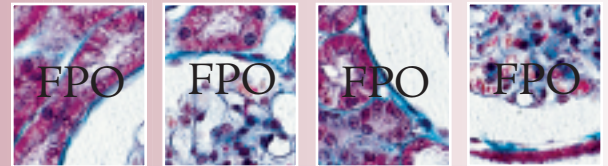


16 The Kidney

J. Charles Jennette



CONGENITAL ANOMALIES

- Renal Agenesis
- Ectopic Kidney
- Horseshoe Kidney
- Renal Dysplasia

CONGENITAL POLYCYSTIC KIDNEY DISEASES

- Autosomal Dominant Polycystic Kidney Disease (ADPKD)
- Autosomal Recessive Polycystic Kidney Disease (ARPKD)
- Nephronophthisis–Medullary Cystic Disease

ACQUIRED CYSTIC KIDNEY DISEASE

GLOMERULAR DISEASES

- Nephrotic Syndrome
- Nephritic Syndrome
- Glomerular Inflammation and Immune Mechanisms
- Minimal-Change Glomerulopathy
- Focal Segmental Glomerulosclerosis (FSGS)
- Membranous Glomerulopathy
- Diabetic Glomerulosclerosis
- Amyloidosis
- Hereditary Nephritis (Alport Syndrome)
- Thin Glomerular Basement Membrane Nephropathy
- Acute Postinfectious Glomerulonephritis
- Type I Membranoproliferative Glomerulonephritis
- Type II Membranoproliferative Glomerulonephritis (Dense Deposit Disease)
- Lupus Glomerulonephritis

- IgA Nephropathy (Berger Disease)
- Anti-Glomerular Basement Membrane Glomerulonephritis
- ANCA Glomerulonephritis

VASCULAR DISEASES

- Renal Vasculitis
- Hypertensive Nephrosclerosis (Benign Nephrosclerosis)
- Malignant Hypertensive Nephropathy
- Renovascular Hypertension
- Thrombotic Microangiopathy
- Cortical Necrosis

DISEASES OF TUBULES AND INTERSTITIUM

- Acute Tubular Necrosis (ATN)
- Pyelonephritis
- Analgesic Nephropathy
- Drug-Induced (Hypersensitivity) Acute Tubulointerstitial Nephritis
- Light-Chain Cast Nephropathy
- Urate Nephropathy

RENAL STONES (NEPHROLITHIASIS AND UROLITHIASIS)

OBSTRUCTIVE UROPATHY AND HYDRONEPHROSIS

RENAL TRANSPLANTATION

MALIGNANT TUMORS OF THE KIDNEY

- Wilms' Tumor (Nephroblastoma)
- Renal Cell Carcinoma (RCC)
- Transitional Cell Carcinoma

{AU1}

The kidney serves as the principal regulator of the fluid and electrolyte content of the body. The task is accomplished by the complex filtering mechanism of the glomerulus and the selective tubular reabsorption of solutes from the filtrate. The kidney also has endocrine function secreting renin, which regulates sodium me-

*tabolism and blood pressure as well as erythropoietin, a hormone that stimulates red cell production in the bone marrow. **The nephron** is the architectural unit of the kidney and includes the glomerulus and its tubule, the latter terminating at the common collecting system (see Fig. 16-4).*

The kidney consists of the glomerular, vascular tubular, and interstitial anatomic compartments. Many renal diseases are best understood in relation to the compartments affected and the associated functional impairment.

CONGENITAL ANOMALIES

Renal Agenesis Is the Complete Absence of Renal Tissue

Most infants born with bilateral renal agenesis are stillborn and have Potter sequence (see Chapter 6). Bilateral agenesis is often associated with other congenital anomalies, especially elsewhere in the urinary tract or lower extremities. Unilateral renal agenesis is not a serious matter if there are no associated anomalies, because the contralateral kidney undergoes sufficient hypertrophy to maintain normal renal function.

Ectopic Kidney Is an Abnormal Location of the Organ

The misplaced kidney is usually in the pelvis. Most commonly, this condition results from failure of the fetal kidney to migrate from the pelvis to the flank. Renal ectopia may involve only one kidney, or it may be bilateral.

