ANNALS OF CLINICAL AND LABORATORY SCIENCE, Vol. 6, No. 6

Acute Toxic Nephropathies: Clinical Pathologic Correlations

ROBERT C. MUEHRCKE, M.D.,* FREDERICK I. VOLINI, M.D.,†
ARTHUR M. MORRIS, M.D.,† JOSEPH B. MOLES, M.D.,†
and ARTHUR G. LAWRENCE, M.D.,†

*West Suburban Kidney Center
and
†West Suburban Hospital,
Oak Park, IL 60302*

ABSTRACT

Man's ever increasing exposure to numerous drugs and chemicals, which are the results of medical and industrial progress, produces a by-product of acute toxic nephropathies. These include acute toxic renal failure, drug-induced acute oliguric renal failure, acute hemorrhagic glomerulonephritis, nephrotic syndrome, tubular disturbances and potassium deficiency. In depth information is provided for the previously mentioned disorders.

Introduction

Acute toxic nephropathy is a by-product of man's ever increasing exposure to a vast array of various chemicals and drugs that result from industrial and medical progress. The kidney, with its rich blood supply, numerous enzyme systems and superior excretory function, is especially vulnerable to the adverse effects of chemicals, biologic products and drugs.[44,226] The kidneys comprise 0.4 percent of the total body weight and require a high oxygen consumption. The kidney's oxygen required is supplied through approximately 20 to 25 percent of the cardiac output.

Although the kidneys are of relatively small weight, they have the greatest surface area of endothelial cells when compared to other organs. The kidneys with their numerous enzyme system are second only to the liver in complexity of metabolic function. Finally, the kidneys have extremely vascular renal medullae and rete mirabile that function in the final dilution and concentration of the urine. This complex mechanism results in hypertonicity of the renal interstitium with concentration of nephrotoxic chemicals, biologic products and drugs.

In our experience, approximately 25 percent of all patients with acute oliguria have renal failure induced by drugs or chemicals.[188] The other main clinical syndrome of toxic nephropathy include the nephrotic syndrome,[133,180,256] tubular disorders,[96] acute hemorrhagic glomerulonephritis and chronic renal failure.

Mechanism

Nephrotoxic chemicals have exerted these adverse effects on the kidney either singly or through a combination of pathopharmacologic mechanisms. One mechanism is the direct action of the

nephrotoxic substance as a protoplasmic poison. The nephrotoxic agent passes into the glomerular filtration in an amount proportionate to the filtered plasma water. As the nephrotoxic substance is a foreign compound and has no specific renal tubular transport process, it is progressively concentrated within the tubular lumen. The concentration of the nephrotoxic agent is so great that it damages the tubular epithelial cells. Moreover, other nephrotoxic substances[204,228,238] may increase in their concentration to reach toxic levels within the medullary interstitium by the osmotic concentration of fluids. When sufficient quantity is accumulated, the kidney interstitium is damaged. Chronic phenacetin nephritis is one example of such a condition.[103,147,224]

Some nephrotoxic substances penetrate the cell to interact with cellular constituents and, subsequently, poison the cell. One example of this mechanism is the nephrotoxic effect of meralluride (Mercuhydrin), which reacts with enzyme systems of the sulfhydryl groups within the wall of mitochondria. Other nephrotoxins couple with enzymes to inactivate them. Some nephrotoxins affect enzymes within the mitochondria, while other toxins affect cytoplasmic enzymes. This functional interference may result in no apparent tubular morphologic abnormalities when the tissue is studied by light or electron microscopy. Other protoplasmic toxins, when concentrated, may coagulate protein and may result in either severe tubular necrosis or diffuse bilateral renal cortical necrosis.

TABLE I

Common Chemicals that Induce Acute Oliguric Renal Failure

Chemical	*Mean Lethal Dosage (Approximately per 70 kg)*
Anilin	10 g
Arsine gas (AsH_3)	MAC* 30 ppm
Camphor	2 g
Carbon tetrachloride	4 ml (MAC* 25 ppm)
Chlordane	8 g
Chloroform	25 ml
Copper compounds	15 g
Creosote	10 g
Essential (volatile) oils	1 g
Ethylene dischloride	MAC* 100 ppm
Ethylene glycol	100 ml
Formaldehyde (formalin)	30 ml
Guaiacol	2 g
Mercury compounds	MAC* 0.1 mg/M^3
	1 g
Naphthalene	5 g
Oxalates	5 g
Paradichlorobenzene	15 g
Pentachlorophenol	1 g
Phenol	10 g
Phosphorus, yellow	0.05 g (MAC* 1 g/M^3)
Resorcinol	2 g
Tetrachloroethane	MAC* 5 ppm
Thymol	2 g

*MAC - maximum allowable concentration

Other nephrotoxic agents produce their adverse effects through an immunological pathopharmacologic mechanism. The best example of such a model is duck egg albumin. The morphologic site involved is usually the large endothelial surface of the glomerular capillaries, arterioles and arteries. The duck egg albumin acts as an antigen evoking a production of antibody. Immune complexes formed in the presence of complement produce damage to glomerular capillaries.

Another important additional site involved by hypersensitivity reactions is the renal interstitium. This hypersensitivity interstitial reaction was reported more than 75 years ago by Councilman.[60] Known as "Councilman's interstitial nephritis," it is characterized by interstitial infiltrates of plasma cells, small lymphocytes, and eosinophils. A few of the drugs that cause this hypersensitivity reaction are phenindione, diphenylhydantoin (Dilantin), methicillin, phenylbutazone and meralluride (Mercuhydrin).

In general, substances toxic to the kidney include chemicals, as presented in table I, in any physical state (liquids, solids, and gases); biologic products such as horse serum, fungi (mushrooms), and vaccines; and drugs given orally or par-

enterally. Drugs produce other clinical syndromes of renal disease, including the nephrotic syndrome, chronic renal failure, tubular disturbances and acute hemorrhagic glomerulonephritis. In some situations, the damage is mild and transitory. In other situations, the damage is severe and irreversible leading to the patient's death.

Acute (Toxic) Renal Failure

The more common nephrotoxins producing acute renal failure are heavy metals, organic solvents, glycols, analine, insecticides, arsine, cresol and a miscellaneous group of chemicals. They usually act directly on the tubular cells to disrupt their metabolic and morphologic integrity.

Mercury Compounds

The inorganic salt bichloride of mercury (mercuric chloride) is also known as corrosive sublimate. Mercuric chloride is usually ingested accidentally,[175] in suicidal attempts,[34] or following its use as an abortive agent. The dose required to induce renal failure is difficult to assess.[71] In most reports the patients with acute renal failure had ingested two or three tablets (0.5 g each).[129] When more than four tablets were taken, acute oliguric renal failure was fatal. Renal lesions developed within three hours after ingestion.[47,245] Emetic and gastric lavage solutions can be made from a glass of skimmed milk with three to four teaspoons of table sugar, two tablespoons of baking soda and three eggs.

Schreiner and Maher described 11 patients who had mercuric chloride-induced acute oliguric renal failure.[225,223] Five patients who survived were treated within 48 hours after ingesting mercuric chloride; hemodialysis and dimercaprol (BAL) infusion were the methods of treatment.[138,167,169] Six patients were treated after uremia occurred, and only three of those six survived.[168] BAL appears to enhance the removal of mercuric ions by 7 to 11 percent with the use of hemodialysis.[15]

The clinical symptoms of inorganic mercury poisoning begin with a lingering bitter and metallic taste in the mouth. The patient experiences a sensation of throat constriction, suffocation, substernal burning, gastritis, abdominal pain and, finally, nausea and vomiting.[109] Persistent vomiting leads to retching of blood. Ulceration may be noted in the palate. The patient goes into circulatory failure; the pulse becomes weak and rapid. Syncope and shock are followed by a scanty urinary output. Finally, a fatal anuria develops. Jaundice occurs in approximately 35 percent of the patients.

The kidneys of patients with inorganic mercury poisoning are usually enlarged and weigh up to 250 g each. The renal cortex is pale and thickened. The renal medullae are a slightly darker brown than normal. The most striking morphologic abnormalities occur in the proximal convoluted tubules.[97] There is extensive cellular necrosis and the lumina are filled with granular eosinophilic material believed to be derived from the cytoplasm of necrotic cells.[61] Less striking abnormalities are found in the ascending limbs, distal convoluted tubules and collecting tubules. In approximately one week, the luminal necrotic debris clears, probably because of digestion by plasmolytic enzymes. In addition, the debris is washed down the nephron lumen by the glomerular filtrate. The proximal tubule appears to be dilated and lined by flat epithelial cells.[181] Patchy calcification may occur in severely damaged tubules. Interstitial edema is noted early; if oliguria is prolonged, interstitial fibrosis ensues. Mercurials have produced the nephrotic syndrome in some patients.[17]

Carbon Tetrachloride

Carbon tetrachloride (CCl_4) is widely used as an industrial solvent, as a household cleaning agent, as a constituent in certain types of fire extinguishers, in some hair lotions, as an antihelmintic agent and as a vermifuge.[2] It is a volatile, heavier than air liquid that accounts for the high incidence of exposure in poorly ventilated areas. Carbon tetrachloride is toxic in concentrations greater than 100 ppm.[86] It is absorbed through the lungs, the skin and the gut. It concentrates in fatty tissue such as the brain and bone marrow.

Carbon tetrachloride is soluble in ethanol. Therefore, the drinking of alcoholic beverages and the simultaneous exposure to carbon tetrachloride tend to increase or enhance carbon tetrachloride absorption and subsequent toxicity. *In vitro*, carbon tetrachloride is oxidized to phosgene and later can condense with ethyl alcohol to form ethyl chloroformate. The latter is an extremely nephrotoxic substance. In the absence of ethyl alcohol, phosgene condenses with ammonia to form urea.

Carbon tetrachloride appears to be more dangerous in obese or in undernourished individuals. In France, carbon tetrachloride was the commonest chemical producing acute renal failure. The clinical features of acute poisoning are variable. Males are more often afflicted than females by a ratio of 14 to 1. Inhalation is the most frequent route of exposure. Toxicity caused by ingestion carries a grave prognosis. Initially, the patient has surface or superficial irritation to the exposed skin and mucous membranes. Later the patient has headache, nausea, vomiting, abdominal pain and mental confusion leading to convulsions and coma. Although liver damage is a very striking feature of carbon tetrachloride toxicity, acute renal failure is the most frequent cause of death.

The onset of oliguria is prolonged and may occur seven to ten days after exposure. Some patients may have forgotten their exposure to this solvent. Absolute anuria may last from one day to several weeks. One patient had carbon tetrachloride-induced oliguria for 67 days. In the present author's experience, patients with acute renal failure caused by carbon tetrachloride were usually "do-it-yourselfers." They usually worked indoors, generally in the basement during the winter months. This meant that the windows were closed and there was no source of ventilation. They usually drank several cans of beer while they refinished furniture or cleaned outboard motors or clothes, — usually neckties.

Morphologic abnormalities occur in the cortical convolutions and Henle's loops. Tubular necrosis is most prominent in the outmost cortical portion. Acute tubular necrosis may be severe with tubular coagulation and degranulation.[236] Ultrastructural study of the glomeruli reveals them to be normal. Initially interstitial edema is common; later, interstitial fibrosis occurs.[233]

Tetrachloroethylene

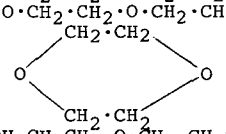
Tetrachloroethylene is a colorless liquid with an ethereal odor. It is soluble in organic solvents. Tetrachloroethylene has replaced carbon tetrachloride in the treatment of hookworm infestation. It is placed in soft gelatin capsules of either 0.2, 1.0 or 2.5 ml. Tetrachloroethylene produces inebriation, giddiness and liver damage. It is less nephrotoxic than carbon tetrachloride but has produced acute oliguric renal failure from acute tubular necrosis.

Glycol Toxicity

Glycols, as presented in table II, are found in automobile antifreeze, solvents for plastics, paints (especially lacquers, textiles, and cosmetics) and flavoring

TABLE II

The Toxic Glycols

Glycol	*Formula*
Ethylene glycol (antifreeze)	$HO \cdot CH_2CH_2 \cdot OH$
Ethylene glycol diacetate	$CH_3CO \cdot O \cdot CH_2 \cdot CH_2 \cdot O \cdot CO \cdot CH_3$
Propylene glycol	$HO \cdot CH_2 \cdot CH \cdot OH \cdot CH_3$
Diethylene glycol (diglycol)	$HO \cdot CH_2 \cdot CH_2 \cdot O \cdot CH_2 \cdot CH_2 \cdot OH$
Ethyl diethylene glycol (carbitol)	$C_2H_5 \cdot O \cdot CH_2 \cdot CH_2 \cdot O \cdot CH_2 \cdot CH_2 \cdot OH$
Methyl diethylene glycol (methyl carbitol)	$CH_3 \cdot O \cdot CH_2 \cdot CH_2 \cdot O \cdot CH_2 \cdot CH_2 \cdot OH$
Butyl diethylene glycol (butyl carbitol)	$C_4H_9 \cdot O \cdot CH_2 \cdot CH_2 \cdot O \cdot CH_2 \cdot CH_2 \cdot OH$
Diethylene dioxide (dioxane)	
Dipropylene glycol	$CH_3 \cdot OH \cdot CH \cdot CH_2 \cdot O \cdot CH_2 \cdot CH \cdot OH \cdot CH_3$

extracts. Allen has classified the toxic glycols.[5] The more important nephrotoxic glycols are ethylene glycol and diethylene glycol. Ethylene glycol dinitrite, a yellow liquid used in the explosive industry, produces symptoms resembling those of nitroglycerol toxicity. Methemoglobinuria and acute tubular necrosis are the prominent renal features. Propylene glycol produces hemoglobinuria and prolonged oliguria without crystals in the tubular lumen. Ethylene dichloride may produce shock, pulmonary edema and tubular necrosis.

Ethylene glycol. Ethylene glycol is the main substance in antifreeze and was made popular during World War I. It is a colorless odorless liquid and is ingested by mistake during "alcoholic bouts." Some describe its taste as unpleasant and waxy; others describe it as sweet.[164] When it is mixed with water and is swallowed, it imparts a feeling of warmth to the mucous membranes and produces acute inebriation. Ethylene glycol is converted to the more nephrotoxic intermediaries, — glycolaldehyde, glycolic acid and oxalic acid.[137,206] Each of the intermediary compounds is a precursor of oxalate.

Although calcium oxalate crystals are found within the renal tubules and other organs, acute oliguric failure does not result from the simple obstructive effects of oxalate. It is the direct nephrotoxic effects of ethylene glycol or one of its intermediary products that induces acute oliguric renal failure. The most likely nephrotoxic product is oxalic acid. The lethal dose of ethylene glycol (100 ml) would be converted to three to 10 g of oxalic acid. As small a dose of oxalic acid as two g would be fatal.[95] Gastric lavage and sodium bicarbonate infusion are two important aspects of initial therapy.

When large quantities of ethylene glycol are ingested, the clinical features are dominated by three distinct stages.[145] The first extends from 30 min to 12 hrs after ingestion and is characterized by central nervous system symptoms with initial hyperactivity progressing to coma. If the patient survives the initial complication, he enters the second stage which is characterized by cardiac and pulmonary features with tachypnea, cyanosis and pulmonary edema. The third stage is caused by deposition of calcium oxalate crystals within the kidney, and acute oliguric renal failure occurs. In the early stage of renal affliction the urine may contain oxalate crystals and protein.

Treatment includes the initial gastric lavage with a 5 percent solution of sodium bicarbonate. Intermediate dialysis is important to remove the glycol.[200] Intravenous ethanol is helpful in competing with

liver enzymes (e.g., dehydrogenase) that metabolize ethylene glycol. Morphologic abnormalities of epithelial cell destruction with intact basement membrane are common. Tubules are filled with masses of calcium oxalate crystals that are birefringent under polarized light. Intrarenal hydronephrosis is noted. Interstitial edema and focal cellular infiltrates of mononuclear cells are present. In addition, oxalate crystals are found within other organs such as the brain, the heart and the lungs.

Diethylene glycol. Diethylene glycol is a colorless liquid which was used with catastrophic results as a medicinal vehicle in an elixir of sulfanilamide. During September and October of 1937, at least 76 patients died within a few days after taking the elixir which contained 72 percent diethylene glycol and a 10 percent solution of sulfanilamide. This drug-induced disaster occurred in an era before the United States Food and Drug Administration had its drug evaluation program in effect. The recommendation of Geiling and Cannon in a report on the toxicity of the sulfanilamide elixir can be used as an excellent guideline for the pharmaceutical evaluation of drugs.[105] Their report is recommended to individuals who have any doubts of the necessity for drug toxicity evaluation.

Grossly, the kidney was pale, flabby and swollen. Microscopically, there was severe hydropic tubular degeneration similar to that seen in the proximal tubules of potassium-depleted patients. The epithelial cells were swollen and their lumina were patent. Spoke-like deeply basophilic crystals were seen in the distal convoluted tubules. Bilateral renal cortical necrosis was seen in a large group of individuals following sulfanilamide elixir ingestion.

ANILINE

Aniline and its derivative, phenylhydroxylamine, have low molecular weights (93 and 109, respectively). They pass through the semipermeable membrane of the hemodialysis unit. Acute poisoning by pure anilin is rare.[118] However, poisoning does occur in industrial workers and in children exposed to inks, colored wax crayons and shoe polishes. Diapers freshly stamped with aniline marking ink have resulted in fatal methemoglobinuria and acute renal failure in infants.

Aniline poisoning has been caused by the percutaneous absorption of aniline from freshly dyed shoes or blankets. Aniline and its derivative produce hemolysis, methemoglobinuria,[53] shock, cyanosis, dyspnea, headache, dizziness and blurring of mental functions. If the aniline poisoning is severe, the manifestations are shock, cyanosis, coma, anemia and, finally, fatal anuria.[259]

The diagnosis is made when methemoglobinuria is found. This is detected as a well-defined absorption band at 630 wavelengths and immediately disappears after the addition of a few drops of 5 percent potassium cyanide (KCN) solution. Diazo-reacting compounds can be found in the blood, urine, and hemodialysate. Comparisons of the diazo-reacting compounds in blood, urine and dialysate are used to obtain an optimal clinical end point for dialysis.

Treatment for the poisoning is the removal of aniline by gastric lavage, purges, and hemodialysis. This removal permits the reducing enzyme system of the erythrocyte to reconvert methemoglobin to hemoglobin rapidly. Intravenously injected methylene blue in doses of 1.0 to 2.0 mg per kg body weight should be given over a period of several minutes. This dose very rapidly reconverts methemoglobin to hemoglobin. It may be necessary to repeat methylene blue injections at hourly intervals. The blood pressure should be supported by whole blood transfusions, vasopressive agents and hemodialysis. Dialysis should be

maintained for longer periods than are usual for treating acute renal failure. Such treatment will remove the toxic derivative mobilized as a lipid soluble material from body tissues. Acute tubular necrosis is the common morphologic change found in aniline poisoning.

