Renal Involvement in Tropical Diseases

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Tropical nephrology is no longer a regional issue. With the enormous expansion of travel and immigration, the world has become a global village. Today, a health problem in a particular region has worldwide repercussions. Typical examples are the acquisition of malaria in European airports, renal disease associated with herbal medications, and increasing encounters of parasitic infections in immunocompromised persons [1–3].

Lessons learned from the study of tropical diseases have considerably enriched worldwide medical knowledge of the basic and clinical aspects of nontropical diseases. Examples include better understanding of macrophage function in vitro, the role of cytokines in acute renal failure, and the importance of immunoglobulin A deposits in the progression of glomerular disease [4–7].

The so-called typical tropical nephropathies are broadly classified as infective or toxic. Infective nephropathies include renal diseases associated with endemic bacterial, viral, fungal, and parasitic infections. Toxic tropical nephropathies include exposure to poisons of animal origin, such as snake bites, scorpion stings, and intake of raw carp bile, and plant origin, such as certain mushrooms and the djenkol bean [3].

Tropical bacterial infections often are associated with renal complications that vary according to the causative organism, severity of infection, and individual susceptibility. The principal acute infections reported to affect the kidneys are salmonellosis, shigellosis, leptospirosis, melioidosis, cholera, tetanus, scrub typhus, and diphtheria [8–16]. Renal involvement in mycobacterial infections such as tuberculosis and leprosy usually pursues a subacute or chronic course [17–19].

CHAPTER

6

The clinical spectrum of renal involvement extends all the way from asymptomatic proteinuria or urinary sediment abnormalities to fatal acute renal failure. The respective renal pathologies include glomerular, microvascular, and tubulointerstitial lesions.

The pathogenesis of renal complications in tropical bacterial infections is multifactorial. The principal factors are direct tissue invasion by the causative organisms and remote cellular and humoral effects of bacterial antigens and endotoxins. The relative significance of the different pathogenetic mechanisms varies with the causative organism.

In tropical zones many viral nephropathies are endemic, such as those associated with human immunodeficiency virus and hepatitis A, B, and C viruses. These are addressed in Chapter 7. Here the focus is on an important viral disease endemic in Southeast Asia that often causes minor epidemics in Africa and other tropical countries, dengue hemorrhagic fever.

Mycotic infections are described in detail elsewhere. Discussed here is a fairly common mycotic infection, mucormycosis, which occurs in underdeveloped tropical regions, particularly among immunocompromised patients. Also described is ochratoxin, a fungal toxin often incriminated in the pathogenesis of Balkan nephropathy. Ochratoxin also contributes to progressive interstitial nephropathy in Africa [20].

Three ways exist by which parasitic infections cause renal disease: 1) direct physical invasion of the kidneys or urinary tract, as in schistosomiasis, echinococcosis, and filariasis; 2) renal injury as a consequence of the acute systemic effects of parasitic infection, *eg,* falciparum malaria; and 3) immune-mediated renal injury resulting from the concomitant host-parasite interaction, *eg,* schistosomiasis, malaria, filariasis, leishmaniasis, trichinosis, echinococcosis, toxoplasmosis, and trypanosomiasis [21–32].

Infective Tropical Nephropathies

Bacterial Infections

CLINICAL MANIFESTATIONS OF TROPICAL BACTERIAL NEPHROPATHIES

Disease	Abnormal sediment	Proteinuria	ARF	CRF	HUS	Hemolysis	DIC	Jaundice	Commonly associated features
Salmonellosis	+++	++++	+	-	+	+	+	+	Gastrointestinal
Shigellosis			+	-	++*	+	+	+	Neurologic[†]
Leptospirosis	++++	++++	++++	-	+	+	+	++++	Hemorrhagic tendency
									Polyuria[‡]
Melioidosis	+++++	+	++	-					Hyponatremia[§]
Cholera			+	-					Hypokalemia, acidosis
Tetanus	+	++++	+++	-					Sympathetic overflow
Scrub typhus	+	++	+	-		+		+	
Diphtheria	+	+	+	-					Myocarditis, polyneuritis
Tuberculosis	++	+/+++		+					Retroperitoneal nodes
Leprosy	++	+++	+	+					Lepromas

*Associated with Shigella serotype I endotoxin [33].

[†]Visual disturbances, drowsiness, seizures, and coma in 40% of cases [34].

[‡]In 90% of cases [12].

[§]Nephrogenic diabetes insipidus [35].

ARF—acute renal failure; CRF—chronic renal failure; DIC—disseminated intravascular coagulation; HUS—hemolytic uremic syndrome; +—<10%; ++—10%–24%; +++—25%–49%; ++++—50%–80%; +++++—>80%.

Dash indicates not reported.

FIGURE 6-1

Clinical manifestations of tropical bacterial nephropathies. Note the wide spectrum of clinical manifestations that may ultimately reflect on the kidneys [33–35].

SPECTRUM OF RENAL PATHOLOGY IN TROPICAL BACTERIAL INFECTIONS

Disease	Glomerulonephritis								Vasculitis	AIN	ATN	Other tubular changes
	MPGN	EXGN	MCGN	MN	NG	CGN	Amyloid	Deposits of immunoglobulins, complement, and antigen				
Salmonellosis	++	++*						G,M,A,C3,Ag†		++	+	Cloudy swelling
Shigellosis	+								+		+	Cloudy swelling
Leptospirosis	+		+					M,C3	+	++	+++	
Melioidosis	+									+++	+	Cloudy swelling
Cholera											++	Vacuolation‡
Tetanus											++	
Scrub typhus	+									+	+	Cloudy swelling
Diphtheria										++	+/++	Degeneration§
Tuberculosis						+				+		
Leprosy	+/+++		+	+		+¶	+	G,M,A,C3		+	+/+++**	Functional defects

*When associated with *Schistosoma mansoni* infection in Egypt [9].

†Vi antigen deposits [8].

‡Hypokalemic nephropathy [36].

§Exotoxin-induced inhibition of protein synthesis in tubule cells [37].

¶Usually complicates amyloidosis: 2.4%–8.4% [18].

**63% in lepromatous leprosy; 2% in nonlepromatous types [38].

AIN—acute interstitial nephritis; ATN—acute tubular necrosis; CGN—crescentic glomerulonephritis; EXGN—exudative glomeru-lonephritis; MCGN—mesangiocapillary glomerulonephritis; MN—membranous glomerulopathy; NG—necrotizing glomerulitis; +—<10%; ++—10%–24%; +++—25%–50%.

FIGURE 6-2

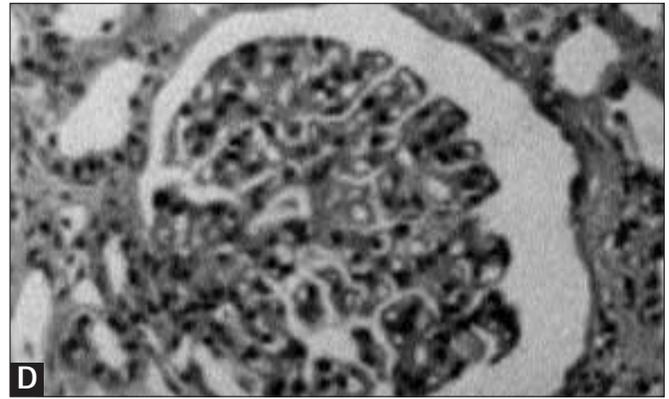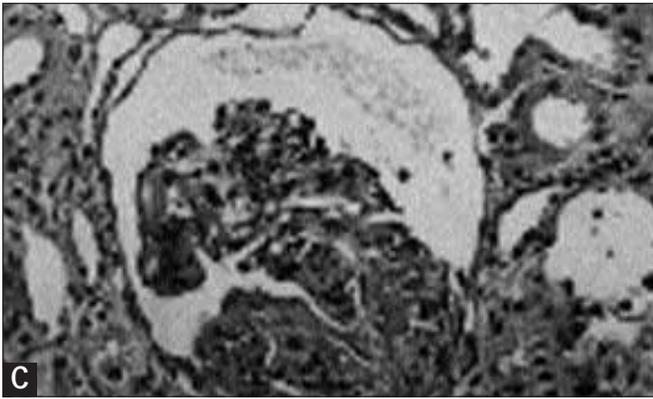Spectrum of renal pathology in tropical bacterial infections [36–38].
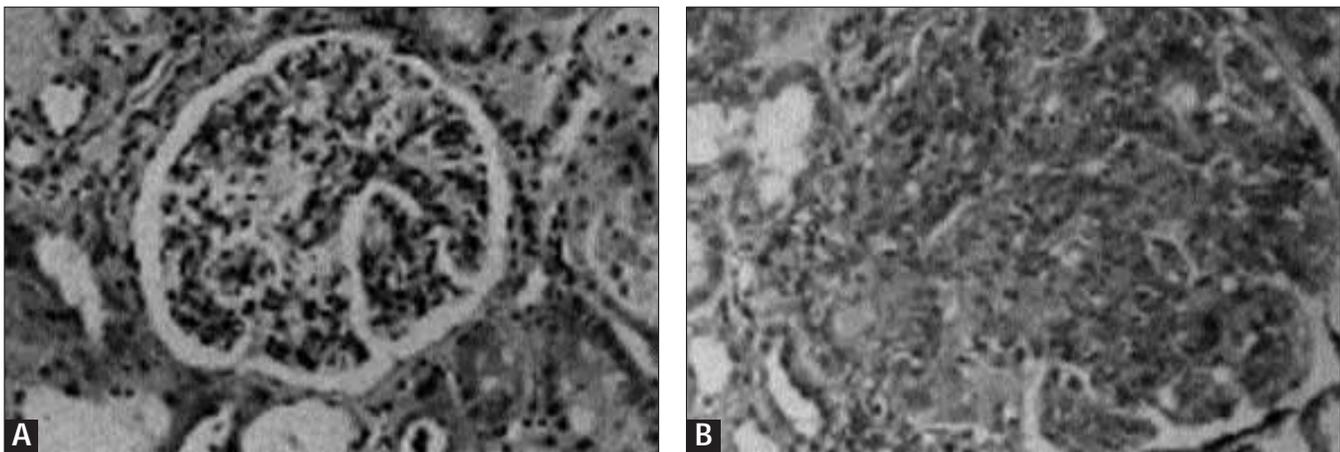
FIGURE 6-3

