurane and halothane. Patients anesthetized with methoxyflurane had dose-related increases in urine volume, urinary inorganic fluoride ($U_F V$) and oxalic acid excretion, and a delayed return of urine concentrating ability (132).

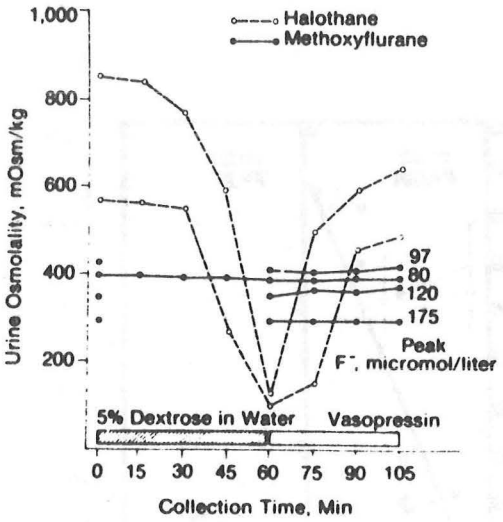


Figure 24. Vasopressin infusion tests in four patients with polyuric renal dysfunction following methoxyflurane anesthesia. Control infusions are shown for two patients following halothane anesthesia. Patients anesthetized with methoxyflurane were unable to decrease urine osmolality in response to a 1 liter fluid load of 5% dextrose in water or increase urine osmolality after vasopressin infusion (132).

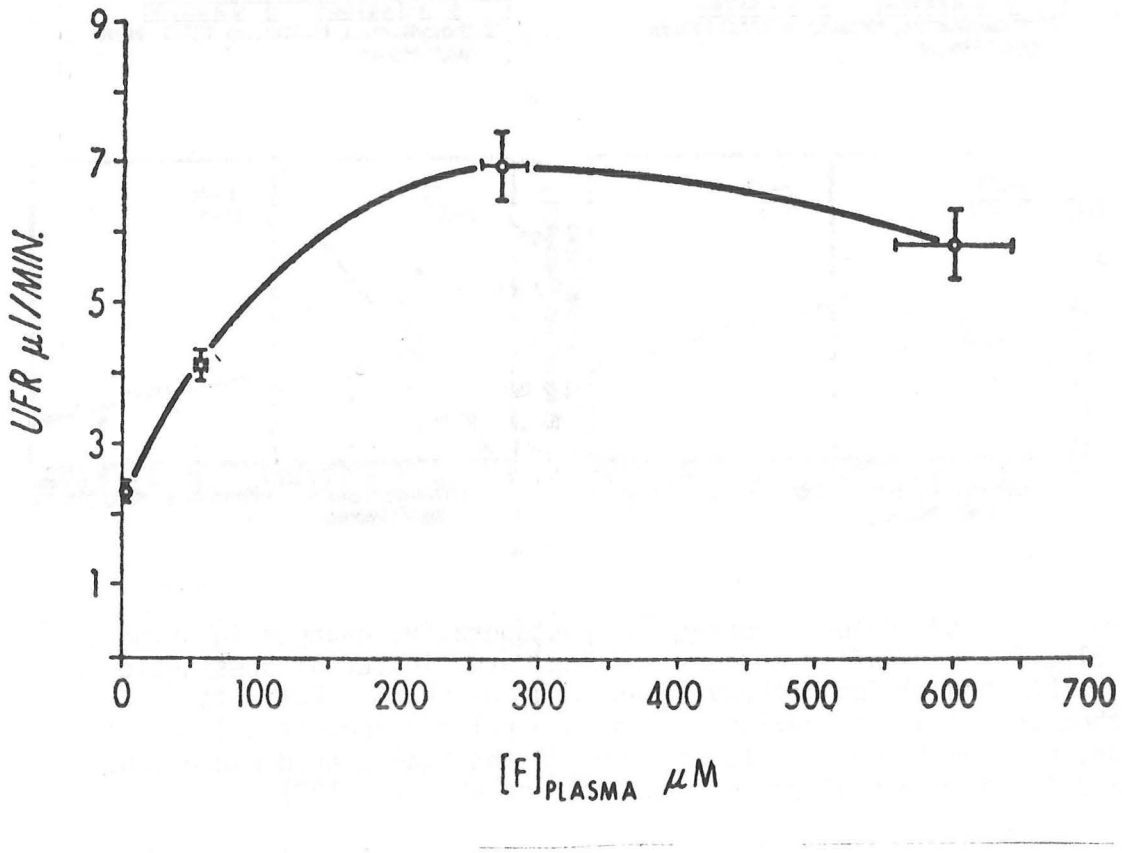


Figure 25. Mean values ± SEM for urine flow rates and plasma fluoride concentrations for all samples within specified fluoride infusion rate groups. (left to right) 0, 100, 500, 1000 nmoles of fluoride/min. Each group receiving fluoride had an increased urine flow rate compared to controls with $p<.001$ (133).