INSECTICIDES

The two main groups of nephrotoxic insecticides are the chlorinated hydrocarbons and the organophosphates. Acute tubular necrosis is the common morphologic finding in patients with acute oliguric renal failure.

Chlordane. The chlorinated hydrocarbon insecticides are stimulants of the central nervous system. They kill insects by overstimulation and may cause the death of man through the same mechanism. The chlorinated hydrocarbon insecticides penetrate the skin of man or are inhaled when the insecticide is in a fine aerosol spray.

Chlordane, one example of this group has produced fatal anuria.[66] The initial clinical symptoms are dizziness, nausea, headache and ataxia. Sudden unexpected convulsions similar to gran mal epilepsy occur and lead to stupor and coma. Pulmonary edema may occur between episodes of repeated convulsions. Shock may occur and may be followed by acute oliguria and death in uremia.

Parathion. Parathion is an organophosphate type of insecticide. Mann and associates observed that renal tubular malfunction occurred in individuals during occupational exposure to parathion. The chronic exposure to pesticides containing parathion produces a chronic irreversible renal tubular dysfunction that increases with duration of exposure.

HEXOL

Hexol is a mixture of a steam-distilled pine oil derivative (70 percent) and neutral soap (30 percent). The pine oil derivative is a mixture of terpin alcohol, predominately terpineol, with 5 to 10 percent each of terpene, borneol and terepene ethers. Hexol is used in the United States as a household disinfectant.

The common toxic effects of pine oil distillates are local irritation on the skin or burning pain in the mouth.[177] They produce central nervous system excitation and, later, depression. Hexol produces headaches, giddiness, ataxia, stupor and death in respiratory failure caused by central nervous system depression.

The pine oil distillates have produced dysuria, hematuria, proteinuria, and glycosuria.[55,132] In general, renal damage is transient and completely reversible. Gornel and Goldman reported a 31 year old woman who had hexol-induced acute oliguric renal failure.[111] She used a syringe and catheter to instill into her uterus three to six ounces of 2:1 mixture of hexol and water. The following day she had anuria, which lasted four days and a diuresis followed. Eleven months later her creatinine clearance was 47 ml per min. Two renal biopsy studies were done, the first at six weeks and the second at five months after anuria. The prominent findings were a completely healed renal tubular lesion, atrophied tubules and interstitial fibrosis.

ARSINE

Arsine-induced renal failure was discussed previously. It usually occurs as an occupational hazard.[67,74] When anuria occurs the prognosis is grave.[33] Arsine (AsH_3) is inhaled and readily combines with the hemoglobin within the erythrocyte to form an arsine-oxyhemoglobin complex.[151] This is initially oxidized to AsH_2-hemoglobin. As the oxidation process continues an arsenic-hemoglobin-bound product occurs. Intravascular hemolysis occurs and results in methemoglobinuria and massive hemoglobinuria. Hemoglobin and erythrocyte casts fill the tubular lumen.[173] A number of

simultaneous conditions occur. The ischemia caused by anemia, the presence of hemoglobin, methemoglobin, and erythrocyte casts and the direct tissue anoxia of arsine on the respiratory enzymes of the nephron all, either singly or in combination, produce acute tubular necrosis.[194]

Cresol

Cresol shares the generalized nephrotoxicity of carbolic acid, naphtol, guaiacol, creosote and other phenols. Lysol (cresol) has been taken for suicide purposes or in excessive concentrated solutions via vaginal douches to induce abortion.[92] Cresol is lethal in a dose of 50 to 100 ml. It produces mucous membrane necrosis, but the patient is not aware of the toxic effect. The clinical features are nausea, vomiting, dizziness, ataxia, abdominal pain and shock. Severe intravascular hemolysis occurs and is followed by hemoglobinuria, proteinuria, hematuria, acute cystitis and acute oliguria caused by acute tubular necrosis. The penetrating smell of cresol makes the diagnosis easier. The mucous membrane of the mouth and tongue may be burned and may appear to be dull white with phenol and darker brown with cresol.

Treatment includes lavage of the stomach with sodium bicarbonate, followed by a purge of magnesium sulfate (6 g in 100 ml). Skin burns should be thoroughly washed with soap and copious amounts of water. This should be followed by a wash with a 10 percent solution of alcohol. The skin should be dressed with gauze soaked in a sterile solution of sodium bicarbonate (0.5 percent). Tracheobronchial secretions should be aspirated to prevent pulmonary infection. The patient may require dialysis.

Potassium Bromate

Accidental poisoning with potassium bromate occurs in infants and children. Potassium bromate was the primary chemical constituent of the neutralizing solution used after Toni permanent wave or Coldwave. Dunsky reported a 17 month old infant who had fatal acute oliguric renal failure following ingestion of the neutralizing solution.[78]

At autopsy the patient had generalized edema and acute tubular necrosis. Warren and Gross reported a two year old infant who was accidentally fed Toni neutralizer.[250] After 38 days of anuria and oliguria, the child gradually recovered.

Chlorate Compounds

Sodium chlorate and potassium chlorate are used in the manufacture of matches, explosives, toothpaste and synthetic pigments. They are also used as weedkillers. Potassium chlorate is used as an oxidizing agent in lozenges and gargles.

If the patient develops acute renal failure, the onset stage varies from 3 to 15 hours. The clinical features are fever, hypotension, jaundice, abdominal pain, nausea, vomiting, diarrhea, extreme fatigue, nervousness and headache. The skin and mucous membranes are deeply cyanosed with a brownish-gray color. The patient has massive hemolysis with hemoglobinuria. Acute tubular necrosis is the common morphologic lesion.[69]

A clinical test can make the diagnosis of chlorate poisoning. Ten grams of kidney obtained at autopsy are minced in 16 ml of warm distilled water and an equal volume of acetone is added. The mixture is centrifuged, the acetone is evaporated and the mixture is filtered. The aqueous filtrate is decolorized by a few drops of a dilute solution of indigo sulfate followed by a few drops of sulfurous acid. Silver nitrate is added followed by sulfurous acid. Silver chloride forms a white precipitate and is used for a quantitative estimate of the chlorates.

Miscellaneous Chemicals

Acute oliguric renal failure has followed exposure to a wide variety of

common chemicals.[27] Listed in table I are these common chemicals, their maximum allowable concentration (MAC) and their mean lethal dosage (MLD). Some of the listed chemicals produce acute renal failure, but such a case is rare.[108] These include methyl chloride,[45,143] arsenic, phenols, copper sulfate,[219] paracetamol,[154] polyvinyl alcohol,[117] formalin, pyrogallol, dischromate,[10] tartaric acid, phosphorus[113] and sodium tetrathionate.

Biologic Products

Acute renal failure can result from biologic products of acute reactions such as anaphylactic allergic reactions, from delayed reactions to horse serum and vaccines or from a biologic toxin such as that found in mushrooms.[230]

Anaphylactic Allergic Reactions. Acute oliguric renal failure has resulted from anaphylactic shock caused by horse serum, penicillin, streptomycin and other antibiotics. They produce sudden and prolonged hypotensive states resulting in acute tubular necrosis. Penicillin most often produces anaphylactic shock on a hypersensitivity basis. The management of patients with anaphylactic shock should be directed toward correction of the hypotensive state and interuptions of the hypersensitivity reaction. Patients with severe, acute anaphylactic reactions should be given epinephrine subcutaneously (0.5 ml to 1 ml of a 0.001 percent solution). An adrenocortical steroid such as hydrocortisone (100 mg) should be administered intravenously and, if necessary, in multiple dosage.

A parenteral antihistaminic should be given. If the anaphylactic reaction is severe, vasopressive agents and adrenocortical steroids should be given by intravenous infusion. If a reduction of urinary output occurs, 25 g of mannitol in a 20 percent solution must be given. If mannitol proves ineffective, ethacrynic acid (50 mg) should be given intravenously. If this is unsuccessful in producing diuresis, then the usual methods of treating acute oliguric renal failure must be employed.

Horse Serum-induced Fatal Glomerulonephritis. In 1962, De LaPava and colleagues reported three patients who had malignant tumors and were treated with horse anti-human cancer serum.[65] All developed a fatal acute renal failure. At au-

TABLE III

Clinical and Morphological Data
Four Patients with Drug Induced Immune Complex Glomerulonephritis and Acute Renal Failure

Patient Sex & Age	*Drug*	*Microscopic Study*		*Fluorescent*	*Beta 1C Complement*	*Tritiated Thymidine Uptake by Lymphocytes*	*Other Organs Involved*	*Response to Prednisone*
		Light	*Electron*					
36/F	Bunamiodyl (Orabilex^{R})	Proliferative glomerulonephritis	Immune complex glomerulonephritis	IgG	-	-	-	Excellent
40/F	Dextran	Proliferative glomerulonephritis	Immune complex glomerulonephritis	IgG	-	-	Angiitis	Excellent
41/F	Methoxy flurane (Penthrane^{R})	Proliferative glomerulonephritis	Immune complex glomerulonephritis	IgG, C_3	Decreased	Positive	Hepatitis	Excellent
58/M	Polyvalent flu vaccine	Proliferative glomerulonephritis	Immune complex glomerulonephritis	IgG, C_3	Decreased	Positive	-	Required additional nitrogen mustard

topsy, a proliferative glomerulonephritis with epithelial crescents was present. The kid ney was studied by electron microscopy. Epithelial humps on the glomerular lamina densa were found. They were similar to humps of antigen-antibody complex seen in poststreptococcal glomerulonephritis, dextran-induced glomerulonephritis and renal disease caused by syphilis. The use of large dosages of adrenocortical steroids has been most beneficial in resolving these lesions of drug-induced diseases.

A horse serum-induced disease was first observed by Rackemann, Longcope and Peters.[208] They noted water retention, decreased urinary output and retention of chloride. They were the first to point out that the mechanisms of horse serum-induced renal failure were immunologically based. Later, the specific immunologic reaction was bound to be caused by soluble antigen-antibody complexes in the presence of excessive antigen.

The authors have studied four patients with drug-induced immune complex glomerulonephritis and acute renal failure as shown in table III. The clinical presentation was a serum sickness-like reaction leading to acute oliguric renal failure.

PATIENT S.B.

A 58 year old white male received 0.5 ml of a polyvalent influenza vaccine containing duck egg albumin. Six days later he developed hematuria. On the eighth day he had oliguria. The patient was admitted to a hospital and found to have an elevated blood urea nitrogen level. A retrograde pyelogram was normal. The patient was referred to the present authors for treatment. His clinical course and blood urea nitrogen level are plotted on the curve (figure 1).

His Beta 1C globulin was normal at 115 mg per dl. An arteriovenous shunt was inserted; hemodialysis was started and was continued frequently. Five renal biopsies were performed with the fifth one done three months after discharge from the hospital. The first renal biopsy study revealed, on light microscopy, proliferative glomerulonephritis (figure 2). By electromicroscopy, electron dense immune complexes were noted on the glomerular basement membrane (figure 3). IgG and Beta 1C globulin were found by immunofluorescence in immune complexes. Unfortunately, the first renal biopsy tissue was lost to further immunocomplexes study using fluorescent tagged antiduck egg albumin. A second biopsy was performed 16 days later with the hope of studying the tissue with fluorescent tagged antiduck egg albumin. To the present authors' surprise, immune complexes were no longer present (figure 4). The third and fourth renal biopsy studies showed gradual recovery of proliferative glomerulonephritis (figures 5 and 6). The beta 1C globulin was normal initially, was low on the 20th and 34th days and returned to normal level after recovery from renal failure. In the acute stage, prednisone therapy was started and nitrogen mustard was given intravenously in four divided doses. The patient made a gradual recovery and was discharged from hospital. A fifth renal biopsy study, performed three months later, was normal. This patient's immunological data are presented in (figure 7).

COMMENT

Note the similarity of the immunological data of patient S.B. to the data of Dixon's serum sickness model. Our patient received duck egg albumin as the antigen in the flu vaccine. Initially, the beta 1C globulin was normal. On the 20th day and 34th day, it was reduced and later returned to normal after renal damage recovered. Renal damage as indicated by hematuria started on the sixth day and subsided at the height of diuresis. Immune complex deposits were found in the glomerular basement membrane by electron microscopic study of the renal biopsy, IgG and beta 1C globulins were found in the immune complexes by immunofluorescent technique. In addition, the patient's incubated lymphocytes reacted positively to duck egg albumin. The immune mechanism of action in this patient paralelled the Dixon model of serum sickness.

Pertussis Vaccine. Acute oliguric renal failure caused by pertussis vaccine is rare.[30] Fatal renal failure has followed eight injections of pertussis vaccine over a six-week period. One week after the eighth injection, the patient developed fever, arthralgia, adenopathy and progressive renal failure. On the eighth day he was comatose, had mild hypertension, and had a BUN of 201 mg per dl. A diffuse healing vasculitis was found to be involving the medium and small arteries, arterioles and veins. The pathologic findings in the kidney were multiple infarction in the cortex and medulla. There were numerous antemortem thrombi and extensive papillary necrosis.

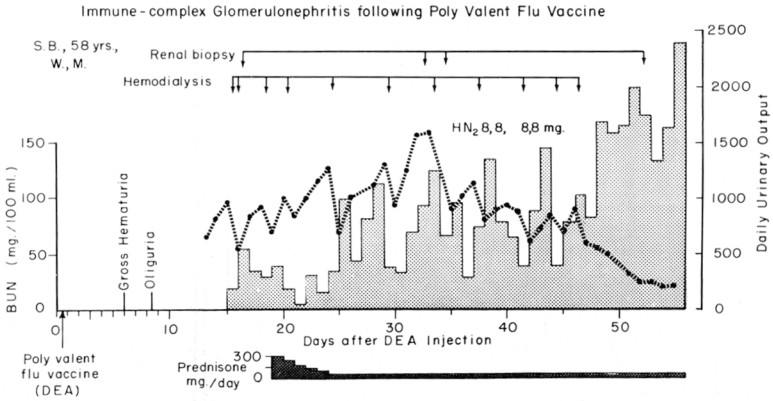


FIGURE 1. Immune-Complex Glomerulonephritis Following Polyvalent Flu Vaccine. The clinical course of patient S.B., aged 58 years, is plotted. He developed gross hematuria and oliguria following an injection of a polyvalent flu vaccine containing duckegg albumin (DEA). The blood urea nitrogen is plotted in the broken line. The daily urinary volume is the shaded grey area. He was treated by hemodialysis. Four renal biopsy studies were done. An immune-complex glomerulonephritis was found and adrenal corticosteroids were given (bar graph at bottom of figure).

Typhoid Vaccine. Four patients given typhoid vaccine intravenously for two to three days died in shock and acute oliguric renal failure. One patient died in acute renal failure four days after receiving the vaccine. Another patient developed the hepatorenal syndrome. The third patient died six hours following injection of the vaccine. Acute tubular necrosis and acute necrosis of the liver were noted.

The fourth patient, a seven month old boy who had hereditary agammaglobulinemia, developed complete anuria following one injection of thyphoid vaccine. At autopsy, acute renal cortical ne-

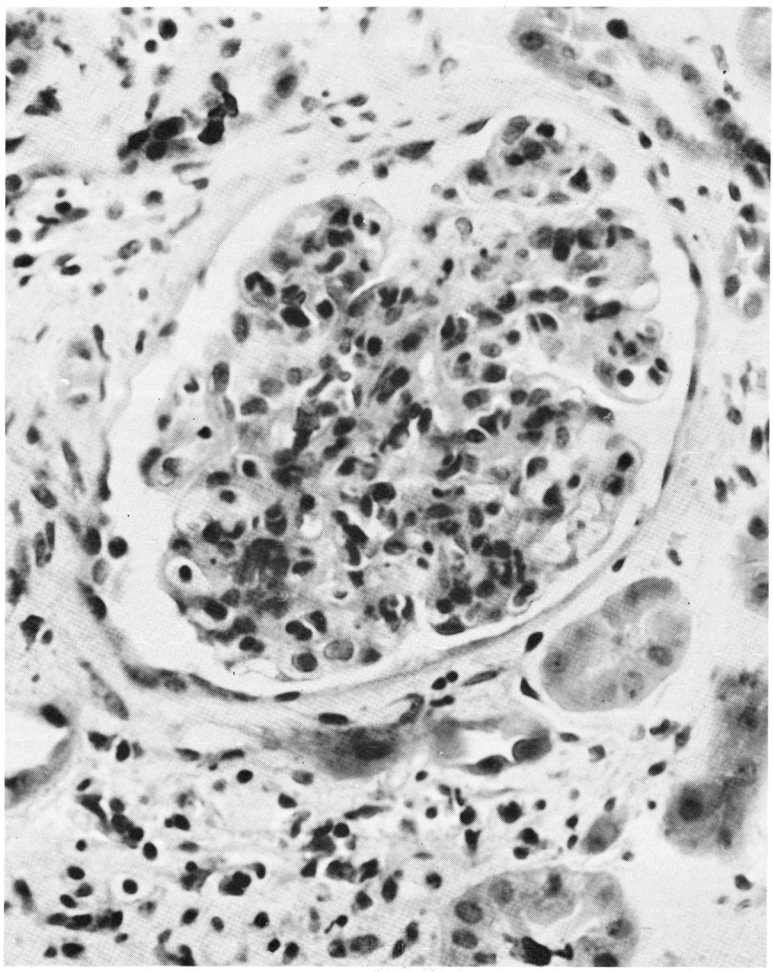


FIGURE 2. Light Microscopic Study Antigen-Antibody Glomerulonephritis was found on renal biopsy study of S.B., a 58 year old laborer. A polyvalent flu vaccine containing duckegg albumin was given 15 days before. Note the proliferative lesions in the glomeruli associated with interstitial edema. (H & E × 400).