Glomerular lesions associated with tropical bacterial infections. **A,** Simple proliferative glomerulonephritis in a patient with shigellosis. **B,** Exudative glomerulonephritis in a patient with salmonellosis.
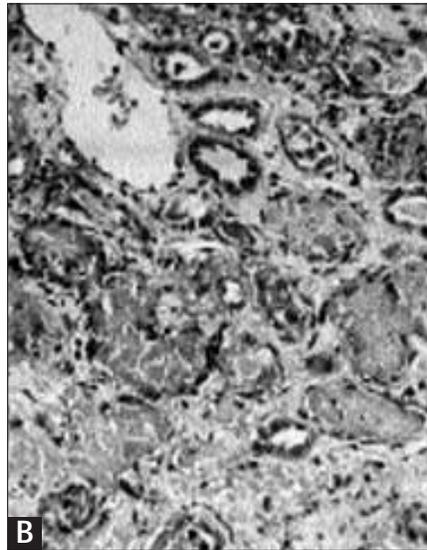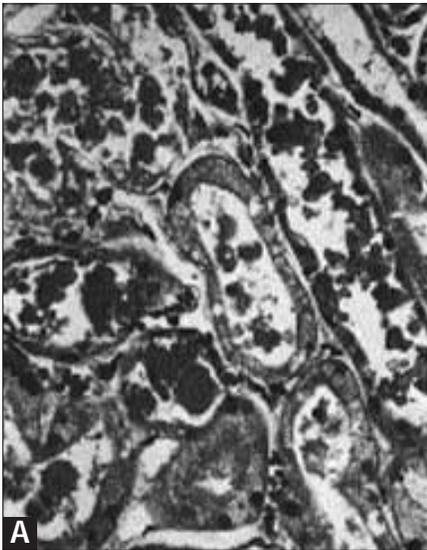
(Continued on next page)

FIGURE 6-3 *(Continued)*

C, Necrotizing vasculitis in a patient with leptospirosis. **D,** Membranous nephropathy associated with leprosy. (Hematoxylin-eosin stain × 150.)
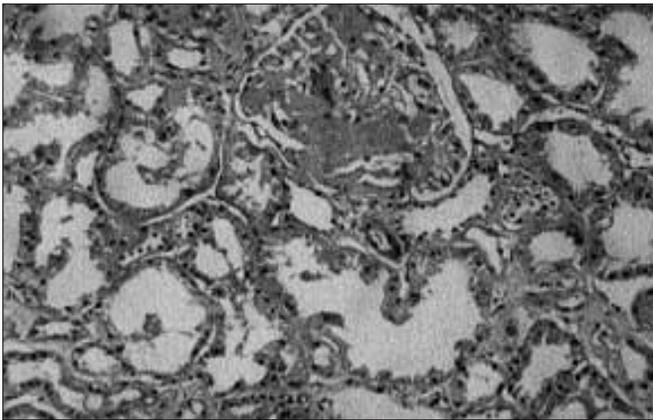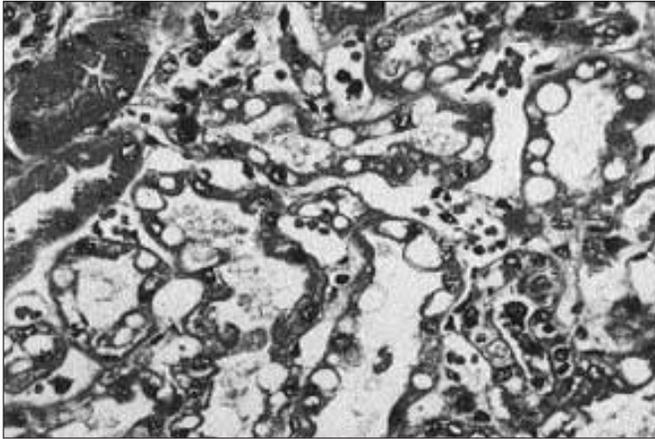

FIGURE 6-4

Glomerular amyloid deposits in a patient with leprosy. (Hematoxylin-eosin stain × 200.)

FIGURE 6-5

Acute tubular pathology associated with bacterial infections. **A,** Acute tubular necrosis with erythrocyte aggregates in the tubular lumina in a patient with leptospirosis. (Hematoxylin-eosin stain × 250.) **B,** Cortical necrosis in a child with severe shigellosis and hemolytic uremic syndrome. (Hematoxylin-eosin stain × 200.)

FIGURE 6-6
Extensive vacuolation of the proximal tubules (hypokalemic nephropathy) in a patient with cholera. (Hematoxylin-eosin stain × 300.) (*From* Sinniah and coworkers [39]; with permission.)
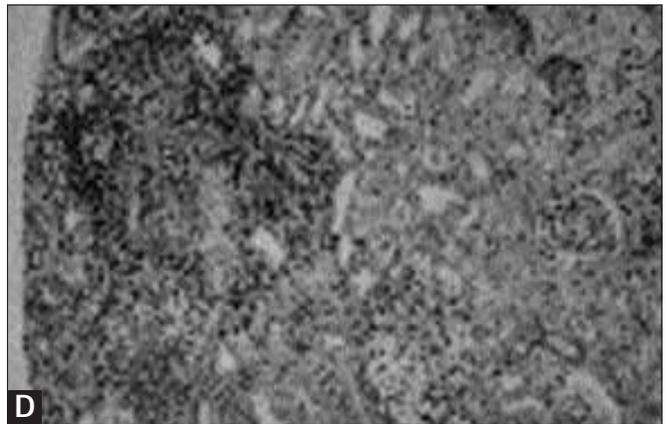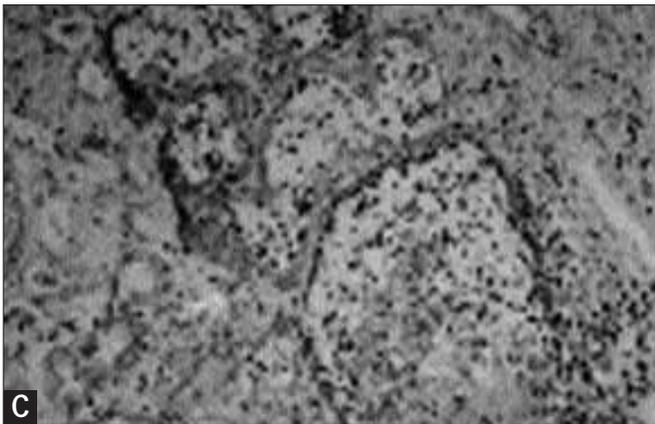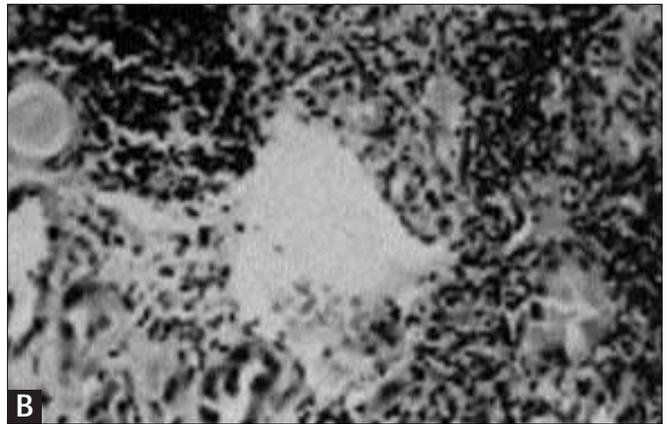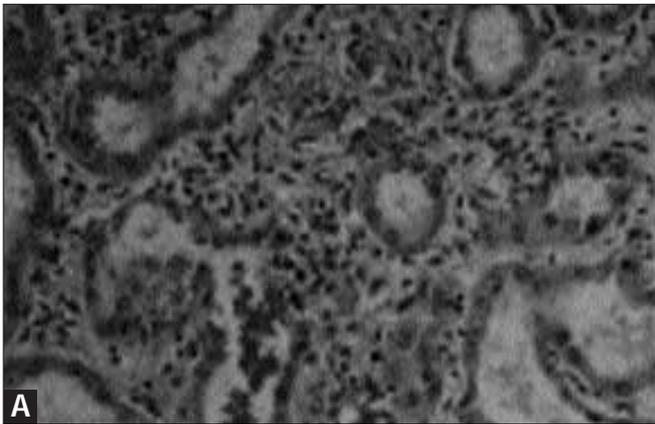
FIGURE 6-7
Interstitial lesions associated with bacterial infections. **A,** Acute interstitial nephritis in a patient with diphtheria. (Hematoxylin-eosin stain × 100.) **B,** Perivenular monocytic infiltration in a patient with scrub typhus. (Hematoxylin-eosin stain × 100.) **C,** Renal abscess in a patient with septicemic melioidosis. (Hematoxylin-eosin stain × 75.) **D,** Micro-abscesses in a patient with typhoid fever [40]. (Hematoxylin-eosin stain × 75.)
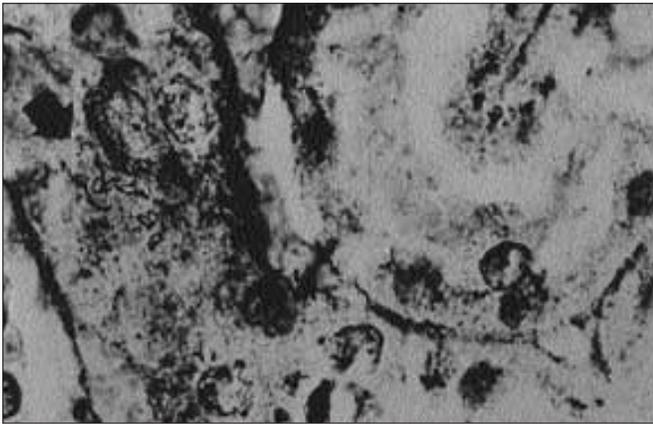
FIGURE 6-8