Cousins and associates (134) compared the metabolism and renal effect of enflurane and halothane in 10 surgical patients and compared this to earlier results with methoxyflurane (Figure 26).

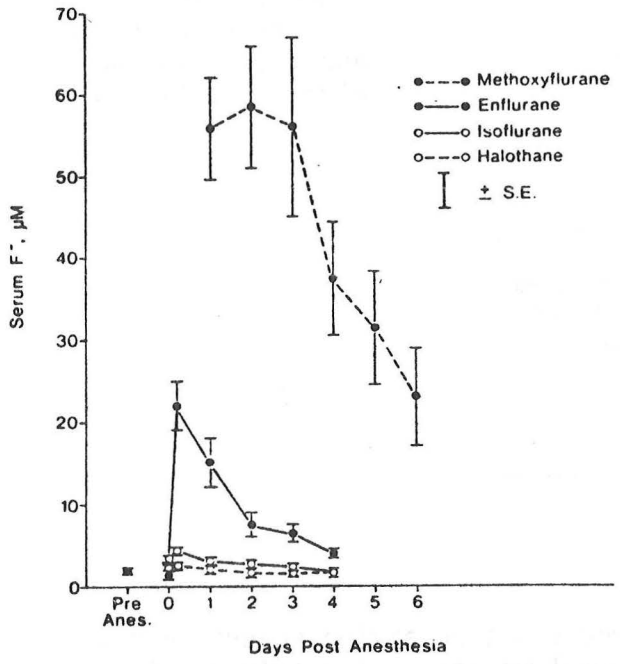


Figure 26. Serum inorganic fluoride concentrations prior to and following several anesthetics (134).

They found that serum fluoride concentration increased following enflurane but far less so than with a similar exposure to methoxyflurane. Also, oxalic acid excretion was not increased after enflurane suggesting that the latter was not an enflurane metabolite. In two of their patients, however, serum inorganic fluoride concentrations during and after enflurane anesthesia rose higher than the mean for the other eight patients (Figure 27).

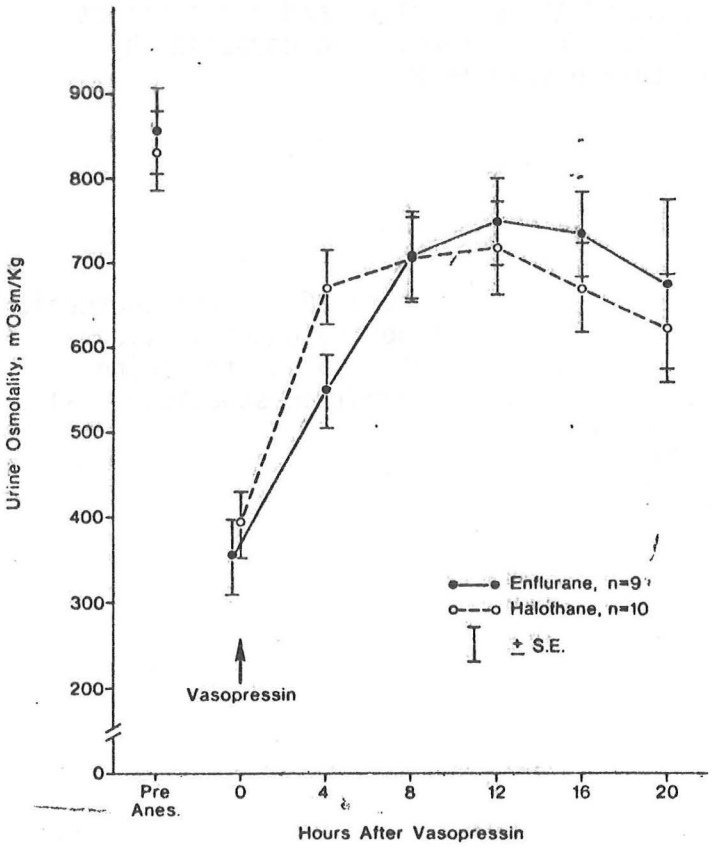


Figure 27. Serum inorganic fluoride (F^-) concentrations during and after enflurane anesthesia in two atypical patients (134).