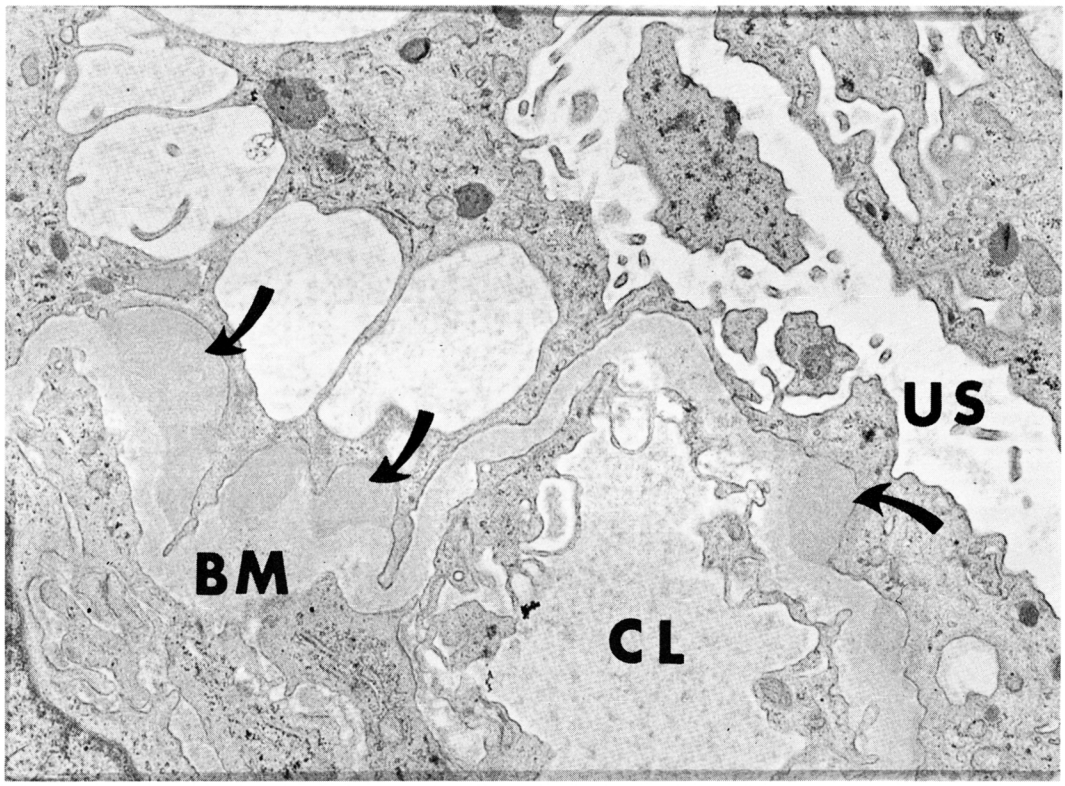


FIGURE 3. Immune Complex Glomerulonephritis. The first renal biopsy study taken 15 days after injection of duckegg albumin revealed proliferative glomerulonephritis. Electronmicroscopic study revealed immune-complex (arrows) on the glomerular capillary basement membrane (BM). Proteinaceous material is seen in the capillary lumen (CL) and in the urinary space (US). (× 900).

crosis was found. In addition, there was diffuse thrombosis of the glomerular capillaries. This patient may have had an increased susceptibility to the thyphoid vaccine in view of an inadequate or underdeveloped reticuloendothelial system.

Mushroom-induced Acute Oliguria. The terms "mushroom" and "toadstool" have no specific identifying meaning and are used interchangeably by some mycologists. There are approximately 2,000 species of mushrooms, of which about 30 are poisonous. Some mushrooms are toxic if eaten (1) in excessive quantities, (2) during certain seasons, (3) at specific stages of growth or (4) by a susceptible individual.[43] In England and Wales, there were 38 fatal cases of mushroom poisoning between 1921 and 1949. In the United States, the overall mortality rate is difficult to estimate. The common poison mushroom is the *Amanita phalloides*. It can be distinguished from the common field mushroom *(Agaricus campestris)* by noting the presence of the volva on the phalloides. It is strongly recommended that "mushroom amateurs" purchase mushrooms from commercial sources and neither pick them nor accept them from a neighbor.

Prolonged anuria may result from the mycetous toxins of *Amanita phalloides*.[187] Acute tubular necrosis is the common morphologic lesion and involves both proximal and distal convoluted tubules. The glomeruli are usually not affected. Following recovery from prolonged anuria, diffuse interstitial fibrosis de-

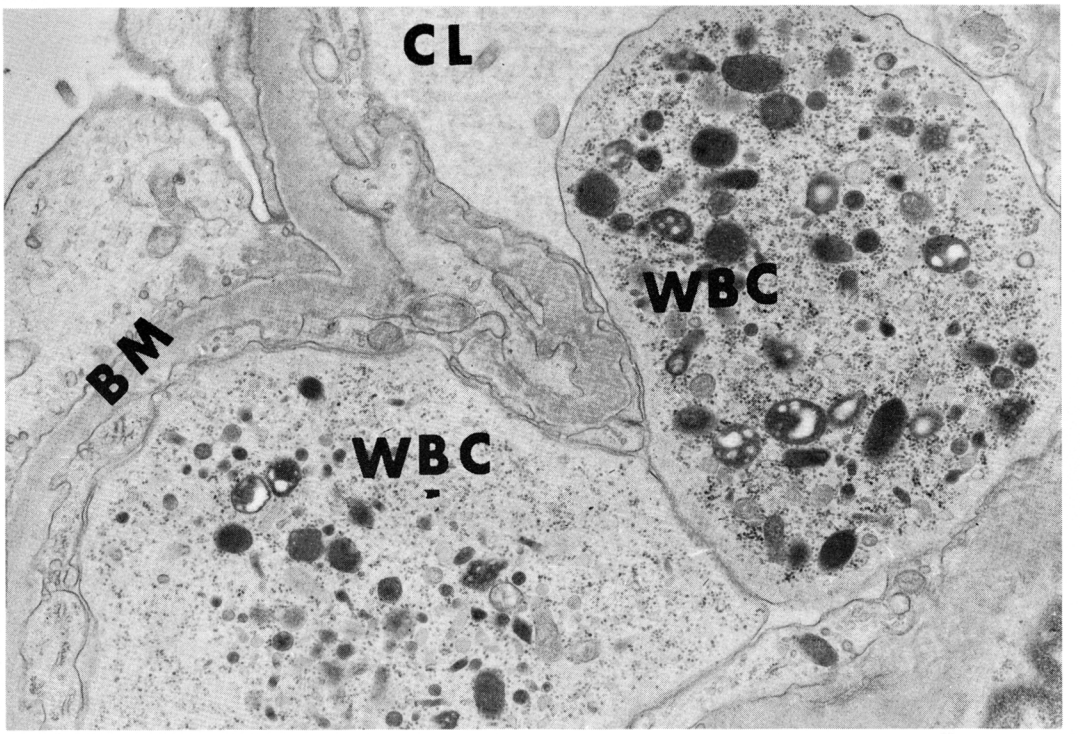


FIGURE 4. Clearing of Immune Complexes. A second renal biopsy study was done on the 32nd day after a polyvalent flu vaccine injection. No immune complexes were seen by electronmicroscopic study. The glomerular basement membrane (BM) appeared normal. Numerous polymorphonucleocytes (WBC) were noted in the capillary lumen (CL). (× 14,350).

velops and is associated with thickening of the cortical convoluted tubular basement membrane. The creatinine clearance remains reduced for several months until diffuse interstitial fibrosis becomes more focal in its renal distribution. The creatinine clearance may then approach normal values.

Treatment is directed toward sustaining life by the use of conservative measures and dialysis. Peritoneal dialysis is the method of choice, especially if albumin is added to the peritoneal fluid to remove mycetous toxins. If toxicity is induced by *Amanita muscaria*, atropine is effective in neutralizing the muscarine effects of poisonous mushrooms.

DRUGS

In general, drugs induce renal damage through any one of or a combination of many pathopharmacologic mechanisms. Of these, the nephrotoxicity mechanism is the most common and is dose-related. In general, excessively large doses are used. Drugs such as methicillin, penicillin, phenylbutazone,[172] sulfonamide,[93,163] diphenylhydantoin (Dilantin),[123] phenindione[11] and meralluride (Mercuhydrin)[189] produce acute oliguric renal failure when administered in either the usual dosages or in very small amounts. Hypersensitivity to these drugs can produce acute renal failure. There are also metabolic,[75] mechanical and secondary mechanisms that produce the disease; the latter are usually caused by drug-induced hemolytic anemia.

The tetracyclines may produce prerenal azotemia through a metabolic mechanism, such as their antianabolic ac-

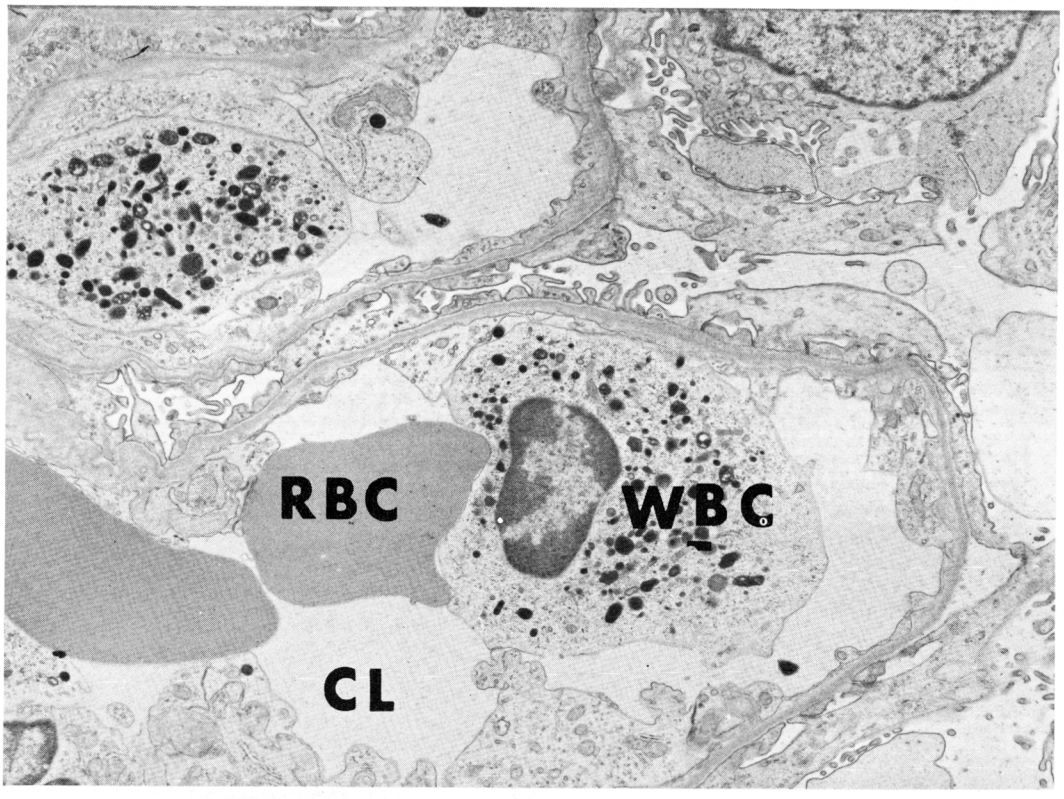


FIGURE 5. Resolution of Immune-Complex Glomerulonephritis. Renal biopsy study was done on the 34th day after injection of polyvalent flu vaccine. The glomerular capillary lumen (CL) was patent. Erythrocytes (RBC) were noted in the lumen. Numerous polymorphonuclear leukocytes (WBC) were noted. (× 3,300).

tion on the proximal tubules.[87,100] This is reflected by proteinuria, amino-aciduria, phosphaturia, hypokalemia,[99] a low plasma urate and acidosis. Tetracycline may undergo spontaneous degradation during storage, especially under warm and moist conditions. Anhydrotetracycline and epianhydrotetracycline are the nephrotoxic degradation products that produce the Fanconi syndrome.[114,158]

In addition to classification according to the pathopharmacologic mechanism, nephrotoxic drugs can be classified according to the site of morphologic damage. Finally, drug-induced acute renal failure can be classified therapeutically, e.g., antibiotics and chemotherapeutic agents, diuretic agents, radiologic contrast media and others. In this section, nephrotoxic drugs will be reviewed by therapeutic classification and will emphasize the morphologic site of drug interaction.

Drugs interact at specific morphologic sites within the kidney to produce acute renal failure. On a structural basis drugs interact at all four major components: the vessels, the glomeruli, the tubules and the interstitium. Arteritis has resulted from arsenic, bismuth, diphenylhydantoin (Dilantin),[190] gold salts,[112] horse serum, iodides, penicillin, propylthiouracil, chlorathizides[148] and sulfonamides. Glomerulonephritis has followed hydralazine,[3,4] bunamiodyl (Orabilex), phenylbutazone[77] and sulfonamides.[72] Acute tubular necrosis has followed a large variety of drugs. These include am-

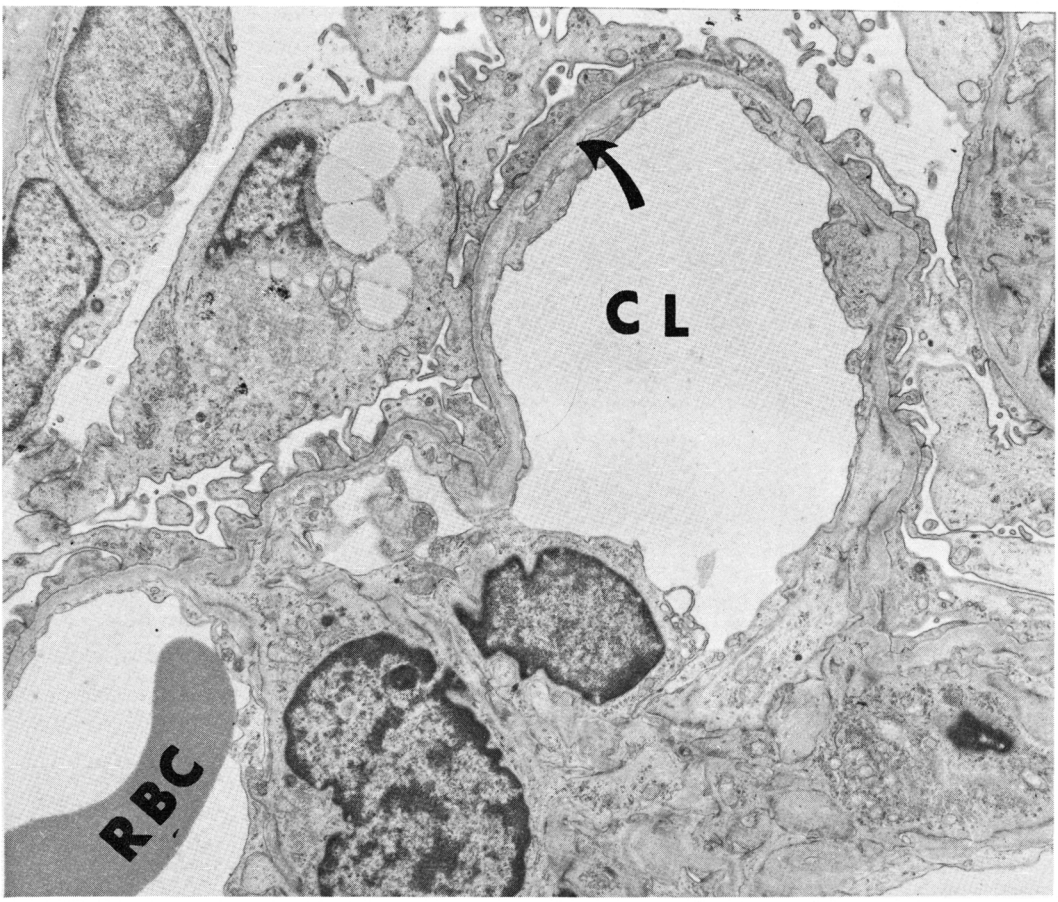


FIGURE 6. Recovery period. Renal biopsy study was done three months after discharge from hospital (145 days after exposure to duckegg albumin). The glomerular capillary lumen (CL) were patent and contained erythrocytes (RBC). Although renal function was recovered, the glomerular basement membrane was thickened on the endothelial side (arrows). (× 4,400).

photericine B,[21,49] aristolochic acid,[191] bacitracin, colistin,[83] ferrous sulfate,[136] kanamycin,[25] meralluride (Mercuhydrin), neomycin,[79] bunamiodyl (Orabilex), para-aminosalicylic acid,[174] penicillin, phenylbutazone,[165] quinine sulfate, salicylates and sodium acetrizoate (Urokon).

Acute interstitial nephritis and subsequent acute renal failure have followed treatment with meralluride (Mercuhydrin),[56] methicillin,[88] nitrofurantoin,[203] penicillin, phenacetin,[7] phenindione,[38] polymyxin B,[20] sulfonamides,[98] diphenylhydantoin (Dilantin)[211] and phenylbutazone.

Drug-induced Acute Oliguric Renal Failure

Radiologic Contrast Media

The essential ingredient in all absorbable radiologic contrast media is iodine. Individuals sensitive to iodine in any form may have mild to severe hypersensitivity reactions to contrast media. When inorganic iodine was used, such as sodium iodide in a concentration of 80 to 100 percent, numerous hypersensitivity reactions occurred. These varied from iodine mumps, dermatologic lesions and anaphylactic shock to fatal acute oliguric renal failure.[28] Although contrast media

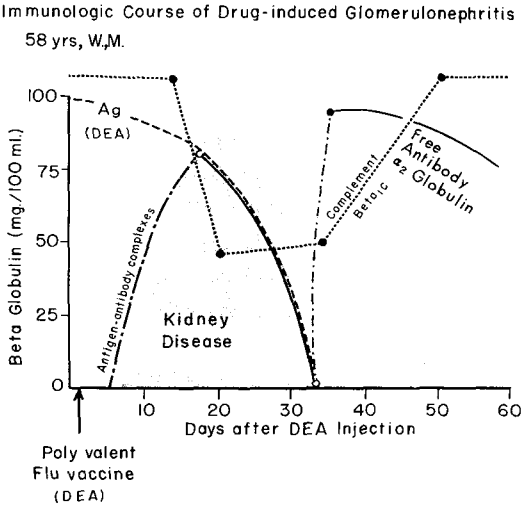


FIGURE 7. Immunological Course of Drug-Induced Glomerulonephritis. The figure illustrates the clinical course of S.B., a 58 year old white male. He received a polyvalent flu vaccine containing an antigen (Ag) duckegg albumin (DEA). Six days later renal disease was evident by gross hematuria followed by oliguria. The serum $Beta_{1C}$ globulin was normal on the 12th day but reduced on the 18th and 32nd day. The third component of complement was normal on the 48th day. The first renal biopsy study on the 15th day revealed antigen-antibody complexes with a proliferative glomerulonephritis. The second renal biopsy study on the 32nd day revealed no antigen-antibody complexes. The $alpha_2$ globulins were elevated on the 35th day. The patient's course is similar to the Dixon's animal model of antigen-antibody glomerulonephritis.

containing organic iodides are safer than those containing inorganic iodides, the former have been implicated in a steady flow of reports of severe nephrotoxicity.[130]

Physicians depend on radiologic contrast media for diagnosis of biliary diseases, vascular diseases as well as diseases of the kidneys and genitourinary tract. These agents are usually administered orally to evaluate the biliary tract, intravenously to evaluate the arterial circulation and the kidneys, and by retrograde injections into the renal pelvis to evaluate the upper genitourinary tract.[6,26,32]

ANTIBIOTICS AND CHEMOTHERAPEUTIC AGENTS

Antibiotics and chemotherapeutic agents have become indispensable in the treatment of urinary tract infection as well as in the treatment of systemic and local infections. As these agents become more extensively used, their adverse side effects and nephrotoxicity become more apparent.[102,237] In the presence of underlying renal disease, it may be difficult to recognize nephrotoxicity of a specific antibiotic.[149] Moreover, when antibiotics are used in combination with other antibiotics or with chemotherapeutic agents their exact nephrotoxic effect as well as the specific agent of the adverse reaction may be impossible to determine.[14] Nephrotoxicity caused by chloramphenicol or erythromycin has not been observed by the present authors.