Low-power electron micrograph. Here leptospires (*arrow*) in the peritubular cortical interstitial space are seen in a patient with leptospirosis. (Magnification × 12,000.)
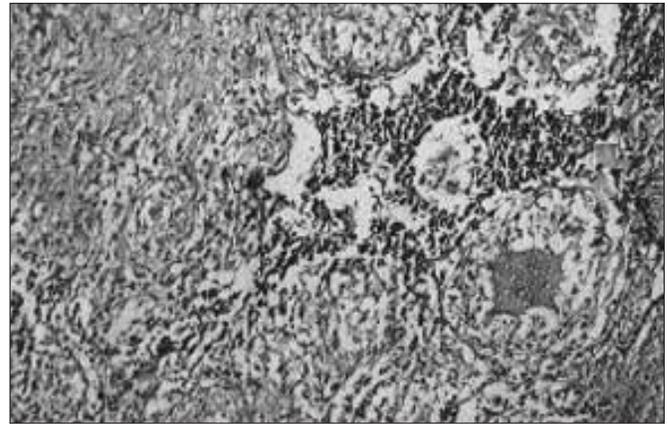

FIGURE 6-9

Renal tuberculosis. Seen here are multiple tuberculous granulomata with Langhans' giant cells. Diffuse interstitial tuberculosis without definite granulomatous formation also has been described. (Hematoxylin-eosin stain × 200.)
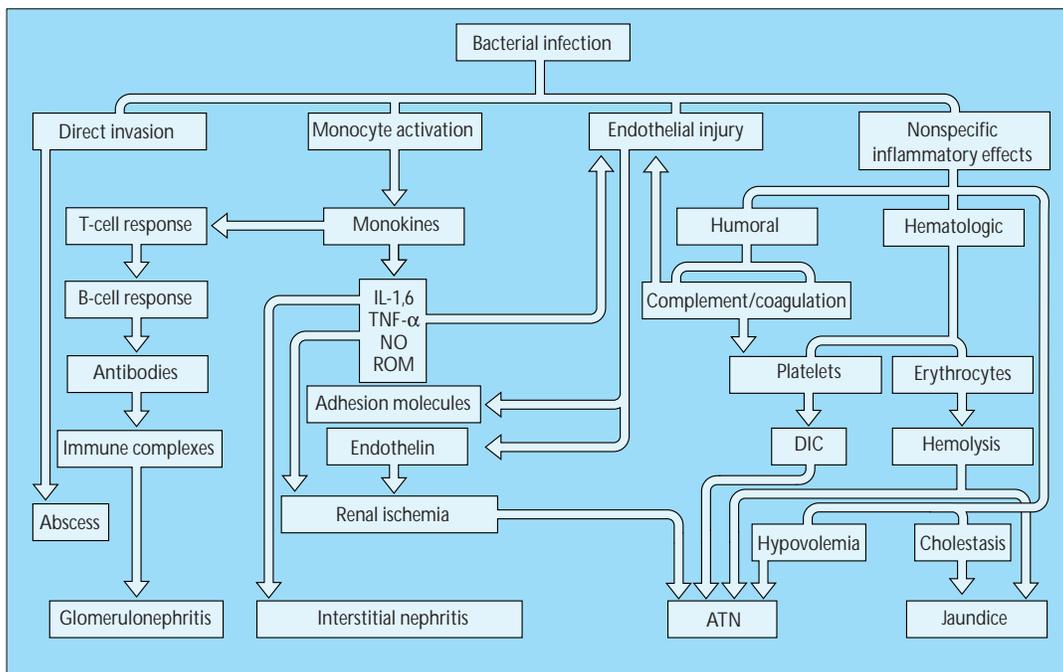

FIGURE 6-10

Common pathogenetic mechanisms of renal injury in tropical bacterial infections. Depending on the bacterial species and strain, as well as on the host's resistance and genetic background, bacteria may directly invade the renal parenchyma, induce an immune reaction, injure the capillary endothelium or provoke a nonspecific humoral or hematologic response. The subsequent evolution of these pathways may lead to different forms of renal injury. The *asterisk* indicates that the role of hemolysis is augmented in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency. ATN—acute tubular necrosis; DIC—disseminated intravascular coagulation; IL—interleukin; NO—nitric oxide; ROM—reactive oxygen molecules; TNF-α—tumor necrosis factor-α.

PATHOGENETIC MECHANISMS IN ACUTE TUBULAR NECROSIS

Disease	Monokines	Hypovolemia	Hemolysis	Rhabdomyolysis	Disseminated intravascular coagulation	Complement activation
Salmonellosis	+	+	+	+	+	++
Shigellosis	+	++	+	+	+	
Leptospirosis	++	+	+		+	+
Melioidosis	+	+		+		+
Cholera	+	+++		++*		
Tetanus	++	+				
Scrub typhus	+	+	+			
Diphtheria	+	+				
Leprosy	+	-				

*Elevated creatine phosphokinase in 88%, myoglobinuria in 39% of cases [14].
+—<10%; ++—10%–24%; +++—24%–50%.

FIGURE 6-11

Pathogenetic mechanisms in acute tubular necrosis associated with bacterial infections.
Note the multiplicity of factors depending on the bacterial species and their host targets.

Viral Infections
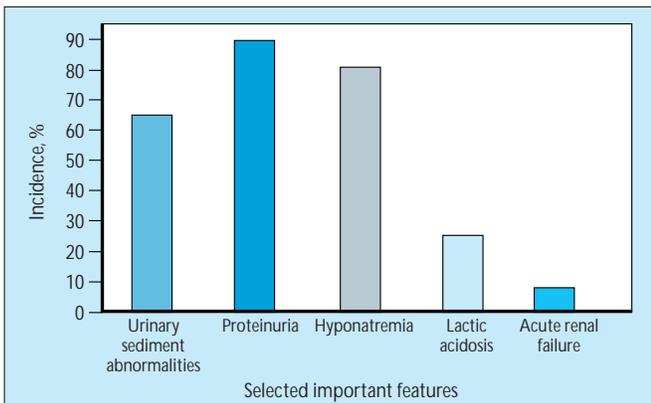
FIGURE 6-12

Clinical manifestations of renal involvement in dengue hemorrhagic fever. Note that proteinuria and abnormal urinary sediment are the most common manifestations. Also note the high incidence of hyponatremia, like with many other tropical infections [40,41].
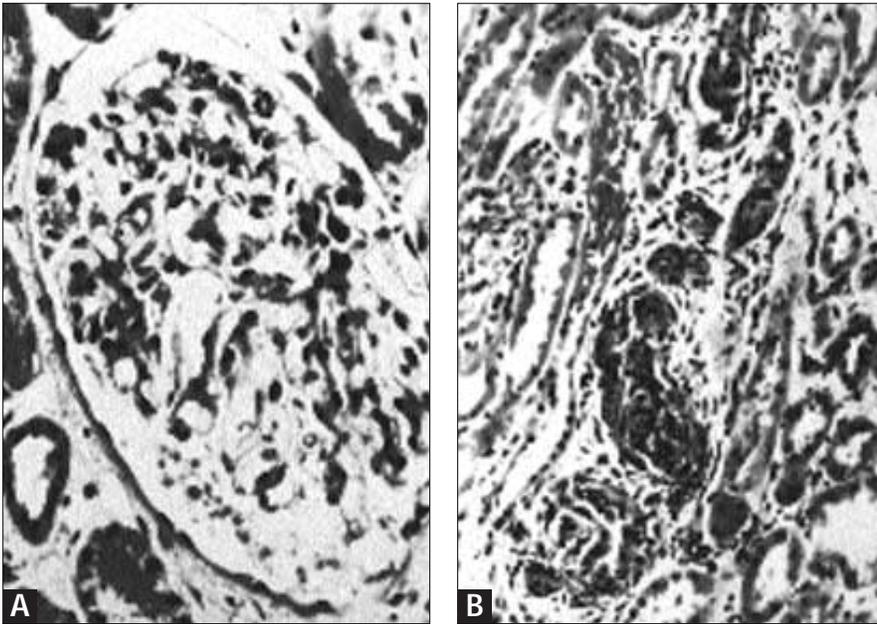
Renal lesions in a patient with dengue hemorrhagic fever. **A,** Mesangial proliferative glomerulonephritis, which usually is associated with deposits of immunoglobulins G and M and complement 3. (Hematoxylin-eosin stain × 200.) **B,** Acute tubular necrosis, which is associated with interstitial edema and mononuclear cell infiltration. (Hematoxylin-eosin stain × 175.)