Horseshoe Kidney Is a Single, Large, Midline Organ

Horseshoe kidney results when an infant is born with fused kidneys, usually at the lower poles. This anomaly usually has no clinical consequences but can increase the risk for obstruction and pyelonephritis (see below) because the ureters must cross over the junction between the two kidneys that are fused at their lower pole.

Renal Dysplasia Is a Developmental Disorder

Renal dysplasia is characterized by undifferentiated tubular structures surrounded by primitive mesenchyme, sometimes with heterotopic tissue such as cartilage. Cysts often form from the abnormal tubules.



PATHOGENESIS: Renal dysplasia results from an abnormality in metanephric differentiation that reflects multiple genetic and somatic causes. Some familial forms of dysplasia probably result from abnormal differentiation signals that affect the inductive interactions between the ureteric bud and the metanephric blastema. Many forms of dysplasia are accompanied by other urinary tract abnormalities, especially those that cause obstruction of urine flow. This association suggests that an obstruction to urine flow in utero can cause dysplasia.



PATHOLOGY: The histologic hallmark of renal dysplasia is undifferentiated tubules and ducts lined by cuboidal or columnar epithelium. These structures are surrounded by mantles of undifferentiated mesenchyme, which sometimes contain smooth muscle and islands of cartilage (Fig. 16-1). Rudimentary glomeruli may be present, and the tubules and ducts may be cystically dilated. Renal dysplasia can be unilateral or bilateral, the involved kidney can be abnormally large or very small, and the kidney may contain multiple cysts.



CLINICAL FEATURES: In most patients with cystic forms of renal dysplasia, a palpable flank mass is discovered shortly after birth, although small multicystic kidneys may not become apparent until many years later. Unilateral dysplasia is adequately treated by removing the affected kidney. Bilateral aplastic dysplasia in the fetus can cause oligohydramnios and the resulting Potter sequence and life-threatening pulmonary hypoplasia.

CONGENITAL POLYCYSTIC KIDNEY DISEASES

Congenital polycystic kidney diseases are a heterogeneous group of genetic disorders that are characterized by distortion of the renal parenchyma by numerous cysts. The diseases vary in age of onset, severity, mode of inheritance, and structure of cysts (Fig. 16-6).

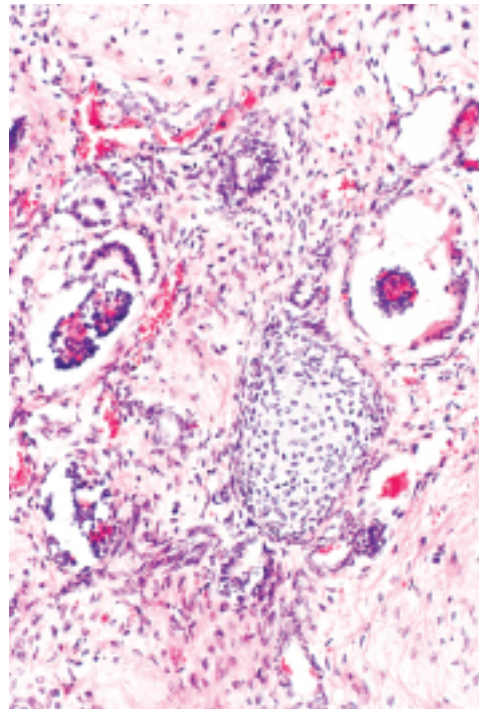


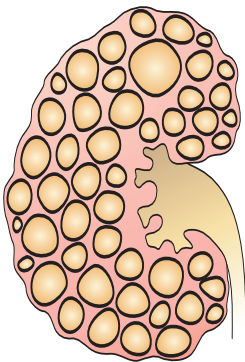
FIGURE 16-1. Renal dysplasia. Immature glomeruli, tubules, and cartilage are surrounded by loose, undifferentiated mesenchymal tissue.

Autosomal Dominant Polycystic Kidney Disease (ADPKD) Features Enlarged Multicystic Kidneys

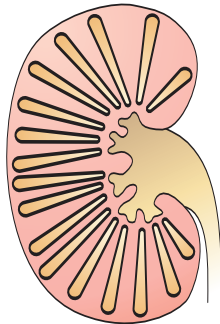
Autosomal Dominant Polycystic Kidney Disease (ADPKD) is the most common of a group of congenital diseases that are characterized by numerous cysts within the renal parenchyma (Fig. 16-2). It affects 1:400 to 1:1000 individuals in the United States. Half of all patients with this disease eventually develop end-stage renal failure.