Sulfonamides. Damage to the kidney is the most serious and frequent complication of sulfonamide treatment.[40,243,246] Sulfonamides were the first effective chemotherapeutic agents to have nephrotoxic properties.[110,254] The incidence of renal abnormalities varies considerably and depends in a great part on the solubility of sulfonamides.[59,76] Acute oliguric renal failure has been induced by sulfonamide treatment of parenchymal lesions[179,192] and of obstructive uropathy caused by sulfonamide crystallization[142] of the unchanged drug or of its acetyl derivative within the renal pelvis.[23,122] The method of prevention of sulfonamide obstructive uropathy is the preferential use of a more soluble sulfonamide, adequate hydration, and alkalinization of the urine with sodium bicarbonate. Obstructive uropathy caused by the low solubility of sulfonamides is more frequently observed than are the parenchymal lesion of tubular necrosi s, focal-granulomatous interstitial lesions, diffuse interstitial nephritis, hypersensitivity glomerulonephritis and acute hypersensitivity arteritis.

Several hundred patients have been reported with renal failure caused by sulfonamide crystallization.[205] The most frequent sulfonamides implicated were sulfapyridine, sulfathiazole and sulfadiazine.[35] The solubility of sulfonamides depends on a number of factors that include the drug concentration, state of dehydration, urinary pH and renal function.[217] Sulfadiazine is the most dangerous.[258] Sulfadimidine and sulfisoxazole form more soluble crystals and are less hazardous.[170,260] The finding of sulfonamide crystals in the urine leads the physician to suspect acute sulfonamide crystallization within the renal pelvis. The method of treatment is retrograde catheterization of the ureters and lavage of the renal pelvis with warm alkalinized solution (10 percent $NaHCO_3$).

Acute tubular necrosis can occur with or without sulfonamide crystallization. The tubular lumina are plugged with amorphous debris containing erythrocytes, leukocytes, hemoglobin casts and crystals. When sulfonamides induce a hypersensitivity renal lesion, one of three sites is involved. In some hypersensitivity reactions, the intrarenal arteries were involved with angiitis or with polyarteritis nodosa. In a second type of hypersensitivity reaction, the glomeruli were involved with hypersensitivity glomerulonephritis.[264] The third site for sulfonamide-induced hypersensitivity reaction was the renal interstitium. Acute interstitial nephritis was the more common interstitial lesion and was similar to a Councilman acute interstitial nephritis.[182] A focal interstitial granulomatous interstitial nephritis was a less common interstitial lesion.

Polymyxin B. The polymyxins A, B, C, D and E are a group of closely related cyclic polypeptides. Polymyxin B is an antibiotic composed of amino acids and a fatty acid. It is active against a variety of gram-negative bacilli.[42] These include *Pseudomonas, Escherichia, Klebsiella, Aerobacter, Salmonella, Shigella* and *Hemophilus* species.[227] Polymyxin B is antibacterially more active than polymyxin E. Nephrotoxicity of polymyxin is dose-related.[186,262] Following administration of polymyxin B sulfate, proteinuria, epithelial cells, and casts appear in the urine and azotemia develops.[134] In the presence of normal renal function, the nephrotoxicity is negligible at 2 mg per kg body weight per day.

Beirne and colleagues reported a 44 year old male who developed an acute oliguric renal failure caused by acute interstitial nephritis.[171] Polymyxin B sulfate seemed the most capable of several antecedent agents. The patient had an eosinophilia of 25 percent but had no dermatologic lesion. The patient gradually recovered when polymyxin B was withdrawn. A renal biopsy study done on the second day of oliguria revealed a Councilman type of acute interstitial nephritis.

Colistin methanesulfonate. Colistin, which differs from polymyxin B only by the absence of a single amino acid, is known to be identical with polymyxin E.[155] Because of this close structural relationship, colistin shares some of the nephrotoxic potential of polymyxin B. Colistin is an antibiotic produced by the soil bacterium *Bacillus polymyxa* var. garyphalus. Its antibacterial activity is against a number of gram-negative bacteria.

Toxicity studies in animals have demonstrated that colistin produces impaired renal function and renal lesions.[156] Partial to complete necrosis of the proximal tubules was found on histologic examination.[141] The effect of intramuscular colistin on renal function in man is unpredictable. Healthy individuals and patients with chronic pyelonephritis and other forms of renal disease have received the drug without significant changes in urinalysis

or BUN.[128,202] In other patients with azotemia further elevation of BUN has occurred. Oliguria developed in a five year old child who received an accidental overdose of colistin (37.7 mg per kg body weight per day for two days and 9.4 mg per kg body weight per day for three more days). When colistin was discontinued, renal function returned to normal.

Although the mechanism of colistin nephrotoxicity is unknown, it may be related to the ability of the drug to disrupt the integrity of certain cell membranes,[89] probably by acting as a cationic detergent that destroys the cellular osmotic barrier, combines with polyphosphates and thus allows leakage of substances essential to cell function. Such an action is therapeutically valuable when limited to the cell wall of various bacteria but may be harmful if human renal tubular cells exposed to high concentrations of the drug share this susceptibility. In this respect, colistin nephrotoxicity may resemble that of amphotericin B; the latter also disrupts cell membranes, but does so by binding to sterols rather than to polyphosphates. Mammalian cell membranes contain sterols, and amphotericin B[131] has been shown to damage both tissue cells in culture and human renal tubular cells may be damaged in like manner by high luminal concentrations of the drug.

Streptomycin. Streptomycin is an antibiotic that was discovered in 1944 by Schatz, Bugie and Waksman in cultures of the actinomycete *Streptomyces grieseus*.[220] Streptomycin, a carbohydrate derivative, is N-methyl-L-glucosaminido-strepto-sidostreptidine and has a wide spectrum of antibacterial activity.[126] Streptomycin, vancomycin, kanamycin and neomycin have several features in common. They are relatively strong organic bases that cross cell membranes very slowly; therefore, they are poorly absorbed from the gut.[121] They are almost entirely distributed in the extracellular fluid and are excreted mainly in the urine.[253] In addition, all four antibiotics have ototoxicity. The nephrotoxicity is increased in patients in whom there is a reduction of glomerular filtration rate. If these antibiotics are used in combination their nephrotoxicity is greatly increased.

In individuals with normal renal function, approximately 70 percent of parenterally injected streptomycin is excreted unchanged in the urine within 24 hours. In patients with renal insufficiency, less than 2 percent of an injected dose of streptomycin is excreted in the urine. Vestibular damage caused by streptomycin is frequent in patients with severe renal failure. Dialysis has been useful in the removal of streptomycin in the treatment of neurotoxicity and nephrotoxicity.

During the course of treatment with streptomycin, proteinuria and cylinduria may occassionally occur. McDermott reported a patient with acute oliguric renal failure caused by acute tubular necrosis following a daily dosage of four g of streptomycin.[193]

Kanamycin. The nephrotoxicity of kanamycin has been described in numerous reports whenever its clinical application was mentioned.[153,261] Kanamycin nephrotoxicity was related neither to dose level nor to duration of treatment but occurred more frequently in elderly patients.[24,255] Kanamycin nephrotoxicity occurred in doses of 20 to 50 mg per kg body weight per day and was clinically evident by mild proteinuria, nitrogen retention, microscopic hematuria and fine granular casts in the urinary sediment. In approximately 10 percent of patients treated with kanamycin, there were azotemia. Severe tubular necrosis was reported by Kleeman and Maxwell.[215] In general, nephrotoxicity was reversible when kanamycin administration was stopped.

Kuntz noted oliguria in eight patients out of ten receiving kanamycin.[157] Schriener and Maher observed acute tubular necrosis in two patients following treatment of kanamycin.[184] One of these patients died in uremia.

Ototoxicity is the most common toxic effect of kanamycin.[222] It is likely to occur in patients with renal insufficiency or dehydration. When kanamycin is given to patients with anuria or oliguria or to a diabetic patient with nephropathy, it is imperative to reduce the dose by careful calculation of it and to prescribe kanamycin in "spread out" doses. (A recommended kanamycin dosage is 0.5 g every three or four days.) Approximately 29 to 63 percent of the injected dose of kanamycin can be removed by effective peritoneal dialysis. In an anuric patient, approximately 30 percent of kanamycin can be removed by hemodialysis in an eight hour period.

During peritoneal dialysis, however, 25 mg of kanamycin can be given safely daily. The morphologic change owing to kanamycin nephrotoxicity is always seen in proximal tubules of the kidney. When acute oliguric renal failure occurs, it is the result of acute tubular necrosis. When administration of kanamycin is stopped, diuresis follows within five days and renal function usually returns to normal within two months.

Bacitracin. Bacitracin is a polypeptide antibiotic produced by the Tracy 1 strain of *Bacillus subtilis*.[229] Bacitracin has proved to be highly effective against gram-positive cocci and organisms that cause gas gangrene. Its chemical use is limited to topical application and local infiltration. Transitory urinary abnormalities or proteinuria, cylinduria, azotemia and occasional oliguria were noted in nearly all reported patients. Bacitracin is very nephrotoxic and produces both proximal and distal tubular necrosis.

Genkins, Uhr and Bryer reported a 57 year old housewife with prior normal renal function.[107] She developed a fatal acute oliguric renal failure following five divided doses of 50,000 units daily of bacitracin. On the third day of bacitracin treatment, she developed proteinuria, oliguria and azotemia. The patient died on the tenth day after intramuscular bacitracin treatment. Acute tubular necrosis was found at autopsy.

Neomycin. Neomycin is an antibiotic discovered by Waksman and Lechevalier. It is derived from the metabolic products of *Streptomyces fradiae*. Neomycin is primarily a topical antibiotic and is used for its local antibacterial action within the lumen of the gut.[140,249] It is extremely nephrotoxic and damages the eighth cranial nerve.[196,207] Although the drug is poorly absorbed, it crosses the peritoneal cavity much more readily. Therefore, renal damage can occur when neomycin is administered into the peritoneal cavity.

Emmerson and Pryse-Davies[84] found neomycin to be very nephrotoxic and to cause severe proximal tubular necrosis.[91] Randall reported four patients who suffered adverse effects from injections of 4, 6, 8 and 72 g of neomycin, respectively.[209] Two patients developed deafness, one patient developed acute oliguric renal failure and one subsequently had permanent renal insufficiency. Hemodialysis and peritoneal dialysis removed large amounts of neomycin, and mannitol prevented acute renal failure in two patients. Hemodialysis rapidly reduced serum neomycin concentration in two other patients, while mannitol diuresis removed significant amounts in another. Peritoneal dialysis was the least effective of all methods.

Penicillin. Penicillin induces acute oliguria through a hypersensitivity mechanism.[19] Dehydration was a possible contributing factor in two infants with ab-

normal renal function. When acute oliguria occurs, it is usually associated with dermatologic lesions and eosinophilia.[265]

Randall reported acute oliguric renal failure caused by hypersensitivity manifestations of ampicillin, oxacillin, oral penicillin and intramuscular penicillin G.[152] Two patients died, one of whom was a 24 year old student who received oral penicillin. He developed clinical features of the hemolytic uremic syndrome and necrotizing arteriolitis was found at autopsy. The other patient had a marked acute interstitial nephritis characterized by interstitial cellular infiltrates of plasma cells. Penicillinase may be helpful in treatment of acute renal insufficiency caused by penicillin hypersensitivity.[244]

Methicillin. Methicillin (Staphcillin) does not differ in its sensitizing potential from other penicillins.[46] The clinical hypersensitivity features of methicillin are dermatologic lesions, nephropathy and eosinophilia. During the past few years, methicillin-induced nephropathy has been reported by several individuals. The clinical manifestations of renal disease were proteinuria, hematuria, dysuria and azotemia with or without oliguria. Nephropathy usually appeared between 7 and 21 days after treatment was begun. In most instances, it subsided within 24 to 48 hours after cessation of treatment with methicillin.

Patients with methicillin-induced nephropathy had additional manifestations of hypersensitivity,[37] the most common of which was an eosinophilia. In some patients thrombocytopenia was observed. Hypersensitivity dermatologic lesions were noted. They included hemorrhagic bullae, urticaria, maculopapular lesions, purpura with petechiae and exfoliative dermatitis. None of these reported patients with methicillin-induced nephropathy had a renal biopsy study. In general, knowledge regarding the overall morphologic renal changes is insufficient. The complete reversibility of methicillin-induced nephropathy, together with other allergic manifestations, suggests that a pathopharmocologic mechanism of hypersensitivity occurs.

Histologic abnormalities of the kidney include an acute interstitial nephritis with or without tubular damage.[146] This interstitial nephritis is characterized by cellular infiltrates of eosinophils, plasma cells and small lymphocytes. Adrenocortical steroids have been effective in resolving this drug-induced lesion.

Tetracycline. Tetracycline, a so-called broad-spectrum antibiotic, is produced by several *Streptomyces* species. The tetracyclines produce changes in nitrogen metabolism.[251] The tetracyclines are not usually nephrotoxic agents. However, if storage degereration occurs they may produce proximal tubular damage.[63] Chemical deterioration is more likely to occur if the drug is improperly stored under moist or warm conditions. Anhydrotetracycline and epianhydrotetracycline are the nephrotoxic products. The formation of these products is accomplished by temperature elevation, high humidity and reduced pH. They are especially likely to occur when citric acid is added to tetracycline. However, tetracycline preparations containing lactose are less likely to degenerate into nephrotoxic products.

The tetracyclines are concentrated in the liver, teeth and bones and are excreted through the kidneys and bile. Death has resulted from severe hepatic and pancreatic damage with excessive intravenous doses of tetracycline. Aged or degenerated tetracycline produces a reversible Fanconi syndrome[99,232] associated with polyuria, proteinuria, renal glycosuria, phosphaturia, aminoaciduria,[39] acidosis, hypokalemia and a low plasma urate. In general, tetracycline-induced Fanconi syndrome is slowly re-

versible once the drug is discontinued.[114]

Acute nonoliguric renal failure has been reported by Solomon, Galloway and Patterson[235] who prescribed two g of tetracycline daily and observed an increase in BUN from 63 mg to 161 mg per 100 ml. Tetracycline toxicity is also directly related to existing renal insufficiency.[241] Large doses of oxytetracycline have produced azotemia. Prerenal azotemia may be induced by a negative nitrogen balance that produces anorexia, nausea, vomiting and death. Nephrogenic diabetes insipidus has been induced by dimethylchlorotetracycline.[54]

Para-aminosalicylic acid. Para-aminosalicylic acid (PAS) is highly active in inhibiting the growth of tubercle bacilli *in vitro*. The most common hypersensitivity complication of PAS treatment is hepatitis. A reactive hepatitis induced by PAS has been associated with fever, rash, pruritus, conjunctivitis, hemolytic anemia[210] and eosinophilia. Renal involvement[116] owing to PAS was uncommon and was usually confined to patients who had hepatitis.[68] Inasmuch as PAS is an organic acid, it requires a fixed cation to accompany its excretion;[166] therefore, hypokalemia can occur as well as an acidosis in children.[36]

Owen reported a 31 year old man with pulmonary tuberculosis receiving treatment with calcium PAS for 83 days without mishap.[199] After 35 days of sodium PAS treatment, he developed a fever, a pink vesicular rash, massive proteinuria and acute oliguria without hepatitis. The BUN reached 245 mg per 100 ml and spontaneously fell to normal. The patient made a rapid and complete recovery from acute renal failure.

Cephaloridine. Cephaloridine is a semisynthetic derivative of cephalosporin C. Its antibacterial activity is against many gram-positive and gram-negative bacteria. Adverse reactions of cephaloridine occurred in 35 percent of 76 patients. In general, they were minor reactions and included allergic phenomena, phlebitis at infusion sites, transient leukopenia and gastrointestinal symptoms. More serious reactions include acute renal failure, Coombs positive hemolytic anemia, super infections and anaphylaxis. For example, cephaloridine produced anaphylaxis in a nurse who prepared an injection of the drug.[90]

Renal damage caused by cephaloridine appears to be a result of a nephrotoxic mechanism. The drug has been localized by autoradiographic studies to the renomedullary interstitium and proximal tubular cells.[62] Cephaloridine is accumulative and dose-related. In large doses it produces a severe nephropathy, while in low doses it produces proteinuria, hematuria and cylindruria.[139] When the drug is discontinued, urinary abnormalities disappear.

Cephaloridine has produced hypersensitivity reactions such as urticaria, eosinophilia, drug fever and Coombs positive hemolytic anemia. Antibiotics such as ampicillin and polymyxin B have produced a hypersensitivity acute interstitial nephritis. It is suggested by the present authors that cephaloridine will also produce an acute (hypersensitivity) interstitial nephritis and subsequent acute oliguric renal failure.

Diuretic Agents

In the majority of instances the kidney responds favorably to diuretic agents with a prompt diuresis. However, the kidney also becomes the target of untoward effects of diuretic agents. It is not unlikely that acute oliguric renal failure developed in patients following treatment with meralluride (Mercuhydrin), acetazolamide,[64] the thiazides and aristolochic acid.

Mercurial diuretic agent. Calomel (mercurous chloride) was the active diuretic in the famous "Guy's Hospital Pill"

(calomel, digitalis and squill). The diuretic effects of organic mercurial were first discovered as a side effect in patients receiving antisyphilitic treatment. The primary action of the mercurial diuretic agents is their ability to inhibit sulphydryl-containing enzyme systems that normally supply energy for sodium reabsorption. Immediate fatal reactions to mercurial diuretic agents are rare,[120] and when they do occur, they are related to anaphylactic shock. Hypersensitivity reactions induced by mercurial diuretics include generalized pruritus, urticaria, exfoliative dermatitis and asthma. Most organic mercurials are rapidly excreted by active renal tubular secretion bound with cysteine.[115] Mercurial diuretic agents produce acute oliguric renal failure from acute tubular necrosis.[216,248] Schreiner and Maher believe that organic mercurials are slowly converted to inorganic mercury secondary to abdominal renal retention by the kidneys.[225]

Meralluride-induced acute oliguric renal failure has developed as the result of acute tubular necrosis.[81] This is probably the result of a nephrotoxicity mechanism. Acute oliguric renal failure, exfoliative dermatitis, fever and eosinophilia have sometimes followed several injections of meralluride. Adrenocortical steroids were used to reverse this condition. This hypersensitivity reaction produces an acute interstitial nephritis. There have been a few reports of patients developing nephritis following meralluride treatment.[48] The morphologic lesion was tubular degeneration associated with interstitial nephritis.