Mycotic Infections
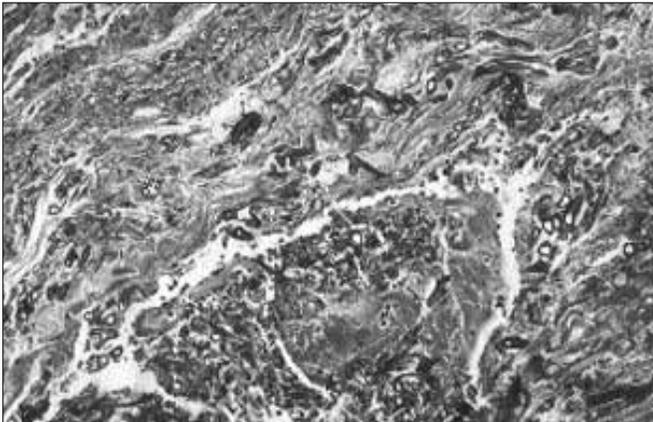
FIGURE 6-14

Section from a patient with mucormycosis, showing extensive tissue necrosis, weak inflammatory cellular infiltration, and fungal hyphae branching at right angles. (Hematoxylin-eosin stain × 150.)
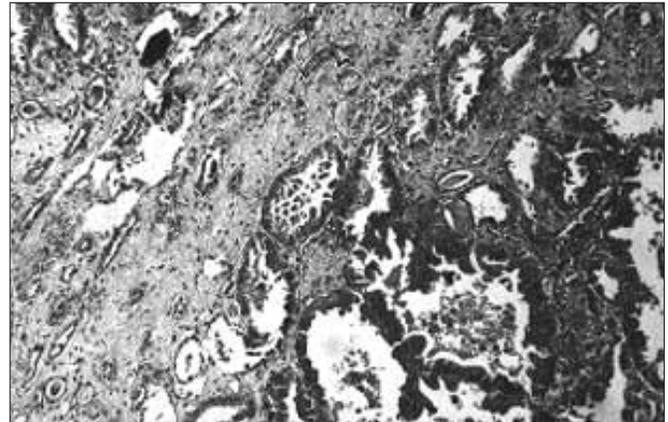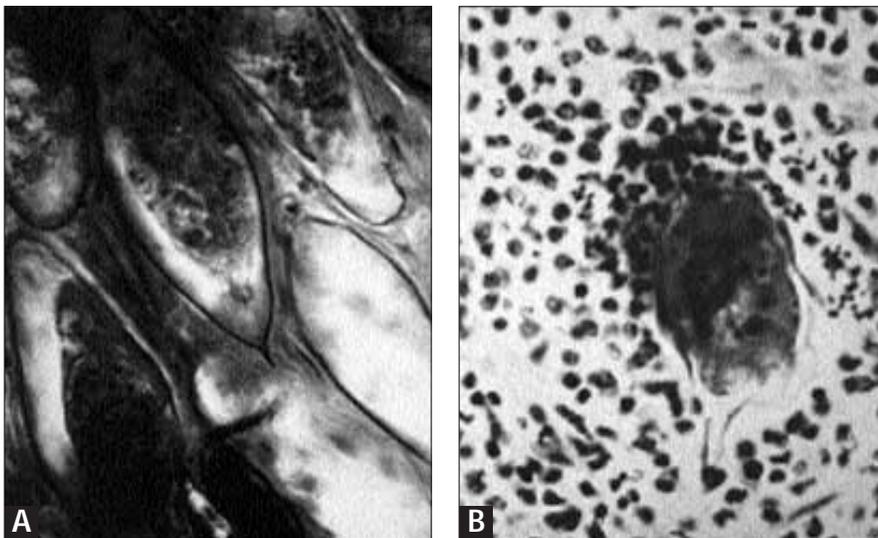

FIGURE 6-15

Ochratoxin-A–induced interstitial fibrosis, showing marked intertubular scarring with patchy atrophy and collapse of tubules. This patient's serum ochratoxin-A and urinary ochratoxin-A levels were 5.18 and 3.87 ng/mL, respectively (the means for a control group were 1.6 and 1.85 ng/mL, respectively) [20]. (Masson trichrome stain × 200.)

Parasitic Infections
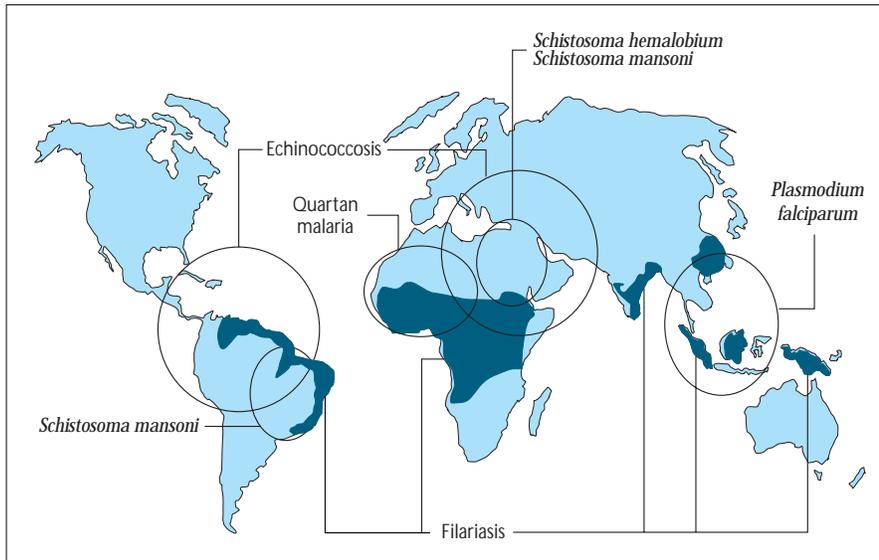
Global distribution of important parasitic nephropathies. Note the high prevalence of schistosomal, malarial, filarial, and echinococcal renal complications in Africa; *S. mansoni* and hydatid in South America; falciparum malaria and filariasis in South East Asia and filariasis in India [3].

Urinary schistosomiasis. **A,** A sheet of *Schistosoma haematobium* ova in tissues. (Silver stain $\times$ 350.) **B,** *S. haematobium* granuloma. Shown is a delayed hypersensitivity reaction of the host to soluble oval antigens released from the ova through micropores in their shells. The granuloma is composed of mononuclear cells, a few neutrophils, eosinophils, and fibroblasts, surrounding a distorted egg. (Hematoxylin-eosin stain $\times$ 300.)
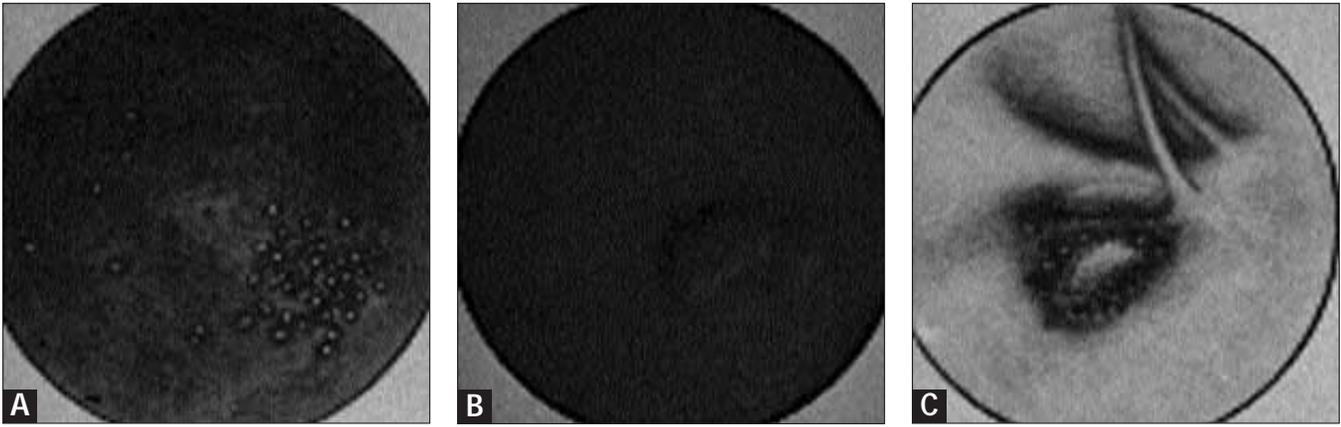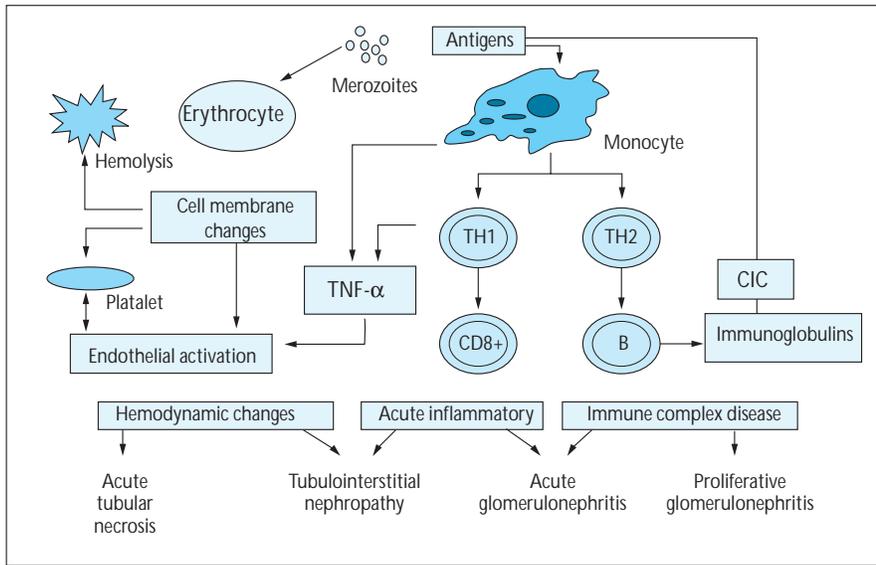
FIGURE 6-18

Cystoscopic appearances of different bladder lesions associated with *Schistosoma haematobium* infection. **A,** Bilharzial (schistosomal) pseudotubercles. **B,** Bilharzial submucous mass covered by pseudotubercles. **C,** Bilharzial ulcer surrounded by pseudotubercles. **D,** Bilharzial ulcer surrounded by sandy patches. (*Courtesy of* N. Makar, MD.)
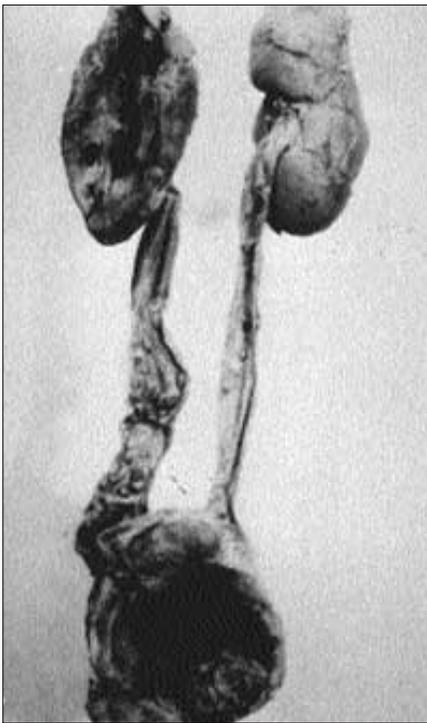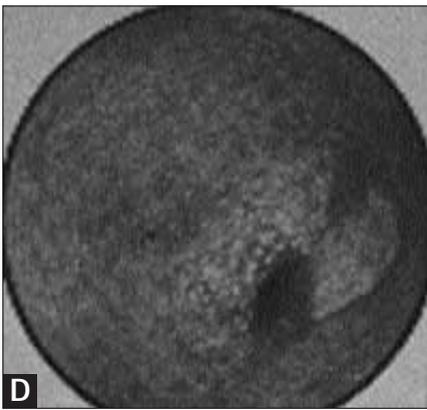
FIGURE 6-19