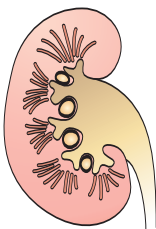
PATHOGENESIS: About 85% of ADPKD is caused by mutations in the polycystic kidney disease 1 gene (*PKD1*) and 15% by mutations in *PKD2*. The products of these genes, polycystin-1 and polycystin-2, are in the primary cilia of tubular epithelial cells. These cilia sense urine flow and regulate tubule growth.



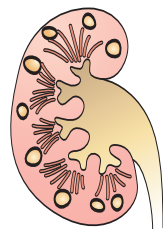
Autosomal dominant polycystic disease



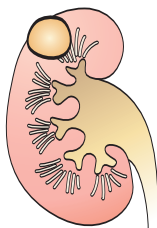
Autosomal recessive polycystic disease



Medullary sponge kidney



Medullary cystic disease complex



Simple cyst

FIGURE 16-2.

Cystic diseases of the kidney.

Cysts arise in segments of renal tubules and develop from a few cells that proliferate abnormally. The wall of the tubule becomes covered by an undifferentiated epithelium composed of cells with a high nucleus-to-cytoplasm ratio and only few microvilli. Eventually, most of the cysts become disconnected from the tubules. Cyst fluid initially accumulates from glomerular filtrate, followed by fluid derived from transepithelial secretion. Cysts originate in less than 2% of nephrons; therefore, factors other than crowding of normal tissue by the expanding cysts likely contribute to the loss of functioning renal tissue.



PATHOLOGY: The kidneys in ADPKD are markedly enlarged bilaterally, each weighing as much as 4,500 g (Fig. 16-3). The external contours of the kidneys are distorted by numerous cysts as large as 5 cm in diameter, which are filled with a straw-colored fluid. Microscopically, the cysts are lined by a cuboidal and columnar epithelium. They arise from virtually any point along the nephron, and areas of normal renal parenchyma are found between the cysts.

One third of patients with ADPKD also have **hepatic cysts**, with a lining that resembles bile duct epithelium. One fifth have an associated **cerebral aneurysm**, and intracranial hemorrhage is the cause of death in 15% of patients with ADPKD.



CLINICAL FEATURES: Most patients with ADPKD do not develop clinical manifestations until the fourth decade of life, although a small minority become symptomatic during childhood. Symptoms include a sense of heaviness in the loins, bilateral flank and abdominal masses, and passage of blood clots in the urine. Azotemia (elevated blood urea nitrogen) is common and in half of patients progresses to uremia (clinical renal failure) over a period of several years.

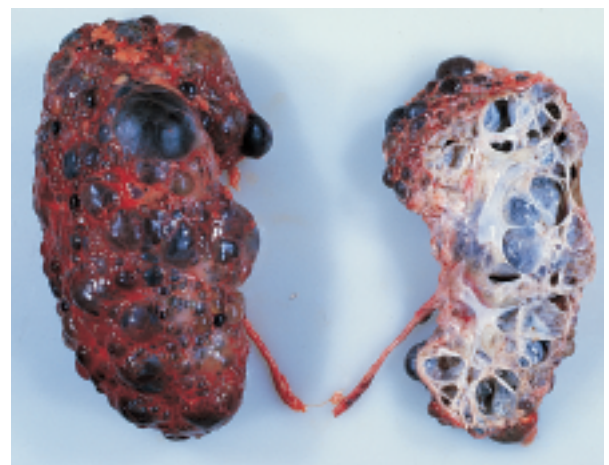


FIGURE 16-3. **Adult polycystic disease.** The kidneys are enlarged, and the parenchyma is almost entirely replaced by cysts of varying size.

Autosomal Recessive Polycystic Kidney Disease (ARPKD) Occurs in Infants

Autosomal Recessive Polycystic Kidney Disease (ARPKD) is characterized by cystic transformation of collecting ducts. It is rare compared with ADPKD, occurring in about 1 in 10,000 to 50,000 live births. Seventy-five percent of these infants die in the perinatal period, often because of pulmonary hypoplasia caused by oligohydramnios (Potter sequence). ARPKD is caused by mutations in the *PKHD1* gene. The gene product, **fibrocystin**, is found in the kidney, liver, and pancreas, and appears to be involved in the regulation of cell proliferation and adhesion. Mutations of *PKHD1* also result in pancreatic cysts, hepatic biliary dysgenesis, and fibrosis.