Thiazide diuretic agents. The thiazides were discovered as a by-product of a search for diuretic agents similar in structure to acetazolamide. In 1958, chlorothiazide was introduced as a potent oral diuretic agent. In a short time numerous other thiazides were found. The untoward effects of the thiazide diuretic agents are potassium deficiency, aggravation of preexisting diabetes mellitus, aggravation of gout and blood dyscrasias.[231] The latter include leukopenia, thrombocytopenic purpura and aplastic anemia.

Thiazide diuretic agents cause acute oliguric renal failure in two ways. The first way is by chlorothiazide and hydrochlorothiazide producing acute renal necrotizing angiitis, glomerulonephritis with interstitial nephritis and acute tubular necrosis.[70] These lesions produce acute renal parenchymal damage, which causes acute oliguric renal failure.

Kjellbo observed a patient who had acute necrotizing angiitis simultaneously in the skin and kidney.[201] His patient was a 62 year old mildly hypertensive woman who developed fever, right kidney pain, gross hematuria, proteinuria and azotemia. Renal biopsy study revealed interstitial granulomatous inflammatory nodules enclosing necrotic arterioles. The glomeruli appeared normal. The granulomas were composed of lymphocytes, histiocytes, plasma cells and neutrophilic leukocytes.

Fitzgerald reported a patient who had fatal glomerulonephritis with interstitial nephritis complicating "allergic purpura" caused by chlorothiazide.[94] Abry and Cavusoglu reported a patient with fatal acute oliguric renal failure caused by acute tubular necrosis following chlorothiazide treatment.[1] Elwood encountered a patient with coexisting thrombocytopenic purpura and acute oliguric renal failure following chlorothiazide treatment.[8]

The second mechanism of acute oliguric renal failure is the more common. Thiazides induce acute oliguric renal failure by a gradual and chronic reduction in the effective circulating blood volume; this reduction is associated with severe hyponatremia.[144] Treatment consists of fluid and sodium chloride replacement. The physician must be very careful so that

he does not excessively expand the blood volume and precipitate the primary illness, especially if the condition is congestive heart failure.

Aristolochic acid. Aristolochic acid has been used experimentally as a diuretic agent and as an anticancer drug. It has produced renal damage in horses, rabbits, rats and mice. It can abolish the antidiuretic effect of vasopressin in rabbits and is therefore thought to have diuretic properties. Peters and Hedwall intensively studied the effects of aristolochic acid toxicity in rats. They found that a single injection of 30 mg per kg body weight of the drug induces reversible renal failure associated with a decrease in glomerular filtration rate as well as increases in BUN and creatinine. Maximum polyuria occurred on the eighth day. Their data reveal a decrease in the permeability of the collecting ducts and proximal tubules to urea.

Anticoagulants

Bishydroxycoumarin (Dicumarol) and phenindione (Hedulin) have been implicated as possible causes of acute oliguric renal failure.

Bishydroxycoumarin. In 1941, Butt and Allen[50] at the Mayo Clinic and Meyer and associates at the University of Wisconsin introduced bishydroxycoumarin as an anticoagulant into clinical medicine. Doses in the therapeutic range have produced nausea, vomiting and diarrhea. In addition, excessive doses caused bleeding. Painless gross hematuria is usually the first evidence of toxicity. This bleeding may arise from the kidney and in some patients is followed by renal pain, ureteral colic and gross hematuria. Ureteral obstruction has followed blood clots within the ureters.

In one patient, retroperitoneal hematoma dissected down around the urinary bladder to produce an external ureteral obstruction and acute oliguria.[135]

Phenindione. Phenindione is known as phenylindanedion (P.I.D.), Danilone, Hedulin and Eridone. It has been used as a short-acting anticoagulant since it is rapidly absorbed from the gut and is rapidly excreted by the kidney. Phenindione interfers with the liver synthesis of prothrombin. Proteinuria is commonly observed during the first day of phenindione treatment. Heavy proteinuria has resulted in the nephrotic syndrome.[239]

Six patients with severe and significant renal damage caused by phenindione have been reported by Brooks and Calleja.[38] Four patients developed acute oliguric renal failure, one had the nephrotic syndrome, and the sixth had a heavy proteinuria.[85,101] Other clinical features were fever, skin rash, jaundice and eosinophilia.[12] The histologic renal abnormality in the patients with oliguria was an acute diffuse interstitial nephritis characterized by interstitial infiltrates of plasma cells, eosinophils and small lymphocytes. In addition, there were interstitial fibrosis and intimal fibrosis of the interlobular artery. The glomeruli were usually normal. Adrenocortical steroids were beneficial in reversing the acute interstitial nephritis caused by phenindione hypersensitivity.

Calcium Versenate

Calcium versenate is a synthetic, water-soluble polyamino acid (calcium disodium ethylenediamine tetraacetic acid). It is an organic chelating agent that is used in the treatment of heavy metal poisonings.

In 1957, Vogt and Cottier reported a 38 year old man with chronic lead poisoning.[247] He was treated with 600 mg per kg body weight of calcium versenate daily for four days (ten times the average dose). Acute anuria developed on the fifth day, and the patient died on the sixth day. Acute tubular necrosis was found with dilated proximal tubular epithelial cells.

In 1957, Moeschlin described two patients who were treated for lead intoxication with calcium versenate.[185] Both died in uremia caused by acute oliguric renal failure. Acute tubular necrosis was found at autopsy.

In 1958, Weinig and Schwerd described acute renal failure associated with a bleeding tendency in a 59 year old factory worker who received three g of calcium versenate.[252] Acute tubular necrosis and dilated proximal tubules were found at autopsy.

In 1960, Reuber and Bradley reported a one year old girl who had lead intoxication.[213] The child was treated with calcium versenate in a dose of one g (125 mg per kg body weight) daily; the subcutaneous dose was given for three days. She developed acute oliguric renal failure 12 days after the first injection and died four days later. Acute tubular necrosis and dilated proximal tubules were found at autopsy.

Dextran

Low molecular weight dextran (Dextran-60, Gentran) has a molecular weight of 40,000.[106] It passes through the glomerular membrane and is used in clinical medicine as a short-term flow improver in small blood vessels and as a "plasma volume expander."[29, 82, 178] The high urinary concentration of dextran creates a urine of high viscosity.[125] An increase in blood clotting time has occurred in a substantial number of individuals receiving dextran. Adverse reactions to dextran originate as hypersensitivity and include urticaria, angioneurotic edema, bronchospasm and severe anaphylactic shock. Hypersensitivity glomerulonephritis caused by Arthus's phenomenon and acute oliguric renal failure are two renal conditions induced by dextran.[150, 242]

Acute oliguric renal failure induced by low molecular weight dextran has produced two distinct renal lesions. The first was observed by Morgan and colleagues in three hydrated patients with acute oliguria following dextran infusion.[183] Renal biopsy studies were performed on each patient and grossly swollen tubular cells were found crammed with a foamy material. Distended cells completely occluded the tubular lumen. Special stains revealed large quantities of dextran within tubules but none in the tubular lumen.

The second lesion occurred in dehydrated patients given dextran.[176] Acute oliguric renal failure was associated with the finding of dextran casts obstructing the tubular lumen.[197] Once within the tubular lumen, the dextran becomes concentrated and a highly viscous urine is formed; this results from the proximal tubular reabsorption of electrolytes and water.[9] The highly concentrated viscous dextran urine forms tubular casts. The massive obstruction within nephrons results in no urine flow and subsequent acute oliguric renal failure. Mannitol infusions (20 percent solution) have been effective in initiating a diuresis.[22]

Ferrous sulfate. The ingestion by children of large doses of ferrous sulfate frequently produces iron poisoning. The mortality rate in a large series of children with iron poisoning was approximately 50 percent. Acute oliguric renal failure occurred as a result of acute tubular necrosis.[136] This renal lesion may be related to gastrointestinal tract damage.[234]

Aminopyrine. Aminopyrine is a closely related compound to antipyrine and to phenylbutazone. It is used clinically as an analgesic and an antipyretic, is rapidly and virtually completely absorbed from the gut and is demethylated in the liver.

The toxic effect of aminopyrine is a severe and often fatal agranulocytosis. It can cause herpes labialis and angioneurotic edema in hypersensitive individuals. Eknoyan and Matson reported a 37 year old woman who developed acute oliguric renal failure.[80] Although she did

manifest renal damage following a brief course of treatment with amphotericin B, a marked decrease in renal function occurred coincident with aminopyrine administration. Recovery occurred after aminopyrine was discontinued. There was a dramatic decrease in renal function coincident with a second course of aminopyrine ingestion. The patient died in uremia; regrettably, no autopsy was done.

Phenylbutazone. Phenylbutazone (Butazolidin) is a congener of aminopyrine and can induce damage to the skin, lungs, heart, liver, bone marrow, adrenal glands and gut.[195] Phenylbutazone has produced both acute nonoliguric renal failure and acute oliguric renal failure.[41, 104, 263]

Richardson and Alderfer reported a 43 year old executive who developed acute nonoliguric renal failure after taking 2.2 g of phenylbutazone for six days.[214] The patient had severe hyponatremia (sodium, 96 mmol per l) and acidosis (CO_2, 14 mmol per l). After massive sodium repletion, the patient recovered. Approximately eight days after the onset of renal failure, findings from a renal biopsy study were normal.

Phenylbutazone-induced acute oliguric renal failure results from three distinct morphologic lesions. These include acute tubular necrosis,[221] acute interstitial nephritis, and thrombotic thrombocytopenic purpura (TTP). Lipsett and Goldman reported a patient with reversible acute oliguric renal failure following treatment with phenylbutazone.[166] A renal biopsy study done on the fifth day of oliguria revealed acute tubular necrosis. Hermann, Hopefeld and Berning reported a patient with fatal acute oliguric renal failure caused by treatment with phenylbutazone.[124] An acute interstitial nephritis was found at autopsy. Dunea and colleagues reported a 44 year old housewife who was treated with phenylbutazone, 600 mg daily for three days; this treatment was followed by acute anuria and jaundice.[77] The patient remained anuric until her death 30 days after the onset of her illness. A renal biopsy study performed during the third week of her illness revealed TTP associated with a hemolytic anemia. *In vitro* phenylbutazone was found to be the antigen to produce a positive Coombs test; the Coombs test became negative after treatment with adrenocortical steroids.

Bismuth compounds. Bismuth compounds have induced nephrotoxicity through repeated intramuscular injections, rectal suppositories, accidental ingestion and idiosyncrasies to heavy metals. The proximal renal tubules are the organs most sensitive to injury.

Although the large number of bismuth compounds formerly available to physicians has been greatly reduced, bismuth compounds have been used extensively in the treatment of syphilis,[18] oral infections such as Vincent's gingivostomatitis and gastroenteritis. Although bismuth compounds have been used in the treatment of verrucae, they have no known beneficial value when so used.

The toxicity of bismuth compounds is directly related to the rapidity of absorption. Approximately 90 percent of the absorbed dose of a soluble bismuth salt is excreted by the kidneys. Bismuth tends to concentrate in renal tissue to amounts five times that in the liver. Therefore, damage occurs to the kidney. Proximal tubular necrosis and intranuclear inclusion bodies are frequently observed in bismuth nephropathy. In addition to kidney damage, these compounds have produced gut, liver, and central nervous system damage. Acute oliguric renal failure was the chief cause of death in patients poisoned with bismuth.

Anesthetic Agent

Methoxyflurane anesthesia can produce renal tubular dysfunction and lead

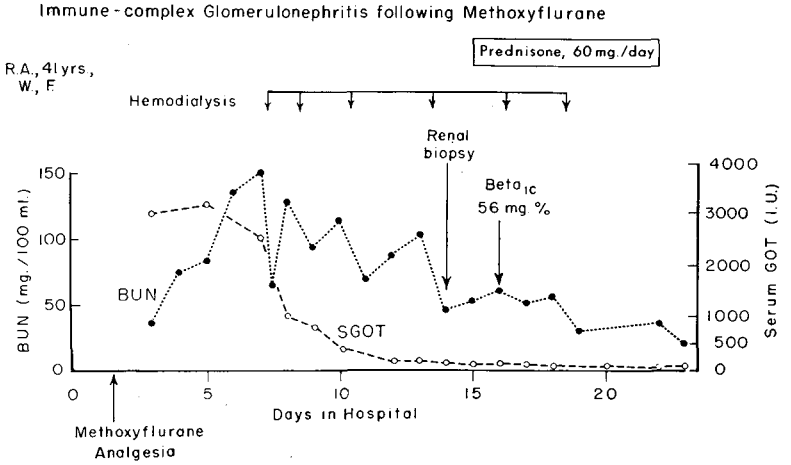


FIGURE 8. Immune-Complex Glomerulonephritis Following Methoxyflurane. The clinical course of R.A., a 41 year old white female, is plotted. On her third exposure to methoxyflurane analgesia she developed jaundice, an erythematous rash, eosinophilia, and acute renal failure. Repeat hemodialysis was started. The BUN is plotted in the dotted line. The SGOT is plotted by the dark line. A renal biopsy study on the 14th day revealed an immune-complex glomerulonephritis. Prednisone was started and the patient rapidly improved.

to acute "high-output" renal failure.[57,160] Calcium oxalatic crystal deposition occurs in renal tubules. The mechanism of nephrotoxicity is the effect of fluoride which blocks the concentrating capacity of the distal nephron.

In man, methoxyflurane is metabolized with liberation of both organic fluoride and organic metabolites containing fluorides.[127] Fluoride may be stored in body fat and slowly but continually released for several days after anesthetic exposure. Thus, a "high-output" renal failure is prolonged.

The authors observed one patient exposed to methoxyflurane analgesia using a face mask-inhaler. The patient, a 41 year old lady was exposed to methoxyflurane during each of three pregnancies at term. At the second exposure she developed jaundice. At the third exposure she developed jaundice, an erythematous skin rash and an immune-complex glomerulonephritis with acute renal failure. She required hemodialysis and adrenal corticosteroids to recover (figure 8).

Acute Hemorrhagic Glomerulonephritis

In general, the patients who develop acute hemorrhagic nephritis develop the clinical syndrome of acute renal failure. This is usually on the basis of antigen-antibody complex glomerulonephritis or hypersensitivity glomerulonephritis. A variety of therapeutic agents used in the treatment of infections, hypertension, convulsions and cardiac dysrhythmia have been known to produce a drug-induced systemic lupus erythematosus. Usually in patients with systemic lupus, the drugs precipitate out a fulminating and florid reaction of systemic lupus erythematosus. Thus, drugs producing lupus usually do not cause lupus nephritis.

An antihypertensive agent such as hydralazine was the first of a number of drugs implicated to produce the clinical syndrome of systemic lupus erythematosus.[31] Other agents include isoniazide, sulfanamidies, penicillin, tetracycline, streptomycin, p-amino-salicylate, methyl and propyl thiouracil, reserpine, alpha-methyldopa, guanoxam, phenobutazone and griseofulvin.[52,58,73] The authors have observed florid lupus nephritis produced by both the anticonvulsive agent diphenylhydantoin and oral contraceptive agents (figure 9). When lupus nephritis was produced by the latter two agents, it was severe and florid in producing rapidly progressive glomerulonephritis with azotemia. Therapy was directed to withdrawal of the agent and use

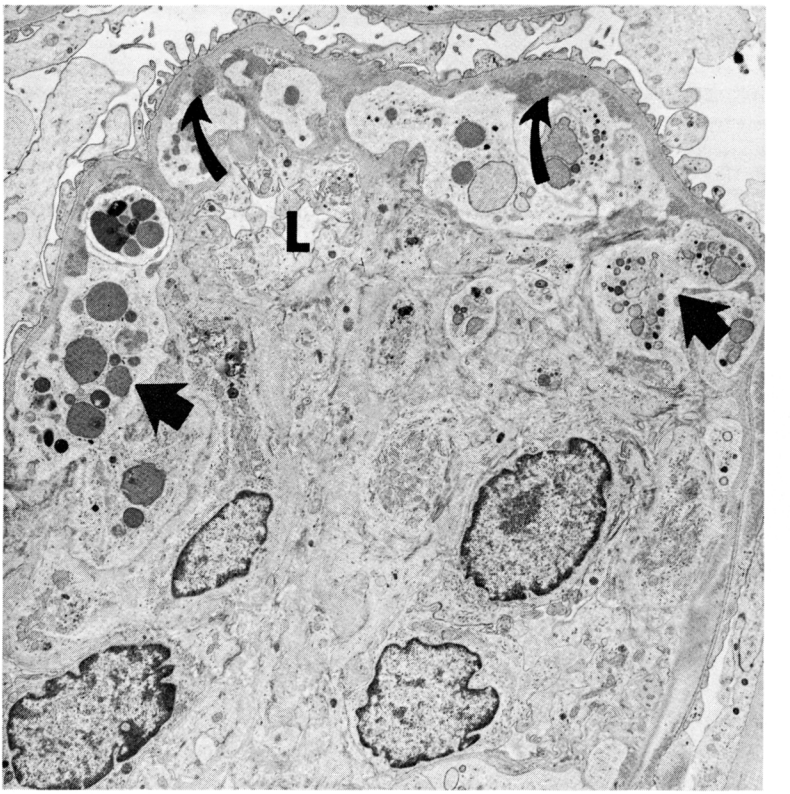


FIGURE 9. Electron-microscopic Photograph of Renal Biopsy Study of Oral Contraceptive-Induce-Lupus Nephritis. A 34 year old housewife ingested oral contraceptives for 20 days. She developed hematuria, massive proteinuria, azotemia and malignant hypertension. Her LE cell test was positive and her serum $Beta_{1C}$ globulin was 47 mg per dl (normal 100 to 170 mg per dl).

A portion of a glomerular capillary is noted. The lumen (L) is small. Numerous polymorphonucleocytes are present (straight arrows). Electron dense immunological deposits are noted below the glomerular basement membrane (curved arrows). Uranyl nitrate (× 4,000).

of high dosage adrenocortical steroids. The serum $Beta_{1C}$ globulin was an excellent "yard-stick" to determine the control of drug-induced disease activity.