Postmortem specimen showing advanced bilharzial involvement of the urinary tract. Note the dirty bladder mucosa, fibrosed muscle layer, and neoplastic growth (histologically a squamous cell carcinoma) cut through transversely. The ureters are dilated, with a clear stricture at the lower end of the right ureter. Also seen in this patient are bilateral hydroureters with submucous cystic lesions (bilharzial ureteritis cystica). The kidneys show considerable scarring, with the right kidney also showing chronic back pressure changes.
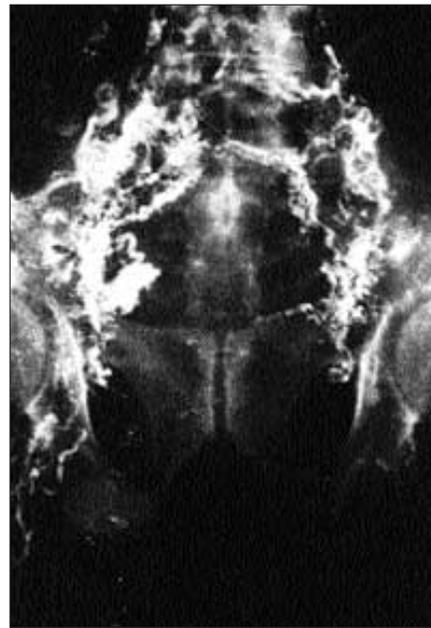
FIGURE 6-20

Filariasis of the abdominal lymphatics. Lymphangiogram shows the dilated retroperitoneal lymphatics in a patient with filarial chyluria.

FIGURE 6-21

The pathogenesis of falciparum malarial renal complications. Note the infection triggers two initially independent pathways: red cell parasitization and monocyte activation. These subsequently interact, as the infected red cells express abnormal proteins that induce an immune reaction by their own right, in addition to providing sticky points (knobs) for clumping and adherence to platelets and capillary endothelium. TNF-α released from the activated monocytes shares in the endothelial activation. As both pathways proceed and interact, a variety of renal complications develop, including acute tubular necrosis, acute interstitial nephritis and acute glomerulonephritis. B—B-lymphocyte; CD8—cytotoxic T cell; CIC—circulating immune complexes; TH—T-helper cells (1 and 2); TNF-α—tumor necrosis factor-α.
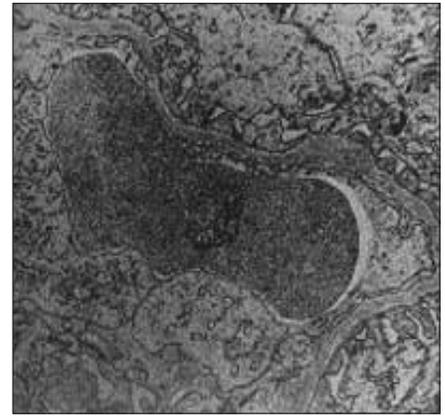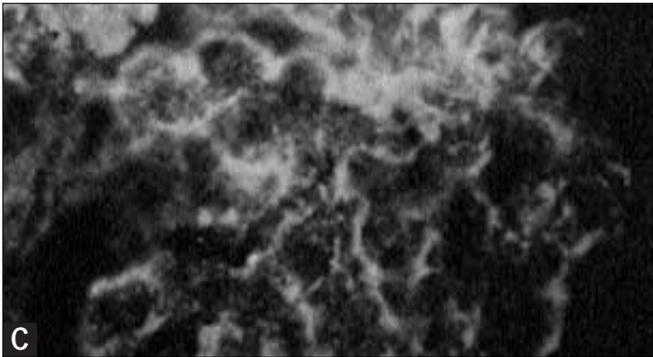
FIGURE 6-22

Erythrocyte knobs in a patient with falciparum malaria [43]. These erythrocyte knobs contain novel proteins, mainly *Plasmodium falciparum* erythrocyte membrane protein (PfEMP), histidine-rich protein 1, and histidine-rich protein 2, that are synthesized under the influence of the DNA of the parasite [44–46]. These proteins constitute the sticky points (*arrows*) by which parasitized erythrocytes aggregate and adhere to blood platelets and endothelial cells [47,48]. EN—electron microphotograph. (Magnification $\times$ 12,000.)
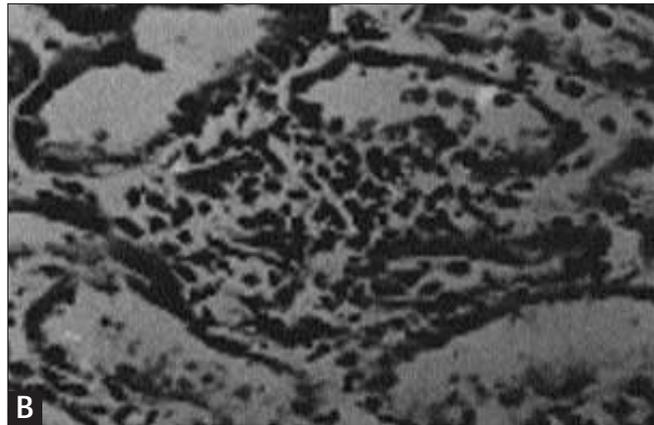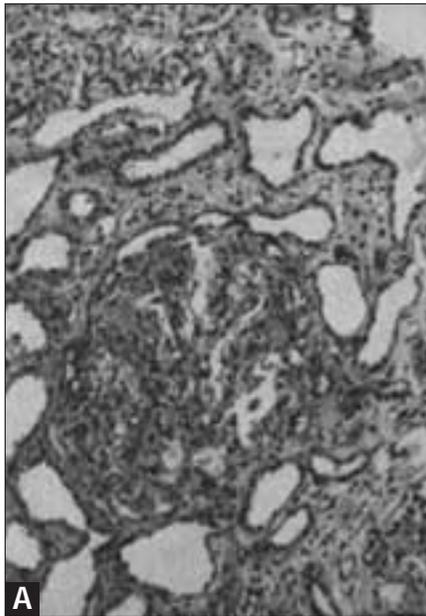
FIGURE 6-23

Renal lesions in a patient with falciparum malaria. **A,** Proliferative and exudative glomerulonephritis, an immune-complex–mediated lesion that may lead to an acute nephritic syndrome, which usually is reversible by antimalarial treatment. (Hematoxylin-eosin stain $\times$ 175.) **B,** Acute tubular necrosis (ATN) associated with interstitial mononuclear cell infiltration. ATN is seen in 1% to 4% of patients with falciparum malaria and in up to 60% of those with malignant malaria. (Hematoxylin-eosin stain $\times$ 200.)

C, Subendothelial and mesangial malarial antigen deposits seen on immunofluorescence. Often, complement 3, immunoglobulins M and G, and fibrinogen also are seen. (Hematoxylin-eosin stain × 200.)
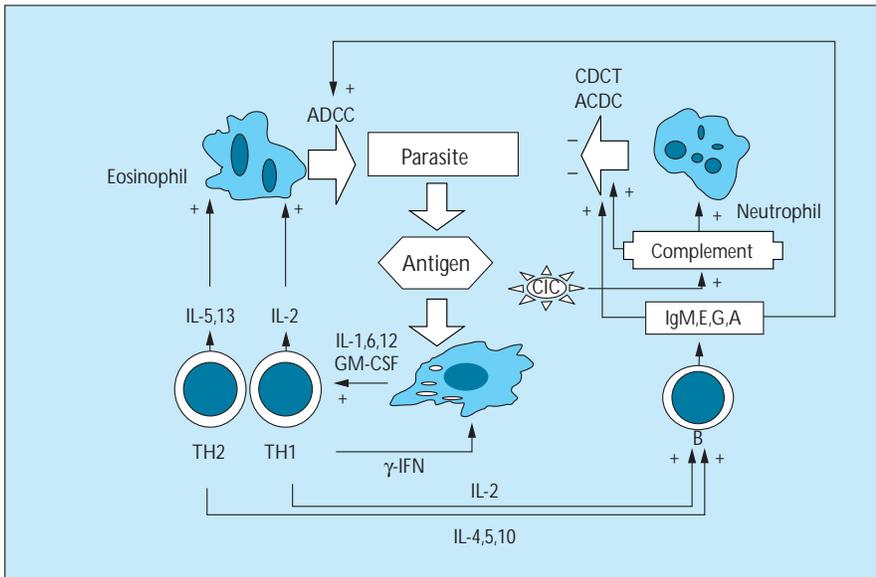
FIGURE 6-24

The broad lines of the immune response to parasitic infections. Note the pivotal role of the monocyte, activated by exposure to parasitic antigens, in stimulating both T-help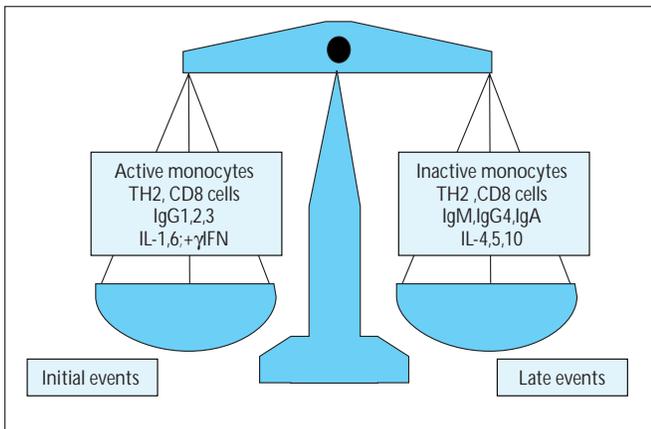er 1 (TH1) and T-helper 2 (TH2) cells. The different cytokine mediators and parasite elimination mechanisms are shown. B—B-lymphocyte; γ-IFN—γ-interferon; CIC—circulating immune complexes; GM-CSF—granulocyte-macrophage colony-stimulating factor; Ig—immunoglobulin; IL—interleukin.