One of these patients prior to surgery was receiving several drugs capable of inducing hepatic microsomal enzymes. The only renal functional abnormality noted in these ten patients occurred in this patient who achieved a serum inorganic fluoride level of 106 μM/L. Following vasopressin administration, this patient failed to maximally concentrate his urine. However, when the mean results for both groups were compared, the response to vasopressin in both groups was similar. This study confirms the general clinical impression that enflurane is a less nephrotoxic anesthetic than methoxyflurane.

However, in the rat, enflurane when administered for prolonged periods of time will produce polyuria of a magnitude comparable to lower doses of methoxyflurane (Figure 28) (135).

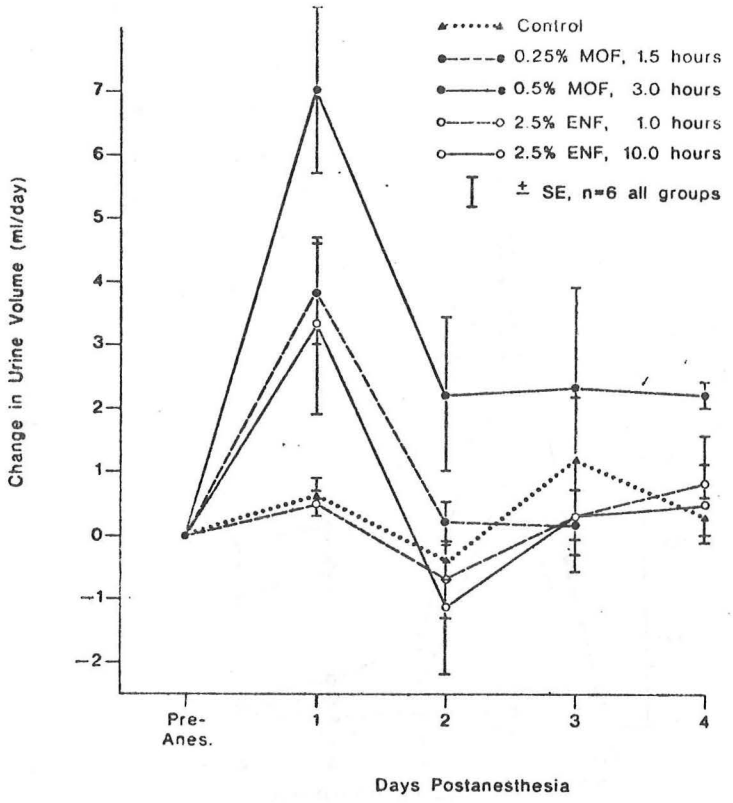


Figure 28. Change in daily urine volume (mean ± S.E.) after anesthesia. The increases in urine volume after 2.5% enflurane (ENF), 10 hours, and 0.25% methoxyflurane (MOF), 1.5 hours, were similar (135).

This defect in urine concentration was associated with urinary inorganic fluoride excretion levels similar to methoxyflurane (Figure 29).