The Nephrotic Syndrome

The nephrotic syndrome has followed the therapeutic administration of a variety of drugs as nephrotoxic agents. A comprehensive list is given in table IV. Following the therapeutic use of a specific drug from a number of unrelated drugs listed, patients have been observed to develop the nephrotic syndrome. When stopping the offending drug a prompt remission usually occurs and is associated with the disappearance of proteinuria. These unrelated drugs include troxidone, paramethadione, probenecid, penicillamine, tolbutamide, perchlorate, gold salts, bismuth salts and other heavy metals.[13, 16, 57]

DRUGS

Renal biopsy study of patients with drug-induced nephrotic syndrome usually reveal no specific glomerular changes by light microscopy; however,

TABLE IV

Nephrotic Syndrome Owing to Adverse Reactions to Drugs and to Hypersensitivity States

Drugs	
	Organic and inorganic mercurial compounds
	Trimethadione (Troxidone)
	Paramethadione
	Probenecid
	Penicillamine
	Tolbutamide
	Perchlorate
	Phenindione
	Aurothiomalate
	Bismuth salts
	Other heavy metals
Hypersensitivity toxins	
	Pollen
	Bee stings
	Poison oak and ivy
	Serum sickness
	Smallpox vaccination
	"Sting" Portuguese man-of-war (sea nettle)

by electronmicroscopy fusion of visceral epithelial foot processes are noted. In patients with d-penicillamide-induced nephrotic syndrome,[51] electronmicroscopy studies have revealed deposition of electron dense material on the epithelial side of the glomerular basement membrane associated with fusion of visceral epithelial foot processes. Immunopathological studies of d-penicillamide-induced nephrotic syndrome suggest these changes may represent antigen-antibody complexes and support the immunological basis for "penicillamine" nephrotoxicity.

In general, it is believed that some drugs produce the nephrotic syndrome as an idiosyncrasy. However, this may not be the situation in the nephrotic syndrome associated with therapy of trimethadione and paramethadione. Children or young adults given trimethadione for several weeks develop the nephrotic syndrome.[240] A number of these patients improve spontaneously after withdrawal of the drug. They have also recovered despite continuing treatment at a lower dose. Another patient improved after a severe illness lasting three months. An additional patient was unimproved following drug stoppage and steroid therapy and five patients died.

Heavy metals appear to produce drug-induced nephrotic syndrome. These include mercury, gold and bismuth. The mercurial toxicity arises when the patient is exposed chronically to a mercurial diuretic agent or to ammoniated mercury ointment. In addition, mercury is an occupational hazard in employees of the disinfectant industry. The patients exposed to this toxicity have developed severe proteinuria and the nephrotic syndrome.[162]

Gold has produced the nephrotic syndrome by producing glomerular lesions. There is a fusion of visceral epithelial foot processes of the epithelial cells. Mandema and colleagues have reported similar abnormalities in patients given mercurial compounds.[161]

Hypersensitivity Agent

Massive proteinuria and the subsequent development of the nephrotic syndrome has been reported to a variety of hypersensitivity toxins.[119,218] These include bee stings, serum sickness, sensitivity to specific pollen and other inhalants. In addition, a delayed reaction to poison ivy or poison oak can produce the nephrotic syndrome. Although patients with hypersensitivity toxin constitute a relatively small group of the nephrotic syndrome, the syndrome does occur following exposure to hypersensitivity toxin. On examination of the renal biopsy material, there were areas of eosinophilic infiltration both in the renal interstitium as well as throughout the glomerular capillaries. A study by electronmicroscopy showed a collescent of the visceral epithelial foot processes. This is very similar to the so-called minimal lesions of glomerulonephritis. It is very possible that a number of patients with recurrent nephrotic syndrome in whom the offending agent has not been delineated may also fall into the category of a hypersensitivity toxin.

Tubular Disturbances

Drugs can directly or indirectly induce tubular disturbances by their toxic effect on specific sites on the nephron. This includes proximal, distal collecting tubules and limbs of Henle. Thus, the clinical syndromes induced by drug toxicity affecting the nephron are related to the site of tubular damage. Renal tubular acidosis and the Fanconi syndrome reflect proximal tubular damage. Potassium deficiency produces reversible damage to the proximal tubules.

The Fanconi syndrome is characterized by aminoaciduria, glycosuria, potassium loss and a defect in hydrogen

ion transport. Outdated tetracycline has induced tubular dysfunction to produce a Fanconi type syndrome.[96]

Tetracycline may degrade spontaneously on storage to form toxic epimers which have been held responsible for the development of a reversible type of Fanconi type syndrome.[114] Azotemia in patients with significant renal impairment has been further activated by the use of tetracyclines. The explanation for this is not clear and cannot be readily elucidated in the presence of pre-existing renal disease. Some believe that this is related to the catabolic effects of tetracycline.[99]

Renal Tubular Acidosis

The nephrotoxic properties of amphotericin B have been well recognized. Necrosis of both the proximal and distal epithelium occurs resulting in a number of functional defects. These defects are related to impairment of concentrating capacity and in hydrogen ion secretion. Thus, the syndrome of renal tubular acidosis occurs. When this becomes chronic, nephrocalcinosis may develop.

Amphotericin B can also induce severe hypokalemia by excessive renal potassium loss. The morphological lesions associated in the proximal tubules of hypokalemia are reversible on discontinuing amphotericin and replenishing potassium.

Toluene inhalation or glue sniffing are other causes of renal tubular acidosis.[198] In recent years young teenagers have been reported developing euphoria from sniffing glue solvents. The incidence of nephrotoxic effects is directly associated with the glue sniffing pastime. One may question the multi-drug abuse of teenagers as related to the adverse effects of glue sniffing.

Distal Tubular Disfunctions

Demeclocycline has produced a primary distal tubular defect. This defect results in inhibiting the distal tubules to the absorption water. The defect is accompanied by a decrease in urinary cyclic adenosine monophosphate (AMP) effect. This effect was thought to be due to interference of cyclic AMP-meditated action of adenine dehydrophosphate (ADH) on the distal tubule. This condition is reversible once Demeclocycline is removed.

Potassium Deficiency

As a group, the modern diuretic agents are remarkably safe drugs. They have produced a variety of metabolic disturbances,[159,212] but their specific toxic effect has not been serious. The use of oral diuretic agents can produce severe potassium deficiency by an excessive urinary loss of potassium.

Potassium depletion owing to use of oral diuretic agents can be easily overlooked by the physician. The symptoms of fatigue and muscular weakness may be attributed to the underlying disease rather than to the treatment. The serum potassium concentration is the best indicator that depletion is present. Measurement of the 24 hour urinary potassium excretion may substantiate potassium loss.

Prolonged potassium deficiency can lead to interstitial fibrosis and subsequent renal scarring. Chronic interstitial fibrosis develops associated with azotemia. Severe renal failure may develop and may require the patient to be placed on chronic hemodialysis.

Summary

Acute toxic nephropathies are byproducts of man's ever increasing exposure to a vast array of toxic chemicals and drugs that result from industrial and medical progress. The kidney is extremely susceptible to nephrotoxic agents. Its numerous enzyme system within the cytoplasm and mitochondria, its rich blood supply, its

complex superior excretory function, its large endothelial surface, and the interexchange of substances in the interstitium predispose the kidney to nephrotoxic effects.

Acute nephrotoxicity can produce several clinical syndromes. These include acute oliguric renal failure; both oliguria and high output. An example of the latter is acute toxicity of methoxylflurane. Other clinical syndromes of acute nephrotoxicity include nephrotic syndrome, acute hemorrhagic glomerulonephritis, and tubular disturbances.

Management includes withdrawal from the specific toxic agent. Electrolyte deficiencies should be corrected. In some patients it is necessary to prolong the well being and life of the patient by use of hemodialysis until the nephrotoxic effects undergo resolution and heal.

Finally, physicians who think they are doing well by their patients may suddenly encounter an adverse drug reaction. In some situations the drug reactions is transitory and completely reversible. In others it may lead to chronic progressive kidney failure with death as an unusual complication of nephrotoxicity.

References

1. ABRY, J. and CAVUSOGLU, M.: Fatal tubular necrosis during chlorothiazide administration N. Y. State J. Med. *60*:1638, 1960.
2. ADDIS, T.: Glomerular Nephritis: Diagnosis and Treatment. New York, The Macmillan Company, 1949.
3. ALARCON-SEGOVIA, D., WAKIM, K. G., WORTHINGTON, J. W., and WARD, L. E.: Clinical experimental studies on the hydralazine syndrome and its relationship to systemic lupus erythematosus. Medicine *46*:1, 1967.
4. ALARCON-SEGOVIA, D., WORTHINGTON, J. W., WARD, L. E., and WAKIM, K. G.: Lupus diathesis and hydralazine syndrome, New Eng. J. Med. *272*:462, 1965.
5. ALLEN, A. C.: The Kidney: Medical and Surgical Diseases. New York, Grune & Stratton, Inc., 1951.
6. ALWALL, N., ERLANDSON, P., and TORNBERG, A.: The clinical course of renal failure occurring after intravenous urography and/or retrograde pyelography: casuistics of 11 cases (including 7 deaths), Acta. Med. Scan. *152*:163, 1955.
7. ANGERVALL, L., LEHMANN, L., and LINCOLN, K.: On the effect of phenacetin and NAPA (N-acetyl-p-aminophenol) on the development of bacterial interstitial nephritis in the rat. Acta Path. Microbiol. Scand., Supplement *154*:61, 1962.
8. ANTES, E. H.: Thrombotic thrombocytopenic purpura. A review of the literature with report of a case. Ann. Int. Med. *48*:512, 1958.
9. ARTURSON, G., GRANATH, K., THORN, L., and WALLENIUS, G.: Renal excretion of low-molecular-weight Dextran. Acta. Clin. Scand. *127*:543, 1964.
10. BAINES, A. D.: Cell renewal following dichromate induced renal tubular necrosis. Amer. J. Path. *47*:851, 1965.
11. BAKER, S. B., DE, C., and WILLIAMS, R. T.: Acute interstitial nephritis due to drug sensitivity. Brit. Med. J. *1*:1655, 1963.
12. BALDWIN, D. S., LEVINE, B. B., MCCLUSKEY, R. T., and GALLO, G. R.: Renal failure and interstitial nephritis due to penicillin and methicillin. New Eng. J. Med. 279:1245, 1968.
13. BARKER, H.: Nephrotic syndrome due to ammoniated mercury. Brit. J. Derm. *80*:288, 1968.
14. BATEMAN, J. C., BARBERIO, J. R., GRICE, P., KLOPP, C. T., and PIERPONT, H.: Fatal complications of intensive antibiotic therapy in patients with neoplastic disease. Arch. Intern. Med. *90*:763, 1952.
15. BATSON, R. and PETERSON, J. C.: Acute mercury poisoning: treatment with B.A.L., and in anuric states with continuous peritoneal lavage. Ann. Intern. Med. 29:278, 1948.
16. BECKER, C. G., BECKER, E. L., MAHER, J. F., and SCHREINER, G. E.: Nephrotic syndrome after contact with mercury. Arch Intern. Med. *110*:178, 1962.
17. BECKER, C. G., BECKER, E. L., MAHER, J. F., and SCHREINER, G. E.: Nephrotic syndrome after contract with mercury: a report of five cases, three after the use of ammoniated mercury ointment. Arch. Intern. Med. *110*:178, 1962.
18. BEERMAN, H.: Fatalities due to bismuth in treatment of syphillis. Arch. Derm. Symph. *26*:797, 1932.
19. BEIDLEMAN, B.: Kidney damage from penicillin sensitivity. Med. Trial Tech. Quart. *10*:39, 1964.
20. BEIRNE, G. J., HASING, C. E., OCTAVIANO, G. N., and BURNS, R. O.: Acute renal failure caused by hypersensitivity to Polymyxin B Sulfate, J.A.M.A. *202*:62, 1967.
21. BELL, N. H., ANDRIOLE, V. T., SABESIN, S. M., and UTZ, J. P.: On the nephrotoxicity of amphotericin B in man. Amer. J. Med. 33:64, 1962.
22. BERGENTZ, S. E., FALKHEDEN, T., and OLSON, S.: Diuresis and urinary viscosity in dehydrated patients: influence of dextran—40,000 with and without mannitol. Ann. Surg. *161*:582, 1965.
23. BERGSTRAND, H.: Comparison between kidney changes in case of "crush syndrome" and

renal injury caused by sulfathiazole. Acta. Med. Scand. *124*:309, 1946.
24. BERMAN, L. B., and KATZ, S.: Kanamycin nephrotoxicity. Ann. N.Y. Acad. Sci. *76*:149, 1958.
25. BERMAN, L. B. and SCHREINTER, G.E.: Pressure flow relationship and urea dialysance: determinations in vivo in the twin-coil kidney. Trans. Amer. Soc. Artif. Intern. Organs *3*:12, 1957.
26. BERMAN, L. B. and TUBLIN, I.: The nephropathies of sickle cell disease. Arch. Intern. Med. *103*:602, 1959.
27. BERNARD, H., GAJDOS, A., GAJDOS-TOROK, M., and RAMBERT, P.: Une intoxication aigue collective par le plomb. Sem. Hop. Paris 29:785, 1953.
28. BERYLINE, N. and BERLYNE, G. M.: Acute renal failure following intravenous pyelography with hyopaque. Acta. Med. Scand. *171*:39, 1962.
29. BIENENSTOCK, J. and HARDING, E. L.: Low-molecular-weight Dextran (Rheomacordex) in ischemic ulceration of the skin. Lancet *1*:524, 1964.
30. BISHOP, W. B., CARLTON, R. F., and SANDERS, L. C.: Diffuse vasculitis and death after hyperimmunization with pertusis vaccine. N. Eng. J. Med. *274*:616, 1966.
31. BLOMGRENE, S. E., CONDEMI, J. J., and VAUGHAN, J. H.: Procainomide-induced lupus erythematosus. Clinical and laboratory observations. Amer. J. Med. 52:228, 1972.
32. BLYTHE, W. B. and WOODS, J. W.: Acute renal insufficiency after ingestion of a gallbladder dye: report of a case, N. Eng. J. Med. *264*:1045, 1961.
33. BOMFORD, R. R. and HUNTER, D.: Arseniuretted hydrogen due to the action of water on metallic arsenides. Lancet *2*:1446, 1932.
34. BOUCHARD, C. J.: Lecons sur les Autointoxications dans les Maladies: Recueillies et Publiees par. Savy, ed. • •, Paris, 1887.
35. BRADFORD, H. A. and SHAFFER, J. H.: Renal changes in a case of sulfadiazine anuria, J.A.M.A. *119*:316, 1942.
36. BRANDER, L., KUHLBACK, B., NIEMISTO, M., and RISKA, N.: The effect of massive doses of PAS on renal function and electrolyte balance. Scand. J. Lab. Clin. Med. *15*:38, 1963.
37. BRAUNINGER, G. E. and REMINGTON, J. S.: Nephropathy associated with methicillin therapy, J.A.M.A. *203*:103, 1968.
38. BROOKS, R. H. and CALLEJA, H. B.: Dermatitis, hepatitis, and nephritis due to phenindione (Phenylindandione). Ann. Intern. Med. 52:706, 1960.
39. BROWN, J. L., SAMIY, A. H., and PITTS, R. F.: Localization of amino-nitrogen reabsorption in the nephron of the dog. Amer. J. Physiol. *200*:370, 1961.
40. BROWN, W. H., THORNTON, W. B., and WILSON, J. S.: An evaluation of the clinical toxicity of sulfanilamide and sulfapyridine, J.A.M.A. *114*:1605, 1940.
41. BRUCK, E., FEARNLEY, M. D., MEANOCK, I., and PATLEY, H.: Phenylbutazone therapy: relation between toxic and therapeutic effects and blood level. Lancet *1*:225, 1954.
42. BRYER, M. S., SCHOEBACH, E. B., and BLISS, E. A.: Pharmacology of polymyxin, Ann. N. Y. Acad. Sci-*51*:935, 1949.
43. BUCK, R. W.: Mushroom toxins: brief review of literature. New Eng. J. Med. *265*:681, 1961.
44. BULL, G. M., JOEKES, A. M., and LOWE, K. G.: Acute renal failure due to poisons and drugs. Lancet *1*:134, 1958.
45. BULMER, F. M. R., ROTHWELL, H. E., POLACK, S. S., and STEWART, D. W.: Chronic arsine poisoning among workers employed in the cyanide extraction of gold: report of 14 cases. J. Indust. Hyg. Toxicol. *22*:111, 1940.
46. BURNS, R. O., HENDERSON, L. W., HAGER, E. B., and MERRILL, J. P.: Peritoneal dialysis: clinical experience. New Eng. J. Med. 267:1060, 1962.
47. BURMEISTER, W. H. and MCNALLY, W. D.: Acute mercury poisoning: a parallel histological and chemical study of the renal and hepatic tissue changes as compared with the rapidity of absorption and the amount of mercury present in the circulating blood at the time such changes occur. J. Med. Res. *36*:87, 1917.
48. BURSTON, J., DARMADY, E. M., and STRANACK, F.: Nephrosis due to mercurial diuretics. Brit. Med. J. *1*:1277, 1958.
49. BUTLER, W. T., BENNETT, J. E., ALLING, D. W., WERTLAKE, P. T., UTZ, J. P., and HILL, G. J.: Nephrotoxicity of amphotericin B: early and late effects in 81 patients. Ann. Intern. Med. *61*:175, 1964.
50. BUTT, H. R., ALLEN, E. V., and BOLLMAN, J. L.: A preparation from spoiled sweet clover 3,3'-Methylene-bis-(4-hydrocycoumarin) which prolongs coagulation and prothrombin time of blood. Proc. Staff Meet, Mayo Clinic *16*:388, 1941.
51. CAMERON, J. S. and TROUNCE, J. R.: Membranous glomerulonephritis and the nephrotic syndrome appearing during mersalyl therapy. Guy's Hosp. Reports *114*:101, 1965.
52. CANNAT, A. and SELIGMANN, M.: Induction by isoniazid and hydralazine of antinuclear factors in mice. Clin. Exp. Immunol. 3:99, 1968.
53. CASCIANO, A. D.: Acute methemoglobinemia due to aniline. J. Med. Soc. New Jersey *49*:141, 1952.
54. CASTELL, D. O. and SPARKS, H. A.: Nephrogenic diabetes insipidus due to demethylchlortetracycline hydrochloride. J.A.M.A. *193*:237, 1965.
55. CHAPMAN, E. M.: Observations on the effect of pain on the kidneys with particular reference to the role of turpentine. J. Indust. Hyg. Toxic. 23:277, 1941.
56. CHRISTIANSEN, W. F.: Nephrotic syndrome after application of mercurial diuretics. Ugeskr. Laeger *121*:200, 1959.
57. CHURCHILL, D., KNAACK, J., CHIRITO, E.,

BARRE, P., COLE, C., MUEHRCKE, R. C., and GAULT, M. H.: Persisting renal insufficiency after methoxyflurane anesthesia. Ann. J. Med. *56*:575, 1974.