FIGURE 6-25

The T-helper1–T-helper 2 (TH1-TH2) cell balance that determines the clinical expression of different parasitic nephropathies. TH1 predominance leads to either reversible acute proliferative glomerulonephritis or acute interstitial nephritis. TH2 predominance tends to lessen the severity of the lesions and may lead to chronic glomerulonephritis in the presence of copathogenic factors such as concomitant infection (malaria, schistosomiasis), autoimmunity (malaria, filariasis, schistosomiasis), or immunoglobulin A (IgA) switching (*Schistosoma mansoni*) [7, 9, 49–52]. CD4—T-helper cells; CD8—cytotoxic cells; γ-INF—γ-interferon; IL—interleukin.
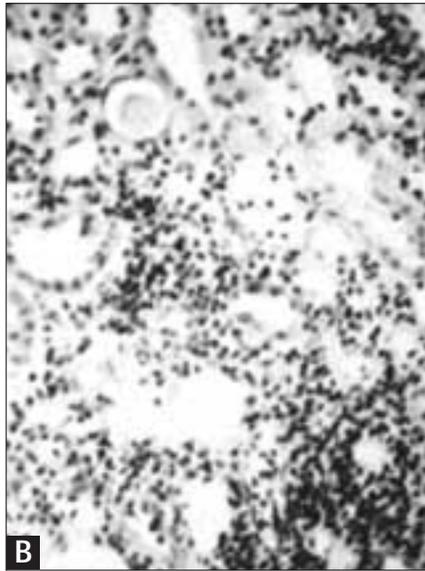
FIGURE 6-26

Leishmaniasis. **A,** Amastigotes in peripheral blood monocytes. Amastigotes downregulate the host cells that show no attempt at eradicating the parasite. (Hematoxylineosin stain × 450.) **B,** Interstitial nephritis representing a TH1 predominant state, which is self-limited owing to the parasite-induced monocyte inhibition [53]. (Hematoxylin-eosin stain × 175.)
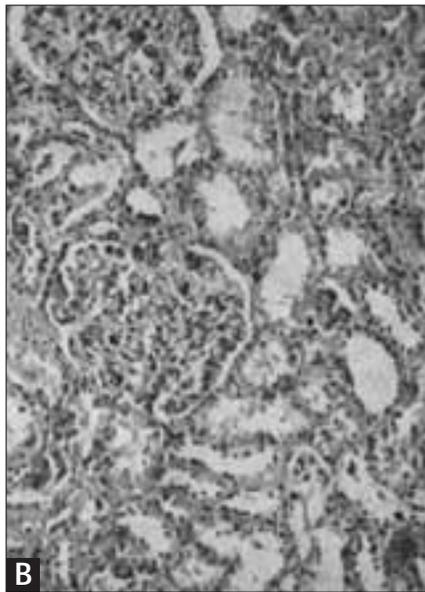
FIGURE 6-27

Trichinosis. **A,** Here *Trichinella spiralis* is encysted in the muscle tissue of a patient. (Hematoxylin-eosin stain × 75.) **B,** Associated proliferative glomerulopathy in a patient. This lesion usually is subclinical but may be manifested as an acute nephritic syndrome that can be resolved with anti-parasitic treatment. This lesion represents a TH1 predominant state. (Hematoxylineosin stain × 150.)
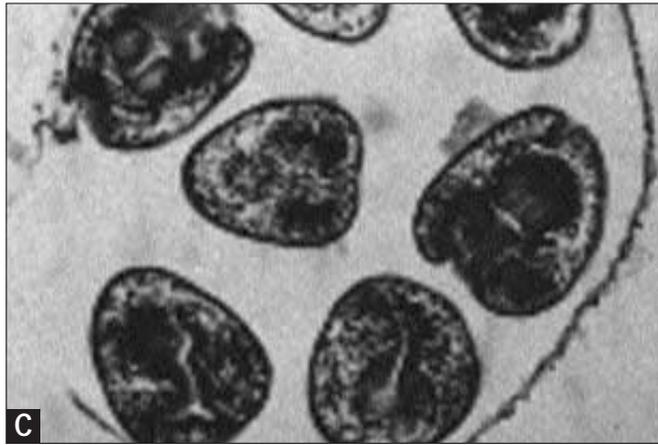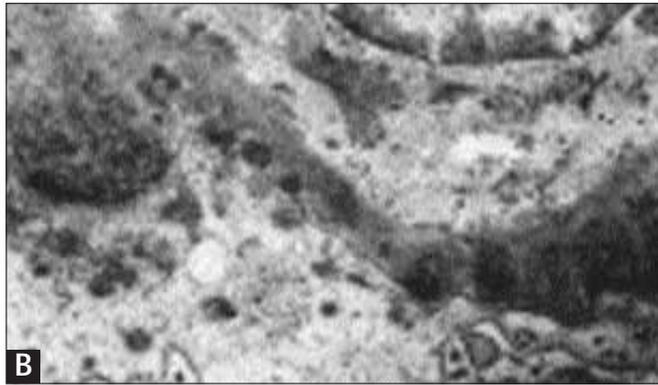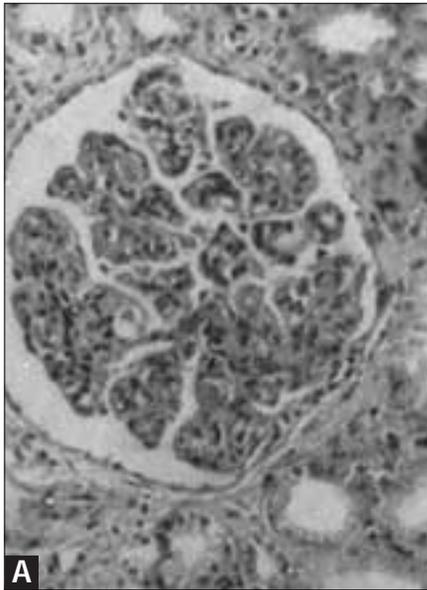
FIGURE 6-28

Echinococcosis. **A,** Mesangiocapillary type III glomerulonephritis. (Hematoxylin-eosin stain × 200.) **B,** Electron micrograph showing subepithelial deposits. (Hematoxylin-eosin stain × 25,000.) **C,** Peripheral part of a hydatid cyst showing the daughter cysts in a patient. (Hematoxylin-eosin stain × 75.)
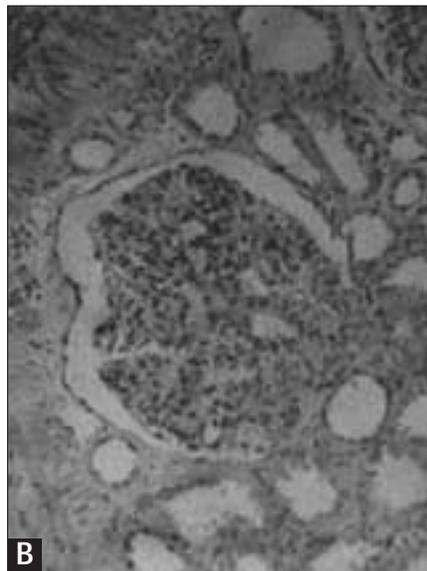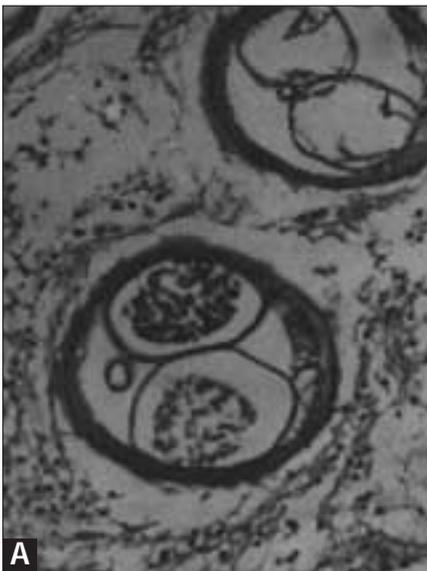
FIGURE 6-29

Onchocercosis. **A,** The parasite *Onchocerca volvulus* deposits lesions in tissues. (Hematoxylin-eosin stain × 150.) **B,** Associated mesangial proliferative lesion. This lesion represents a TH1 predominant state. Some patients, however, develop an autoimmune reaction that leads to progressive glomerulonephritis. (Hematoxylin-eosin stain × 175.)
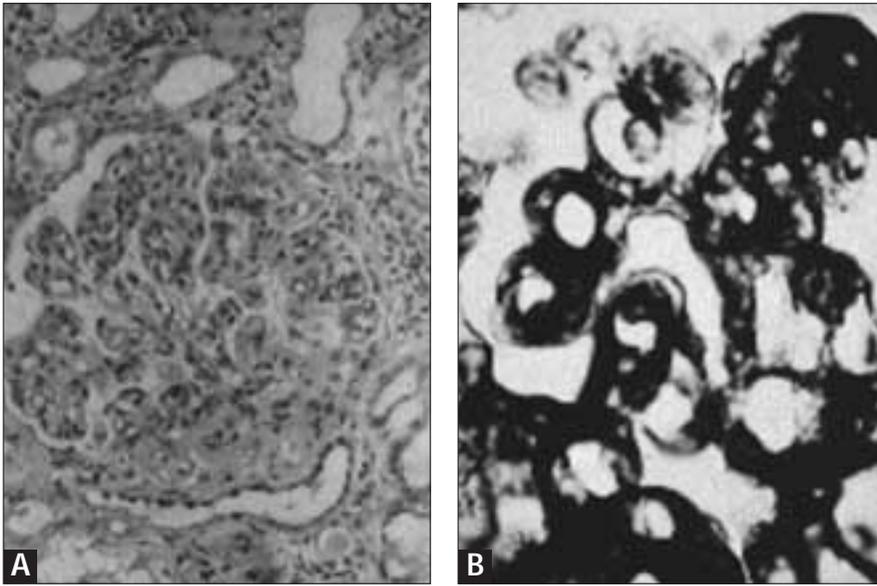
FIGURE 6-30