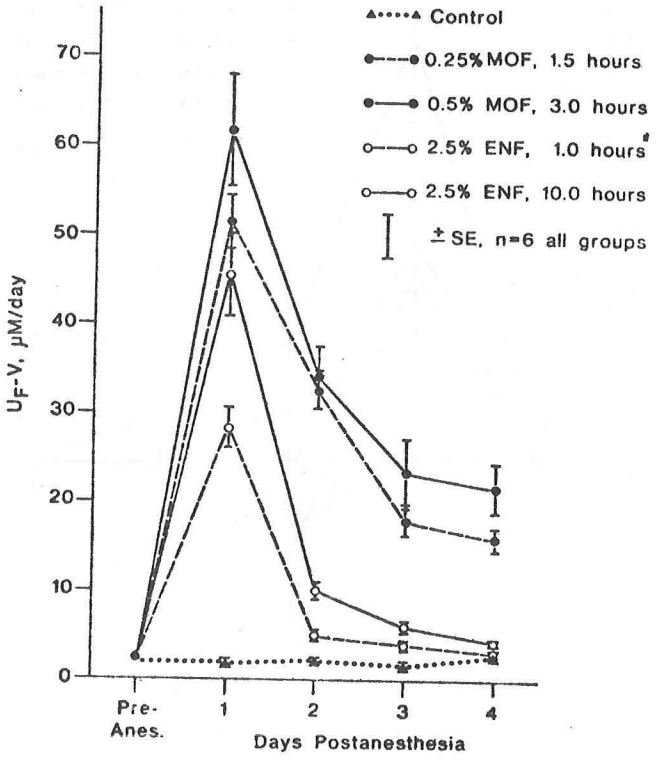


Figure 29. Changes in urinary fluoride excretion (mean ± S.E.) after methoxyflurane or enflurane anesthesia (135).

Similar degrees of polyuria followed both methoxyflurane and enflurane when comparable serum and urinary inorganic fluoride levels were achieved. This study, then, suggests that the difference in clinical toxicity between the two agents reflects the different serum inorganic fluoride levels achieved during the usual administration of each agent. In addition, these authors found that the impairment in urinary osmolality following prolonged administration of enflurane was not reversible following vasopressin administration. Thus, polyuria in this experimental form of enflurane nephrotoxicity is similar to methoxyflurane in being vasopressin resistant.

The role of enzyme induction in the toxicity of methoxyflurane and possibly enflurane administration is an interesting but at the moment, not well explored area. Enzyme induction with phenobarbital prior to a short exposure to methoxyflurane was postulated as the cause of a marked increase in inorganic fluoride production and a paralleled decrease in renal function in one patient (132). Also, phenobarbital administration increased production of the methoxyflurane metabolite oxalic acid (136). However, at least in the rat, enzyme induction does not appear to enhance the nephrotoxicity or the level of serum inorganic fluoride following enflurane administration (135).

The difference in nephrotoxicity of methoxyflurane and enflurane is most likely due to chemical and physical properties of the molecules. It appears that methoxyflurane is more easily defluorinated in vivo. when compared to enflurane. At equivalent anesthetic depths, blood inorganic fluoride concentration following methoxyflurane is approximately twice that of enflurane; however, less fluoride results from intraanesthetic enflurane metabolism despite its greater number of fluoride atoms per molecule (135).

Despite these clinical and experimental reports, enflurane anesthesia is not totally benign. Eichhorn and associates (137) recently documented renal failure following enflurane anesthesia (Table XIV). In contrast to the usual 22 μM per liter peak of inorganic fluoride following enflurane administration, this patient had a serum inorganic fluoride level of 93 μM per liter on the second postoperative day and developed oliguric acute renal failure. A urologic procedure in this patient six weeks earlier was done under enflurane anesthesia and raised the question of enzyme induction in the generation of the high inorganic fluoride levels. The authors speculated that the brief earlier exposure to enflurane caused enzyme induction so that the subsequently longer exposure caused generation of abnormally large amounts of inorganic fluoride ion.

Table XIV

ENFLURANE NEPHROTOXICITY

Postoperative Day	Urinary Output (ml)	Blood Urea Nitrogen (mg/100 ml)	Serum Creatinine (mg/100 ml)	Serum Inorganic Fluoride (μM/L)
0	2,200	29	----	----
1	1,725	28	----	----
2	45	29	3.4	93.6
3	0	41	7.4	27.1
4	90	60	10.3	23.6
5	590	82	11.8	----
6	500	87	10.3	18.2
7	1,070	90	10.3	14.5
8	1,200	75	6.4	----
9	1,580	60	4.3	7.8
10	2,000	33	2.1	----
11	2,160	21	2.0	----
12	1,275	--	----	----
13	2,250	20	2.4	2.8

From Ref. 137

Several patients with permanent renal failure following methoxyflurane have shown on biopsy or autopsy specimens proximal tubular dilitation, interstitial fibrosis, and oxalate deposition (127). Although oxalate deposition does not appear to play a pathogenic role in the acute renal functional impairment following this anesthetic agent, it may be that the chronic irreversible lesion is the result of the combined toxic effect of high levels of inorganic fluoride and oxalic acid deposition in the renal interstitium.

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