58. CONDEMI, J. J., MOORE-JONES, D., VAUGHAN, J. H., and PERRY, H. M.: Anti-nuclear antibodies following hydralazine toxicity. New Eng. J. Med. *276*:486, 1967.
59. COTTET, J. and VARAY, A.: Dissociation de l'elimination de l'elimination de l'uree et de la P.S.P. dans un cas de lithiase par sulfathiazol. J. Urol. Med. Chir. *56*:818, 1950.
60. COUNCILMAN, W. T.: Acute interstitial nephritis. J. Exp. Med. 3:393, 1898.
61. CUPPAGE, F. E. and SCARPELLI, D. G.: Repair of the nephron following injury with mercuric chloride (abstract). Proc. Amer. Assoc. Path. Bact. Am J. Path. *50*:42a, 1967.
62. CURRIE, G. A., LITTLE, P. J., and MCDONALD, S. J.: The localization of cephaloridine and nitrofurantoin in the kidney. Nephron 3:282, 1966.
63. DARMADY, E. M.: Renal Lesions in Relation to Amino-aciduria and Water Diuresis. Ciba Foundation Symposium on the Kidney, Churchill, • •, ed., London, 1954.
64. DAVIES, D. D.: Toxicity of acetazolamide. Brit. Med. J. *63*:1204, 1964.
65. DE LAPAVA, S., NIGOGOSYAN, G., and PICKREN, J. W.: Fatal glomerulonephritis after receiving horse anti-human-cancer serum. Arch. Intern. Med. *109*:67, 1962.
66. DERBES, V. J., DENT, J. H., FORREST, W. W., and JOHNSON, M. F.: Fatal chlordane poisoning. J.A.M.A. *158*:15, 1955.
67. DEROT, M., LEGRAIN, M., JACOBS, C., PRUNIER, P., and HAZEBROUCQ, G.: Intoxication par l'hydrogene arsenie: etude des formes renales a propos d'une intoxication collective (5 cases) J. Urol. Nephrol. 69:407, 1963.
68. DEROT, M., RATHERY, M., DUBRISAY, J., and ROUDIER, R.: Anurie mortelle par choc apres intraveneuse de solution de para-aminosalicylate de sodium. Bull. Soc. Med. Hop. Paris 72:904, 1956.
69. DEROT, M., TANRET, P., SOLIGNAC, H., and DELAVEAU, P.: Hepato-nephrite hemolytique apres ingestion accidentelle de chlorate de sodium: guerison par la dialyse peritoneale et l'exsanguino-transfusion. Bull. Soc. Med. Hop. Paris *64*:1062, 1948.
70. DINON, L. R., KIM, Y. S., and VANDER VEER, J. B.: Clinical experience with chlorothiazide with particular emphasis on untoward responses: report of 121 cases studied over 15 month period. Amer. J. Med. Sci. *236*:533, 1958.
71. DOOLAN, P., HESS, W. C., and KYLE, L. H.: Acute renal insufficiency due to bichloride of mercury. New Eng. J. Med. *249*:273, 1953.
72. DOWLING, H. F., DUMORR-STANLEY, E., LEPPER, M. H., and SWEET, L. K.: Relative toxicity of sulfamerazine and sulfadiazine. J.A.M.A. *125*:103, 1944.
73. DUBOIS, E. L. TUFFANELLI, D. L.: Clinical manifestations of systemic lupus erythematosus. Computer analysis of 520 cases. J.A.M.A. *190*:104, 1964.
74. DUDLEY, S. F.: Toxemic anemia from arseniuretted hydrogen gas in submarine. J. Indust. Hyg. Toxicol. *1*:215, 1919.
75. DUFAULT, F. X. and TOBIAS, G. J.: Potentially reversible renal failure following excessive calciumand alkali intake in peptic ulcer therapy. Amer. J. Med. *16*:231, 1954.
76. DUFF, G. L. and MURRAY, E.G.D.: Pathologic lesions following the administration of sulfonamide drugs. Amer. J. Med. Sci. *205*:439, 1943.
77. DUNEA, G., MUEHRCKE, R. C., NAKAMOTO, S., and SCHWARTZ, F. D.: Thrombotic thrombocytopenic purpura with acute anuric renal failure. Amer. J. Med. *41*:1000, 1966.
78. DUNSKY, I.: Potassium bromate poisoning. Amer. J. Dis. Child. *74*:730, 1947.
79. EINSPRUCH, B. C. and GONZALES, V. V.: Clinical and experimental nephropathy resulting from use of neomycin sulfate. J.A.M.A. *173*:809, 1960.
80. EKNOYAN, G. and MATSON, J. L.: Acute renal failure caused by aminopyrine. J.A.M.A. *190*:934, 1964.
81. ELIAHOU, H. E. and BATA, A.: The diagnosis of acute renal failure. Nephron 2:287, 1965.
82. ELIASSON, R.: Low-molecular-weight Dextran: Symposium Held at Royal Society of Medicine, London, 1963.
83. ELWOOD, C. M., LUCAS, G., and MUEHRCKE, R. C.: Acute renal failure associated with sodium colistimethate treatment. Arch. Intern. Med. *118*:326, 1966.
84. EMMERSON, B. T. and PRYSE-DAVIES, J.: Studies of the nephrotoxic effect of neomycin. Australiasian Ann. Med. *13*:149, 1964.
85. FABRE, J., BALANT, L., and CHAVAZ, A.: Recent drug management advance in renal insufficiency. Advances in Nephrology. Chicago, Year Book Medical Publishers, Inc. 1974.
86. FABRE, R. TRUHAUT, R., and LAHAM, S.: Toxiocologic du tetrachlorure de carbone: establissement d'une methode de dosage applicable aux atmospheres et aux miliux biologigues. Ann. Pharm. Franc. 9:251, 1951.
87. FALOON, W. W., DOWNS, J. J., DUGGAN, K., and PRIOR, J. T.: Nitrogen and electrolyte metabolism and hepatic function and histology in patients receiving tetyracycline. Amer. J. Med. Sci. *233*:653, 1957.
88. FEIGIN, R. D. and FIASCONE, A.: Hematuria and proteinuria associated with methicillin administration. New Eng. J. Med. *272*:903, 1965.
89. FEINGOLD, D. S.: Antimicrobial chemotherapeutic agents: The nature of their action and selective toxicity. New Eng. J. Med. *269*:900, 1963.
90. FELLERS, F. and CRAIG, J.: Analgesic nephritis. J.A.M.A. *186*:610, 1963.

91. FINCKH, E. S., JEREMY, D., and WHYTE, H. M.: Structural renal damage and its relationship to clinical features in acute oliguric renal failure. Quart. J. Med. *31*:429, 1962.
92. FINZER, K. H.: Lower nephron nephrosis due to concentrated lysol vaginal douches: a report of two cases. Canad. Med. Assoc. J. *84*:549, 1961.
93. FISHER, J. H. and GILMOUR, J. R.: Encephalomyelitis following administration of sulfanilamide, with note on histological findings. Lancet 2:301, 1939.
94. FITZGERALD, E. W., JR.,: Fatal glomerulonephritis complicating allergic purpura due to chlorothiazide. Arch. Intern. Med. *105*:305, 1960.
95. FREIDMAN, E. A., GREENBERG. J. B., MERRILL, J. P., and DAMMIN, G. D.: Consequence of ethylene glycol poisoning. Amer. J. Med. 32:891, 1962.
96. FRIMPTER, G. W., TIMPANELLI, A. E., EISENMENGER, W. J., STEIN, H. S., and EHRLICH, L. I.: Reversible "Fanconi syndrome" caused by degraded tetracycline. J.A.M.A. *184*:111, 1963.
97. FREEMAN, R. B., MAHER, J. F., SCHREINER, G. E., and MOSTOFI, F. K.: Renal tubular necrosis due to nephrotoxicity of organic mercurial diuretics. Ann. Intern. Med. *57*:34, 1962.
98. FRENCH, A. J.: Hypersensitivity in pathogenesis of histopathologic changes associated with sulfonamide chemotherapy. Amer. J. Path. *22*:697, 1946.
99. FULOP, M. and DRAPKIN, A.: Potassium-depletion syndrome secondary to nephropathy apparently caused by "outdated tetracycline." New Eng. J. Med. 272:986, 1965.
100. GABUZDA, G. J., Gocke, T. M., JACKSON, G. G., GRISBY, M. E., LOVE, B. D., and FINLAND, M.: Some effects of antibiotics on nutrition in man, including studies of the bacterial flora of the feces. Arch. Intern. Med. *101*:476, 1958.
101. GALEA, E. G., YOUNG, L. N., and BELL, J. R.: Fatal nephropathy due to phenindione sensitivity. Lancet *1*:920, 1963.
102. GARROD, L. P.: The toxicity of antibiotics. Med. J. Aust. 2:947, 1964.
103. GAULT, M. H., BLENNERHASSET, J., MUEHRCKE, R. C.: Analgesic nephropathy, Amer. J. Med. *51*:740, 1971.
104. GAULTIER, M., FOURNIER, E., GERVAIS, P., GORCIEX, A., and FREJAVILLE, J. P.: Intoxication Aigue Volontaire a la Pheynlbutazone: Anurie: Guerison. Bull. Soc. Med. Hop. Paris *113*:3;7, 1962.
105. GEILING, E. M. K. and CANNON, P. R.: Pathologic effects of elixir of sulfanilamide (diethylene glycol) poisoning: a clinical and experimental correlation: final report. J.A.M.A. *111*:919, 1938.
106. GELIN, L. E., SOLVELL, L., and ZEDERFELDT, B.: The plasma volume expanding effect of low viscous dextran and macrodex. Acta. Chir. Scand. *122*:309, 1961.
107. GENKINS, G., Uhr, J. W., and BRYER, M. S.: Bacitracin nephropathy: report of a case of acute renal failure and death. J.A.M.A. *155*:894, 1954.
108. GERMAINE, A. and MARTY, J.: Hepatonephrite Aigue Mortelle par Inhalation de Trichlorethylene. Bull. Soc. Hop. Paris *63*:1044, 1947.
109. GOLDBLATT, S.: Acute mercurial intoxication: report of 38 cases. Amer. J. Med. Sci. *176*:645, 1928.
110. GOODALE, W. T. and KINNEY, T. D.: Sulfadiazine nephrosis with hyperchloremia and encephalopathy. Ann. Int. Med. *31*:1118, 1949.
111. GORNEL, D. L. and GOLDMAN, R.: Acute renal failure following hexol-induced abortion. J.A.M.A. *203*:146, 1968.
112. GREGORIE, F., MALMENDIER, C., and LAMBERT, P.: Syndrome nephrotique apres traitement aux sels d' or. J. Urol. *62*:140, 1956.
113. GREENWALD, I.: The estimation of lipoid and acidesoluble phosphorus in small amounts of serum. J. Biol. Chem. *21*:29, 1915.
114. GROSS, J. E.: *Fanconi syndrome* (adult type) developing secondary to the ingestion of outdated tetracycline. Ann. Intern. Med. *58*:523, 1963.
115. GROSSMAN, J., WESTON, R. E., LEHMAN, R. A., HALPERIN, J. P., ULLMANN, T. D., and LEITER, L.: Urinary and fecal excretion of mercury in man following administration of mercurial diuretics. J. Clin. Invest. *30*:1208, 1951.
116. HAGELSTROM, L., KUHLBACK, B., and RISKA, N.: Renal failure after intravenous para-aminosalicylic acid administration in a case of intestinal and renal amyloidosis. Scand. J. Lab. Clin. Med. *15*:62, 1963.
117. HALL, C. E. and HALL, O.: Polyvinyl alcohol nephrosis: relationship of degree of polymerization to pathophysiologic effects. Proc. Soc. Exper. Biol. Med. *112*:86, 1963.
118. HAMILTON, A.: Hygienic control of the anilin dye industry in Europe. U. S. Month. Labor Rev. 9:1675, 1919.
119. HARDWICKE, J., SOOTHILL, J. F., SQUIRE, J. R., and HOLTI, G.: Nephrotic syndrome with pollen hypersensitivity. Lancet *1*:500, 1959.
120. HARMON, E. L.: Human mercuric chloride poisoning by intravenous injection. Amer. J. Path. *4*:321, 1928.
121. HEILMAN, D. H., HEILMAN, F. R., HINSHAW, H. C., HICHOLS, D. R., and HERRELL, E. W.: Streptomycin absorption, diffusion, excretion and toxicity. Amer. J. Med. Sci. *210*:576, 1945.
122. HELLWIG, C. A. and REED, H. L.: Fatal anuria following sulfadiazine therapy. J.A.M.A. *119*:561, 1942.
123. HEPTINSTALL, R. H.: Pathology of the Kidney. Boston, Little, Brown and Company, 1966.
124. HERRMAN, W. P., HOPFELD, G., and BERNING, H.: Uber Nierenentzundungen Nach

Irgaprin-Be Hundlung (Nephritis After Irgaphyrin Therapy). Z. Klin. Med. *154*:302, 1956.

125. HINT, H.: Proceedings of Conference on Evaluation of Low-molecular-weight Dextran in Shock. National Academy of Science, Division of Medical Sciences, National Research Council, U. S. A., p. 48, 1963.
126. HIRSCH, H. L., VIVINO, H. A., and DOWLING, H. F.: Streptomycin: a review of the basic principles and their clinical application. Med. Ann. Dist. Columbia *17*:311, 1948.
127. HOLADAY, D. A., RUDOFSKY, S., and TREVHAFT. P. S.: The metabolic degradation of methoxyflurane in man. Anesthesiology *33*:579, 1970.
128. HOLMES, K. K.: Toxicity of colistin and polymyxin B. New Eng. J. Med. *271*:633, 1964.
129. HULL, E. and MONTE, L. A.: Acute mercury poisoning. New Orleans Med. Surg. J. *88*:455, 1936.
130. IDBOHRN, H.: Tolerance to contrast media in renal angiography, Acta. Radiol. *45*:141, 1956.
131. IOVINE, G., BERMAN, L. B., HALIKIS, D. N., MOWREY, F. H., CHAPPELLE, E. H., and GIERSON, H. W.: Nephrotoxicity of amphotericin B. Arch. Int. Med. *112*:853, 1963.
132. JACOBZINER, H. and RAYBIN, H. W.: Turpentine poisoning. Arch. Pediat. *78*:357, 1961.
133. JAFFE, I. A.: Effects of Penicillamine on the kidney and on taste. Postgrad. Med. J. Supplement 15, 1968.
134. JAWETZ, E.: Laboratory and clinical observations on polymyxin B and E. Amer. J. Med. *10*:111, 1951.
135. KADEN, W. S. and FRIEDMAN, E. A.: Obstructive uropathy complicating anticoagulant therapy. New Eng. J. Med. *265*:283, 1961.
136. KAHN, M. H. and BERHULST, H. L.: Accidental poisoning in young children-hazards of iron medication. Amer. J. Dis. Child. *99*:688, 1960.
137. KAHN, H. S. and BROTCHNER, R. J.: A recovery from ethylene glycol (anti-freeze) intoxication: a case of survival and two fatalities from ethylene glycol including autopsy findings. Ann. Intern. Med. *32*:284, 1950.
138. KANEE, B. and STOFFMAN, I.: BAL in the successful treatment of mercury poisoning from gray powder. Canad. M.A.J. *60*:292, 1949; J.A.M.A. *140*:1359, 1949.
139. KAPLAN, K., REISBERG, B., and WEINSTEIN, L.: Cephaloridine. Arch. Intern. Med. *121*:17, 1968.
140. KARLSON, A. G., GAINER, U. H., and FELDMAN, W. H.: The effect of neomycin on tuberculosis in guinea pigs infected with streptomycin-resistant tubercule bacilli. Amer. Rev. Tuberc. *62*:345, 1950.
141. KATZ, R.: Renal and possibly hepatic toxicity from coly-mycin. Med. Ann. Dist. Columbia *32*:408, 1963.
142. KEITZER, W. A. and CAMPBELL, J. A.: Renal complications of sulfadiazine. J.A.M.A. *119*:701, 1942.
143. KEGEL, A. H., MCNALLY, W. D., and POPE, A. S.: Methyl chloride poisoning from domestic refrigerators. J.A.M.A. *93*:353, 1929.
144. KENNEDY, R. M. and EARLEY, L. E.: Profound hyponatremia resulting from a thiazide-induced decrease in urinary diluting capacity in a patient with primary polydypsia. New Eng. J. Med. *282*:1185, 1970.
145. KERR, D. N. S. and WALLS, J.: Renal damage due to drugs. Adverse Drug Reaction Bulletin, Nos. 20 and 21, 1970.
146. KIMMELSTIEL, P.: Acute hematogenous interstitial nephritis. Amer. J. Path. *14*:737, 1938.
147. KINCAID-SMITH, P.: Pathogenesis of the renal lesion associated with the abuse of analgesics. Lancet, *1*:859, 1967.
148. KJELLBO, H., STAKEBERG, H., and MELLGREN, J.: Possibly thiazide-induced renal necrotizing vasculitis. Lancet *1*:1034, 1965.
149. KLEEMAN, C. R. and MAXWELL, M. H.: The nephrotoxicity of antibiotics: a review. Biology of Pyelonephritis. Quinn, E. L. and Klass, E. H., eds. Boston, Little, Brown and Company, 1960.
150. KLUTSCH, K., HEIDLAND, A., and KAMMERER, H.: Nierenfunktion nach Infusion von Niedermolekularem Dextran. Med. Klin. *60*:464, 1965.
151. KOBER, G. M. and HAYHURST, E. R.: Industrial Health. Philadelphia, P. Blackiston's Son & Co., 1924.
152. KOLFF, W. J.: Acute renal failure, causes and treatment. Med. Clin. N. Amer. *39*:1041, 1955.
153. KOOTA, G. M., SCHWEINBURG, F. B., and RUTENBERG, A. M.: Role of kanamycin in the management of infections. New Eng. J. Med. *263*:629, 1960.
154. KRIKLER, D. M.: Paracetamol and the kidney. Brit. Med. J. *2*:615, 1967.
155. KUNIN, C. M.: A guide to use of antibiotics in patients with renal disease. Ann. Intern. Med. *67*:151, 1967.
156. KUNIN, C. M. and FINLAND, M.: Restrictions enforced on antibiotic therapy by renal failure. Arch. Int. Med. *104*:1030, 1959.
157. KUNTZ, E.: Klinische Untersuchungen zur Nephrotoxicitat von Kanamycin. Klin. Wchnschr. *40*:830, 1962.
158. LANT, A. F.: Renal Excretion and Nephrotoxicity of Drugs. Renal Disease, 3rd ed., Black, D. A. K., ed. Oxford, Blackwell Scientific Publications, p. 591, 1972.
159. LANT, A. F. and WILSON, G. M.: Diuretics. Renal Disease, 3rd ed., Black, D. A. K., ed. Oxford: Blackwell Scientific Publication, p. 655, 1972.
160. LAPOINTE, A. and BELE-BINDA, N.: Nephrotoxicity associated with methoxyflurane. Conn. Anesth. Soc. J. *17*:145, 1970.
161. LEE, J. C., DUSHKIN, M., EYRING, E. J., ENGLEMAN, E. P., and HOPPER, J.: Renal lesions associated with gold therapy. Light and elec-