Quartan malarial nephropathy. **A,** Proliferative glomerulonephritis with capillary wall thickening. (Hematoxylin-eosin stain × 200.) **B,** Subendothelial deposits with splitting of the basement membrane. (Silver stain × 500.) This lesion occurs under TH2 predominance and usually is encountered in genetically predisposed persons. This lesion also is associated with autoimmunity or concomitant viral infection.
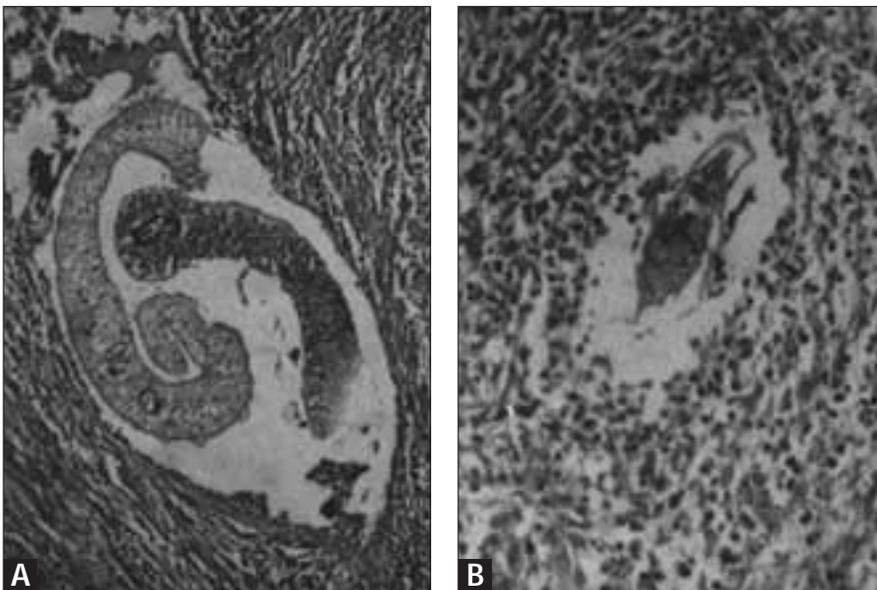
FIGURE 6-31

Intestinal schistosomiasis. **A,** Pair of adult *Schistosoma mansoni* worms in colonic mucosa. (Hematoxylin-eosin stain × 75.) **B,** Colonic granuloma around a viable ovum. (Hematoxylin-eosin stain × 150.)
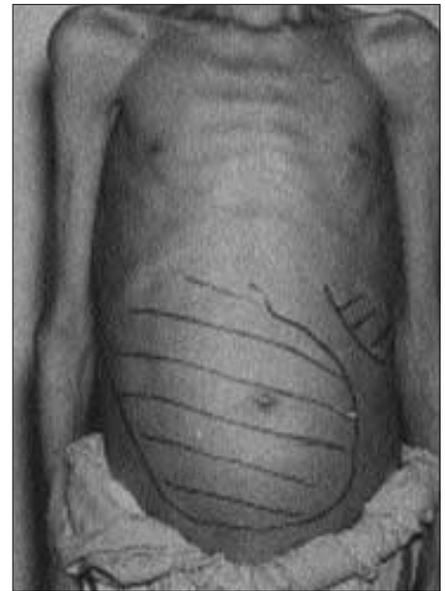
FIGURE 6-32

Patient with hepatosplenic schistosomiasis, complicating intestinal mansoniasis. Note the shrunken liver and very large spleen, surface marked on the abdominal wall by black ink. Of these patients, 15% develop clinically overt glomerular lesions. Half of the 15% become hypertensive, most become nephrotic at some stage, and almost all progress to end-stage disease [54].
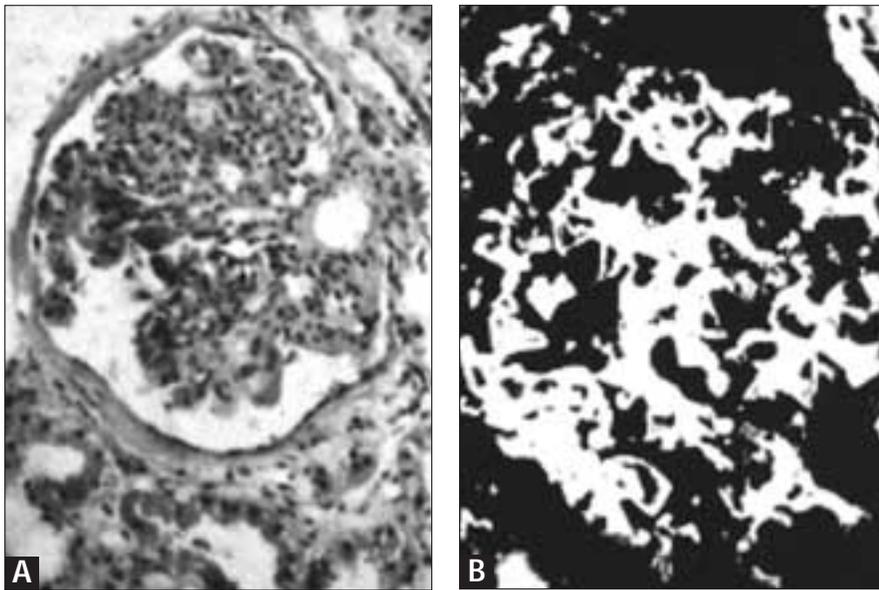
Early glomerular lesion in a patient with schistosomiasis. **A,** Mesangial proliferation. (Hematoxylin-eosin stain × 200.) **B,** Schistosomal gut antigen deposits in the mesangium. Other immunofluorescent deposits at this stage include immunoglobulins M and G and complement C. This lesion may be encountered in infection by *Schistosoma mansoni, S. haematobium,* or *S. japonicum.* The lesion does not necessarily progress any further. (Hematoxylin-eosin stain × 300.)
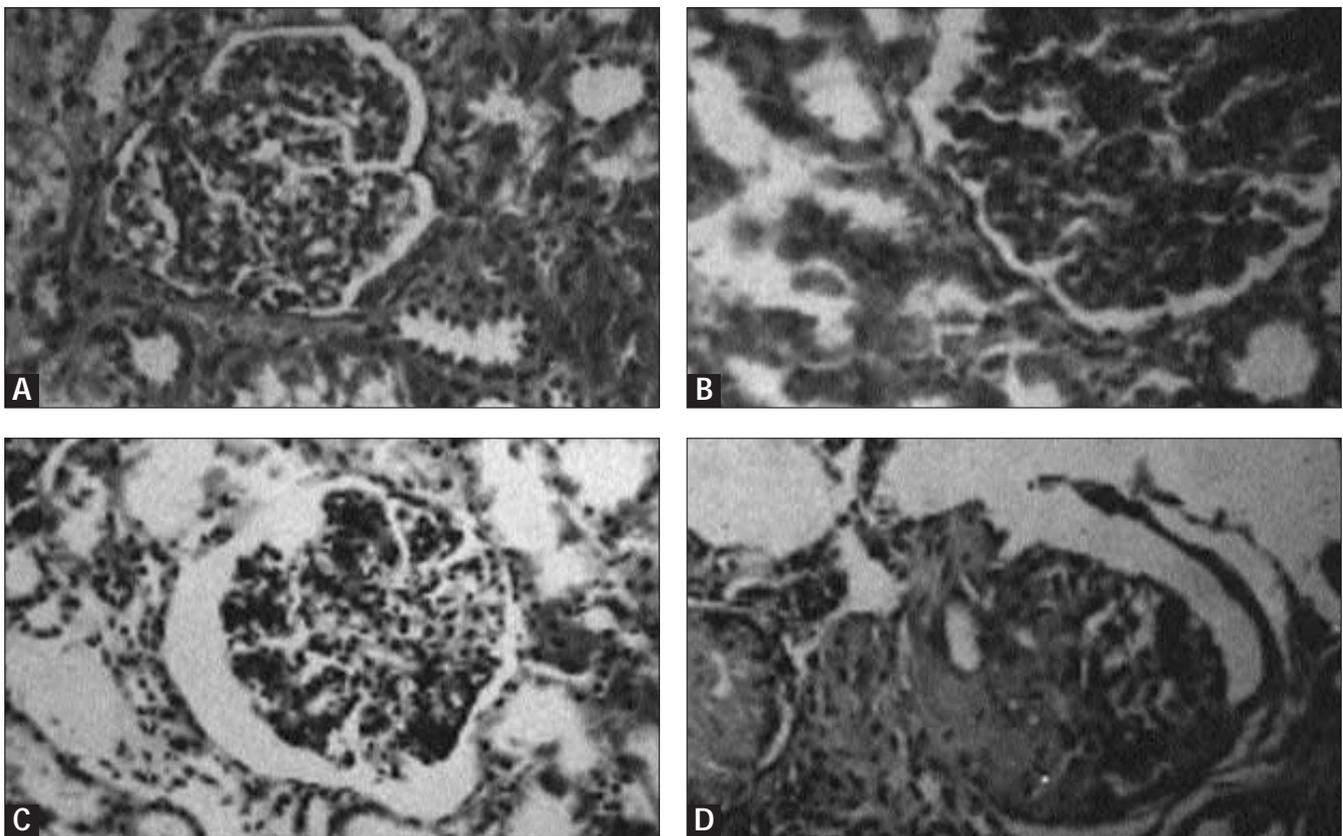
Histologic lesions in a patient with progressive *Schistosoma mansoni* glomerulopathy. **A,** Mesangial proliferative glomerulonephritis. (Hematoxylin-eosin stain × 150.) **B,** Exudative glomerulonephritis, often encountered with concomitant *Salmonella paratyphi A* infection [9]. (Hematoxylin-eosin stain × 150.) **C,** Mesangial proliferation with areas of mesangiocapillary changes. (Hematoxylin-eosin stain × 150.) **D,** Focal and segmental glomerulosclerosis. (Masson trichrome stain × 150.) The two lesions in *panels C* and *D* are associated with advanced hepatic fibrosis, impaired macrophage function, and predominant immunoglobulin A mesangial deposits [7,55]. The lesions shown are categorized, respectively, as classes I to IV schistosomal glomerulopathy according to the classification system of the African Association of Nephrology [54].
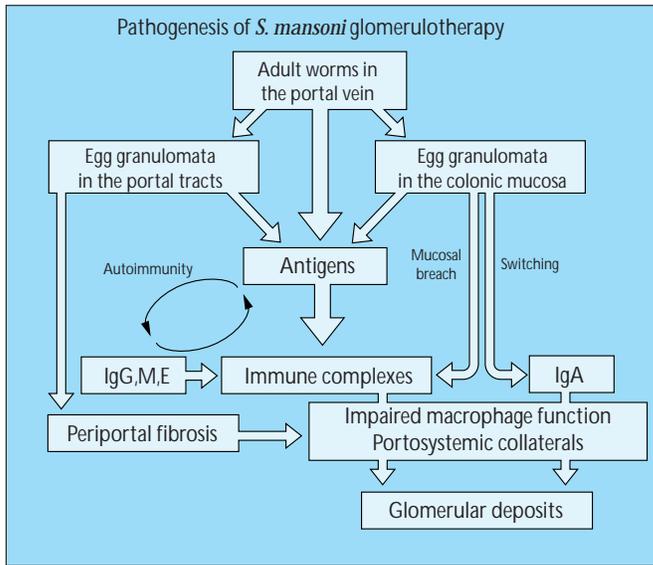
FIGURE 6-35