tron microscope studies. Arth. Rheum. *8*:1, 1965.
162. LEE, R. E., ULSTROM, R. A., and VERNIER, R. L.: Nephrotic syndrome as a complication of perchlorate treatment of thyrotoxicosis. New Eng. J. Med. *264*:1221, 1961.
163. LEHR, D.: Clinical toxicity of sulfonamides. Ann. N.Y. Acad. Sci. *69*:417, 1957.
164. LEVY, R. I.: Renal failure secondary to ethylene glycol intoxication. J.A.M.A. *173*:1210, 1960.
165. LIPSETT, M. B. and GOLDMAN, R.: Phenylbutazone toxicity: report of a case of acute renal failure. Ann. Intern. Med. *41*:1075, 1954.
166. LIVINGSTONE, R. and STREET, E. W.: Acquired idiosyncrasy to sodium p-aminosalicylate. Lancet 2:308, 1950.
167. LONGCOPE, W. T. and LUETSCHER, J. A., JR.: Clinical uses of 2, 3-dimercaptopropanol (BAL). XI. The treatment of acute mercury poisoning by BAL. J. Clin. Invest. *25*:557, 1946.
168. LONGCOPE, W. T. and LUETSCHER, J. A.: The use of BAL (British Anti-Lewisite) in the treatment of injurious effects of arsenic, mercury, and other metallic poisions. Ann. Intern. Med. *31*:545, 1949.
169. LOUGHRIDGE, L. W., LEADER, L. P., and BOWEN, D. A. L.: Acute renal failure due to muscle necrosis in carbon monoxide poisoning. Lancet 2:349, 1958.
170. LUETSCHER, J. A. and BLACKMAN, S. S.: Severe injury to kidneys and brain following sulfathiazole administration: high sodium and chloride levels and persistent renal damage. Ann. Intern. Med. 67:817, 1952.
171. LYONS, H., PINN, V. W., CORTELL, S., ET AL: Allergic interstitial nephritis: reversible renal failure in nephrotic syndrome. New Eng. J. Med. 288:124, 1973.
172. MACCARTHY, J. M. and JACKSON, R. T.: Hepatic necrosis and other visceral lesions associated with phenylbutazone therapy. Brit. Med. J. 2:240, 1955.
173. MACFARLANE, R. G.: Fibrinolysis following operation. Lancet *1*:10, 1937.
174. MACGIBBEN, B. H., LOUHRIDGE, L. W., HOURIHANE, D. O. B., and BOYDE, D. W.: Autoimmune hemolytic anemia with acute renal failure due to phenacetin and p-aminosalicylic acid. Lancet *1*:7, 1960.
175. MACGOVERN, M. E. and RYNER, P. H. W.: Pink disease and primary renal tubular acidosis. Lancet 2:1083, 1964.
176. MAILLOUX, L., SWARTZ, C. D., CAPIZZI, R., KIM, K. E., ONESTI, G., O., and BREST, A. N.: Acute renal failure after administration of low-molecular-weight dextran. New Eng. J. Med. 277:1113, 1967.
177. MARTINEAU, P. G. and HARTMAN, F. W.: The renal lesions in extensive cutaneous burns. J.A.M.A. *134*:429, 1947.
178. MATHESON, N. A., IRVIN, T. T., and HEDLEY, A. J.: The renal response to low-molecular-weight dextran. Lancet 2:501, 1964.
179. MERKEL, W. C. and CRAWFORD, R. C.: Pathologic lesions produced by sulfathiazole: report of four fatal cases. J.A.M.A. *119*:770, 1942.
180. MILNE, M. D.: Drugs, poisons and the kidney. Renal Disease, 2nd ed., Black, D. A. K., ed. Oxford, Blackwell Scientific Publication, p. 546, 1967.
181. MOORE, R. A., GOLDSTEIN, S., and CANOWITZ, A.: The mitochondria in acute experimental nephrosis due to mercuric chloride. Arch. Path. *8*:930, 1929.
182. MORE, R. H., MCMILLAN, G. C., and DUFF, G. L.: The pathology of sulfonamide allergy in man. Amer. J. Path. 22:703, 1940.
183. MORGAN, I. O., LITTLE, J. M., and EVANS, W. A.: Renal failure associated with low molecular weight dextran infusion. Brit. Med. J. 2:737, 1966.
184. MORTON, H. D.: Temporary suppression of urine following double pyelography. J. Urol. *10*:261, 1923.
185. MOSESCHLIN, S.: Zur Klinik und Therapie der Bleivergiftung mit Bericht uber eine Todliche Toxische Nephrose durch Caedta (Calcimversenat). Schweiz Med. Wchnschr. *87*:1091, 1957.
186. MOVAT, H. Z., STEINER, J. W., and HUHN, D.: The fine structure of the glomerulus in acute glomerulonephritis. Lab. Invest. *11*:117, 1962.
187. MYLER, R. K., LEE, J. C., and HOPPER, J.: Renal tubular necrosis caused by mushroom poisoning. Arch. Intern. Med. *114*:196, 1964.
188. MUEHRCKE, R. C.: Acute Renal Failure Diagnosis and Management, St. Louis, The C. V. Mosby Co., 1969.
189. MUEHRCKE, R. C.: Interstitial nephritis. Chicago Med. *71*:211, 1968.
190. MUEHRCKE, R. C., Personal observation.
191. MUEHRCKE, R. C., PIRANI, C. L., and KARK, R. M.: Interstitial nephritis: a clinicopathological and renal biopsy study. Ann. Intern. Med. *66*:1052, 1967.
192. MURPHY, F. D., KUZMA, J. F., POLLEY, T. Z., and GRILL, J.: Clinicopathological studies of renal damage due to sulfonamide compounds: a report of 14 cases. Arch. Intern. Med. 73:433, 1944.
193. MCDERMOTT, W.: Toxicity of streptomycin. Amer. J. Med. 2:491, 1947.
194. MCKINSTRY, W. E. and HICKES, J. M.: Emergency-arsine poisoning. Arch. Intern. Med. *16*:32, 1957.
195. NATHAN, D. A., MEITUS, M. L., CAPLAND, L., and LEV, M.: Death following phenylbutazone (Butazolidin) therapy: report of case. Ann. Intern. Med. 39:1096, 1953.
196. NELSON, A. A., RADOMSKI, J. L., and HOGAN, E. C.: renal and other lesions in dogs and rats from intramuscular injection of neomycin. Fed. Proc. *10*:366, 1951.
197. NIALL, J. F. and DOYLE, J. C.: Renal Failure Associated with Dextran Infusion. Proceedings of the Third International Congress of

Nephrology, Washington, 1966.
198. O'BRIEN, E. T., YEOMAN, W. B., and HOBBY, I. A. E.: Hepatorenal damage from toluane in a glue sniffer. Brit. Med. J. 2:29, 1971.
199. OWEN, D.: Renal failure due to para-aminosalicylic acid. Brit. Med. J. 2:483, 1958.
200. PERIMUTTER, M.: Unusual cases of acute tubular necrosis. Ann. Intern. Med. *47*:81, 1957.
201. Personal observation.
202. PETERSDORF, R. G. and PLORDE, J. J.: Colistin, a reappraisal. J.A.M.A. *183*:123, 1963.
203. PIRANI, C. L.: Personal communication.
204. PLETSCHER, A., STUDER, A., and MIESCHER, P.: Experimental investigations of erythrocytic and organ changes due to N-acetyl-p-aminophenol and phenacetin. Schwiez. Med. Wchnschr. *88*:1214, 1958.
205. PLUMMER, N. and WHEELER, C.: Toxicity of sulfadiazine; observations of 1357 cases. Amer. J. Med. Sci. *207*:175, 1944.
206. PONS, C. A. and CUSTER, R. P.: Acute ethylene glycol poisoning: A clinicopathologic report of 18 fatal cases. Amer. J. Med. Sci. *211*:544, 1946.
207. POWELL, L. W. and HOOKER, J. W.: Neomycin nephropathy. J.A.M.A. *160*: 557, 1956.
208. RACKERMANN, F. M., LONGSCOPE, W. T., and PETERS, J. P.: The excretion of chlorides and water and the renal function in serum disease. Arch. Intern. Med. *18*:496, 1916.
209. RANDALL, R. E., JR.: Renal failure following antibiotics. Ann. Intern. Med. *66*:1056, 1967.
210. REIDENBERG, M. M.: Renal Function and Drug Action. Philadelphia, W. B. Saunders Co., 1971.
211. REIDENBERG, M. M., ODAR-CEDERLOF, I., VON BAHR, C., BORGA, O., and SJOOVIST, F.: Protein binding of diphenylhydantoin and desmethylimipramine in plasma from patients with poor renal function. New Eng. J. Med. *285*:264, 1971.
212. RELMAN, A. S. and SCHWARTZ, W. B.: The kidney in potassium depletion. Amer. J. Med. *24*:764, 1958.
213. REUBER, M. D. and BRADLEY, J. E.: Acute versenate nephrosis occurring as a result of treatment for lead intoxication. J.A.M.A. *174*:263, 1960.
214. RICHARDSON, J. H. and ALDERFER, H. H.: Acute renal failure caused by phenylbutazone. New Eng. J. Med. *268*:809, 1963.
215. ROBSON, J. S.: Drug-induced renal disease. Practitioner *181*:288, 1958.
216. RODIN, A. E. and CROWSON, C. N.: Mercury nephrotoxicity in the rat. I. Factors influencing the localization of the tubular lesions. Amer. J. Path. *41*:297, 1962.
217. RUTENBURG, A. M.: The clinical use of sulfisomidine in urinary tract infection. Ann. N.Y. Acad. Aci 69:389, 1957.
218. RYTAND, D. A.: Fatal anuria, the nephrotic syndrome and glomerulonephritis as sequels to dermatitis of poison oak. Amer. J. Med. *5*:548, 1945.
219. SANGHVI, L. M., SHARMA, R., MIRSA, S. N., and SAMUEL, K. C.: Sulfhemoglobinemia and acute renal insufficiency after copper sulfate poisoning; report of two fatal cases. Arch. Path. *63*:172, 1957.
220. SCHATZ, A., BUGIE, E., and WAKSMAN, S. A.: Streptomycin, a substance exhibiting antibiotic activity against gram-positive and gram-negative bacteria. Proc. Soc. Exper. Biol. Med. *55*:66, 1944.
221. SCHEITLIN, W. and JEANNERET, P.: Uber akute nierenschadigugnen unter phenylbutazontherapie. Schweiz. Med. Wchnschr. *87*:881, 1957.
222. SCHINDEL, L.: Unexpected reactions to kanamycin. Israel Med. J. 23:131, 1964.
223. SCHREINER, G. E.: Acute renal failure. Renal Disease, 2nd ed., Black, C. A. K., ed. Oxford, Blackwell Scientific Publications, p. 309, 1967.
224. SCHREINER, G. E.: The nephrotoxicity of analgesic abuse. Ann. Intern. Med. 57:1043, 1962.
225. SCHREINER, G. E. and MAHER, J. F.: Dialysis of poisons. Acad. Med. New J. Bull. *6*:310, 1960.
226. SCHREINER, G. E. and MAHER, J. F.: Toxic nephropathy. Amer. J. Med. *38*:409, 1965.
227. SCHOENBACH, E. B., BRYER, M. S., and LANG, P. H.: The clinical use of polymyxin. Ann. N.Y. Acad. Sci. *51*:987, 1949.
228. SCHOURUP, K., ORSKOW, I., ORSKOV, F., and BARTERLS, E. D.: Phenacetin as the cause of kidney damage in rabbits. Danish Med. Bull. *10*:85, 1963.
229. SCUDI, J. V. and ANTOPOL, W.: Some pharmacologic characteristics of basitracin. Proc. Soc. Exp. Biol. Med. *64*:503, 1947.
230. SHAFFER, B., BURGOON, C. F., and GOSMAN, J. H.: Acute glomerulonephritis following administration of rhus toxin. Report of a fatal and near fatal case. J.A.M.A. *146*:1570, 1951.
231. SHALDON, S., ROSEN, S. M., SILVA, H., RAE, A. I., POMEROY, J., and RYDER, J.: Effects of chlorothiazide on renal ammonia production, plasma electrolytes and acid-base balance in acute renal failure. Proc. Soc. Exp. Biol. Med. *113*:983, 1963.
232. SHILS, M. E.: Renal disease and the metabolic effects of tetracycline. Ann. Intern. Med. *58*:389, 1963.
233. SIROTA, J. H.: Carbon tetrachloride poisoning in man. 1. Mechanisms of renal failure and recovery. J. Clin. Invest. *28*:1412, 1949.
234. SMITH, J. P.: Pathology of ferrous sulfate poisoning. J. Path. Bact. *64*:467, 1950.
235. SOLOMON, M., GALLOWAY, N. C., and PATTERSON, R.: The kidney and tetracycline toxicity. Missouri Med. *62*:283, 1965.
236. SPUHLER, O. and ZOLLINGER, H. U.: Die chronischinterstitielle nephritis. Ztschr. Klin. Med. *151*:1, 1953.

237. STAEMMLER, M. and KARHOFF, B.: Die akute nephrosen. Nierenschaden durch antibiotica. Arch. Path. Anat. *328*:481, 1956.
238. STEWARD, J. H.: Haemolytic anaemia in acute and chronic renal failure. Quart. J. Med. *36*:85, 1967.
239. TAIT, G. B.: Nephropathy during phenindione therapy. Lancet *2*:1198, 1960.
240. TALANO, R. C. and CRAWFORD, J. D.: Trimethadione nephrosis treated with cortisone. New Eng. Med. J. *15*:269, 1963.
241. TAPP, E. and LOWE, B.: Tetracycline toxicity in haemoglobinuria. Brit. Med. J. *1*:143, 1966.
242. THAYSEN, J. H., GJORUP, S., and KILLMAN, S. A.: Acute renal failure: experiences with conservative and hemodialytic treatment of 32 consecutive cases. Danish Med. Bull. *4*:73, 1957.
243. ULLRICH, G.: Verlauf und Behandlung einer "Akuten Toxischen Niereninsuffizienz" nach Arsenwasserstoffvergiftung. Wiener Klin. Wochenschrift *70*:538, 1958.
244. UNGER, A. M. and NEMUTH, H. I.: Penicillinase treatment of acute renal insufficiency due to penicillin hypersensitivity. J.A.M.A. *167*:1237, 1958.
245. VALEK, A.: Acute renal insufficiency in intoxication with mercury compounds. Acta Med. Scan *177*:63, 1965.
246. VILTER, C. F. and BLANKERNHORN, M. A.: The toxic reactions of the new sulfonamides. J.A.M.A. *126*:691, 1944.
247. VOGT, W. and COTTIER, H.: Nekrotisierende Nephrose nach Behandlung einer Subakutchronischen Bleivergiftung mit Versenat in Hohen Dosen. Schweiz. Med. Wchnschr. *87*:665, 1957.
248. WAIFE, S. O. and PRATT, P. T.: Fatal mercurial poisoning following prolonged administration of mercurophylline. Arch. Intern. Med. *78*:42, 1946.
249. WAISBREN, B. A. and SPINK, W. W.: A clinical appraisal of neomycin. Ann. Intern. Med. *33*:1099, 1956.
250. WARREN, S. A. and GROSS, W. V., JR.: Clinical recovery following prolonged anuria in an infant 2 months of age. Pediatrics *5*:954, 1950.
251. WEGIENKA, L. C. and WELLER, J. M.: Renal tubular acidosis caused by degraded tetracycline. Arch. Intern. Med. *114*:232, 1964.
252. WEINIG, E. and SCHWERD, W.: Gefahren bei der Behandlung der Bleiintoxikation mit Calciumversenat ("Mosatil Komplexon"). Med. Wchnschr. *100*:1788, 1958.
253. WEINSTEIN, L. and EHRENKRANZ, M. J.: Streptomycin and Dihydrostreptomycin: Antibiotics Monographs. New York, Medical Encyclopedia, 1958.
254. WEINSTEIN, L. MADOFF, M. A., and SAMET, C. M.: The sulfonamides. New Eng. J. Med. *263*:793, 1960.
255. WINFIELD, M., CRISP, G. O., MAXWELL, M. H., and KLEEMAN, C. R.: Nephrotoxic effects of kanamycin: a preliminary report. Ann. New York Acad. Sci. *76*:149, 1958.
256. WILKINSON, R. and ECCLESTON, D. W.: Nephrotic syndrome induced by gold therapy. Brit. Med. J.*2*:772, 1970.
257. WREN, J. C. and NUTT, R. L.: Nephrotic syndrome occurring during paramethadione therapy. J.A.M.A. *153*:918, 1953.
258. WRIGHT, D. O. and KINSEY, R. E.: Renal complications due to sulfadiazine. J.A.M.A. *120*:1351, 1942.
259. YOUNG, A. G., MUEHLBERGER, C. W., and MEEK, W. J.: Toxicological studies of acute anilin poisoning. I. Experimental studies of acute anilin poisoning. J. Pharm. Exp. Ther. *27*:101, 1926.
260. YOW, E. M.: Observations on the use of sulfisoxazole in 1,000 consecutive patients with particular reference to the frequency of undesirable side effects. Amer. Pract. Digest. Treat. *4*:521, 1953.
261. YOW, E. M. and ABU-NASSER, H.: Kanamycin: a re-evaluation after three years experience. 2nd International Sumposium Chemotherapy *1*:148, 1963.
262. YOW, E. M., MOYER, J. H., and SMITH, C. P.: Toxicity of polymyxin B. II. Human studies with particular reference to evaluation of renal function. Arch. Int. Med. *92*:248, 1953.
263. ZABLUDOVITCH, S. and MILMAN, F.: Anuria por fenibutazone. Prensa Med. Argentina *45*:3035, 1958.
264. ZEEK, P. M.: Periarteritis nodosa and other forms of necrotizing angiitis. New Eng. J. Med. *248*:764, 1953.
265. ZILBERG, B.: Anuria following penicillin administration. South African Med. J. 32:350, 1958.