Pathogenesis of *Schistosoma mansoni* glomerulopathy. Note the crucial role of hepatic fibrosis, which 1) induces glomerular hemodynamic changes; 2) permits schistosomal antigens to escape into the systemic circulation, subsequently depositing in the glomerular mesangium; and 3) impairs clearance of immunoglobulin A (IgA), which apparently is responsible for progression of the glomerular lesions. IgA synthesis seems to be augmented through B-lymphocyte switching under the influence of interleukin-10, a major factor in late schistosomal lesions [7].
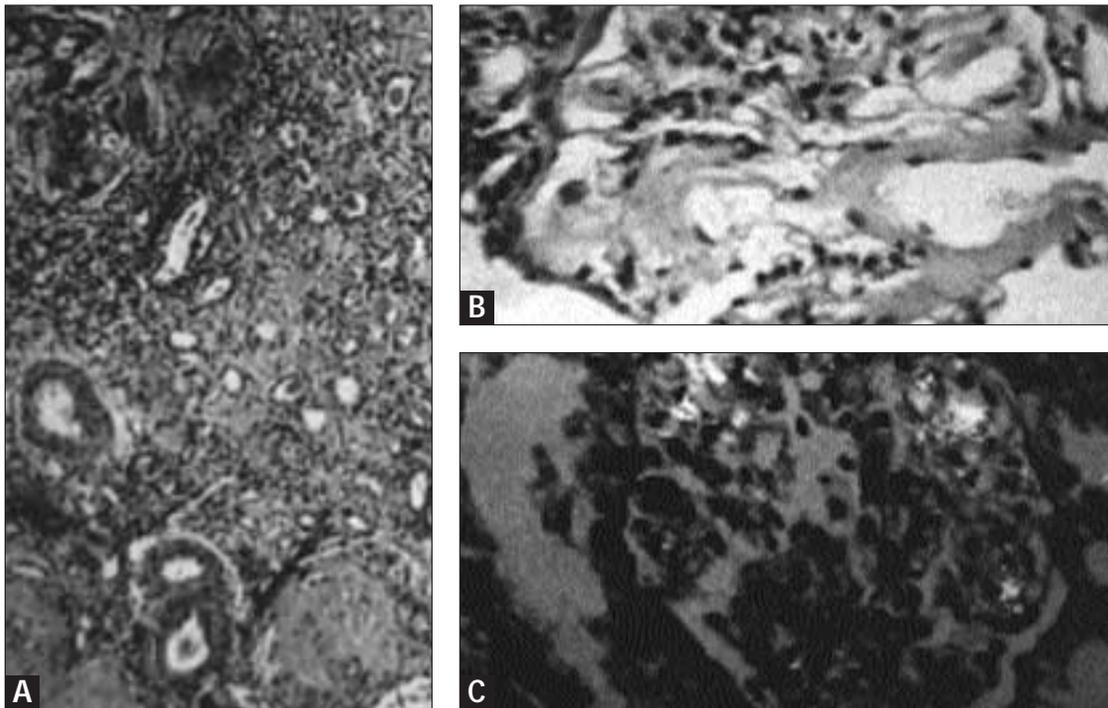
FIGURE 6-36 (*see* Color Plate)

Renal amyloidosis in schistosomiasis. **A,** Schistosomal granuloma (*top*), three glomeruli with extensive amyloid deposits (*bottom*), and dense interstitial infiltration and fibrosis in a patient with massive *Schistosoma haematobium* infection. (Hematoxylin-eosin stain × 75.) **B,** Amyloid deposition in the mesangium associated with mild mesangial cellular proliferation in a patient with *S. mansoni* glomerulopathy (African Association of Nephrology class V). (Hematoxylin-eosin stain × 175.) **C,** Early amyloid deposits seen as green (birefringent) deposits in a glomerulus with considerable mesangial proliferation in a patient with hepatosplenic schistosomiasis. (Congo red stain × 200, examined under polarized light.)
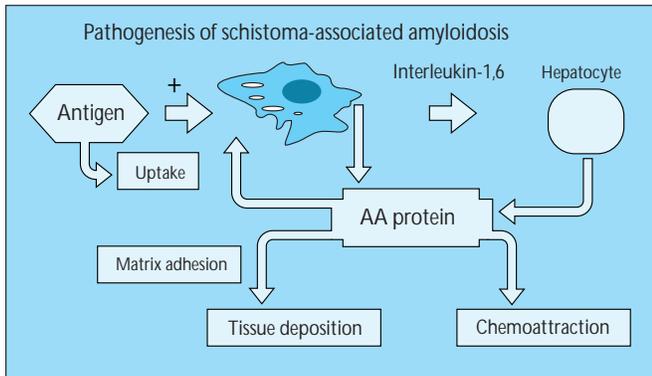
FIGURE 6-37

Pathogenesis of schistosoma-associated amyloidosis. The monocyte continues to release interleukin-1 and interleukin-6 under the influence of schistosomal antigens. These antigens stimulate the hepatocytes to release AA protein, which has a distinct chemoattractant function. The monocyte is the normal scavenger of serum AA protein, a function that is impaired in hepatosplenic schistosomiasis. Serum AA protein accumulates and tends to deposit in tissue.

Toxic Tropical Nephropathies

Toxins of Animal Origin

NEPHROPATHIES ASSOCIATED WITH EXPOSURE TO ANIMAL TOXINS

	Acute renal failure	Vasculitis	Subnephrotic proteinuria	Nephrotic syndrome
Snake bite	+++	+	+ (MPGN)	
Scorpion sting	+			
Insect stings	+			++ (MCD, MPGN, MN)
Jelly fish sting	+			
Spider bite	+			
Centipede bite	+			
Raw carp bile	++			

MCD—minimal change disease; MN—membranous glomerulonephritis; MPGN—mesangial proliferative glomerulonephritis; +—<10%; ++—10%–24%; +++—25%–50%.

FIGURE 6-38

Nephropathies associated with exposure to toxins of animal origin. Note that acute renal failure is the most common and important renal complication. Vascular and glomerular lesions are occasionally encountered with specific exposures [56–62].
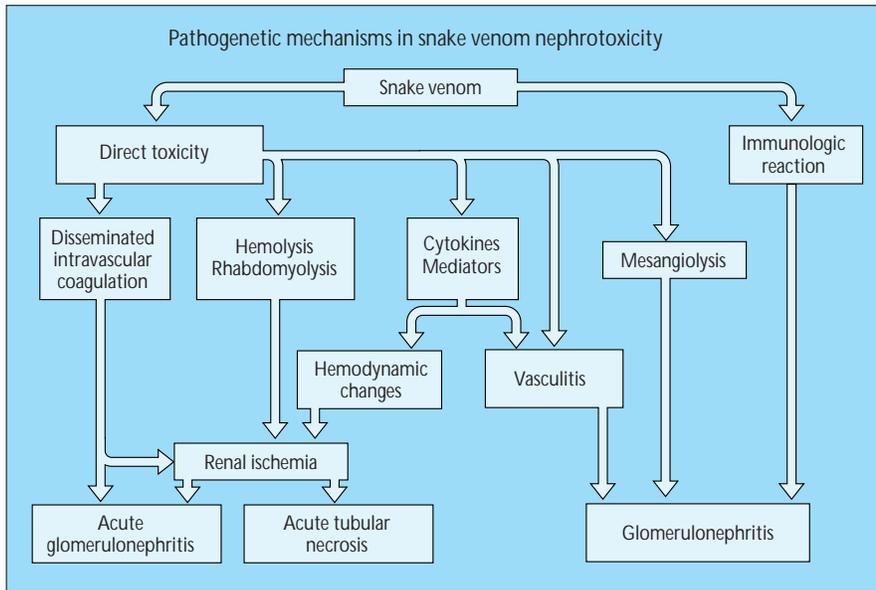
Pathogenetic mechanisms in snake venom nephrotoxicity. The immediate effect of exposure is attributed to direct hematologic toxicity involving the coagulation system and red cell membranes. The massive release of cytokines and rhabdomyolysis also contribute. Late effects may be encountered as a consequence of the immune response to the injected antigens.

Toxins of Plant Origin

Nephropathies associated with exposure to toxins of plant origin. Note that with the exception of Djenkol bean nephrotoxicity, most plant toxins lead to acute renal failure due to hemodynamic effects [63–66].

NEPHROPATHIES ASSOCIATED WITH EXPOSURE TO PLANT TOXINS

	Acute renal failure	Hypertension	Proteinuria	Hematuria
Djenkol bean	+++	++	+++	++++
Mushroom poisoning	+		+	
Callilepis laureola	+++			
Semecarpus anacardium	+			

+—<10%; ++—10%–24%; +++—25%–49%; ++++—50%–80%.

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