PATHOLOGY: In contrast to ADPKD, the external kidney surface in the infantile disorder is smooth. The disease is invariably bilateral. The cysts are fusiform dilations of cortical and medullary collecting ducts and have a striking radial arrangement perpendicular to the renal capsule. Interstitial fibrosis and tubular atrophy are common, particularly in children whose disease presents at an older age. The liver usually is affected by **congenital hepatic fibrosis** (see Chapter 14).

In Nephronophthisis–Medullary Cystic Disease Complex Manifests Tubulointerstitial Injury and Medullary Cysts

Nephronophthisis–medullary cystic disease complex comprises a group of autosomal recessive and autosomal dominant diseases that affect a number of distinct genetic loci and have different ages of onset.



PATHOLOGY: The kidneys are small and when sectioned often display multiple, variably sized cysts (up to 1 cm) at the corticomedullary junction (see Fig. 16-2). The cysts arise from the distal portions of the nephron. Atrophic tubules with markedly thickened and laminated basement membranes and loss of tubules out of proportion to the glomerular loss are early histologic features of the disease. Eventually, corticomedullary cysts may develop, and the remainder of the parenchyma becomes increasingly atrophic. Secondary glomerular sclerosis, interstitial fibrosis, and nonspecific inflammatory infiltrates dominate the late histologic picture.



CLINICAL FEATURES: Medullary cystic disease complex accounts for 10% to 25% of renal failure in childhood. Patients present initially with deteriorating tubular function. Progressive azotemia and renal failure follow, usually within 5 years of symptom onset.

ACQUIRED CYSTIC KIDNEY DISEASE

Simple renal cysts are usually incidental findings at autopsy and are rarely clinically symptomatic unless they are very large. These fluid-filled cysts may be solitary or multiple and are usually located in the outer cortex, where they expand the capsule. Simple cysts less commonly occur in the medulla. Microscopically, they are lined by a flat epithelium.

Long-term dialysis is often associated with the formation of multiple cortical and medullary cysts. The cysts are initially lined by a flat to cuboidal epithelium but hyperplastic and neoplastic proliferation may develop.

GLOMERULAR DISEASES

The glomerulus is a specialized network of capillaries forming a convoluted glomerular tuft covered by epithelial cells and supported by modified smooth muscle cells called **mesangial cells** (see Fig. 16-4, Fig. 16-5, Fig. 16-6, and Fig. 16-7). The glomerular capillaries are lined by fenestrated endothelial cells lying on a basement membrane (see below). The outer surface of this basement membrane is covered by specialized epithelial cells called **podocytes** or **visceral epithelial cells**. Podocytes line the glomerular side of **Bowman's space**, whereas the **parietal epithelial cells** line **Bowman's capsule** on the opposite side.

An extensive variety of renal disorders is caused by injury to the glomerulus. The glomerulus may be the only major site of disease (**primary glomerular disease**; e.g., immunoglobulin [Ig]A nephropathy) or may be a component of a disease that affects multiple organs (**secondary glomerular disease**; e.g., lupus glomerulonephritis). *Renal biopsy evaluation is often the only means of definitive diagnosis for glomerular diseases, although clinical and laboratory data may provide presumptive evidence for a specific illness.*

Nephrotic Syndrome Features Severe Proteinuria

Nephrotic syndrome is characterized by severe proteinuria (>3.5 g of protein/24 hours), hypoalbuminemia, edema, hyperlipidemia, and lipiduria. **Proteinuria**, the major pathogenetic abnormality, results from increased glomerular capillary permeability, allowing protein to be lost from the plasma into the urine (Fig. 16-8).

There are important differences in the rates of specific glomerular diseases that produce nephrotic syndrome in adults versus those in children. For example, minimal-change glomerulopathy is responsible for most (70%) cases of nephrotic syndrome in children but only 15% in adults. Table 16-1 lists the major causes and frequency of the nephrotic syndrome in adults and children. Table 16-2 de-

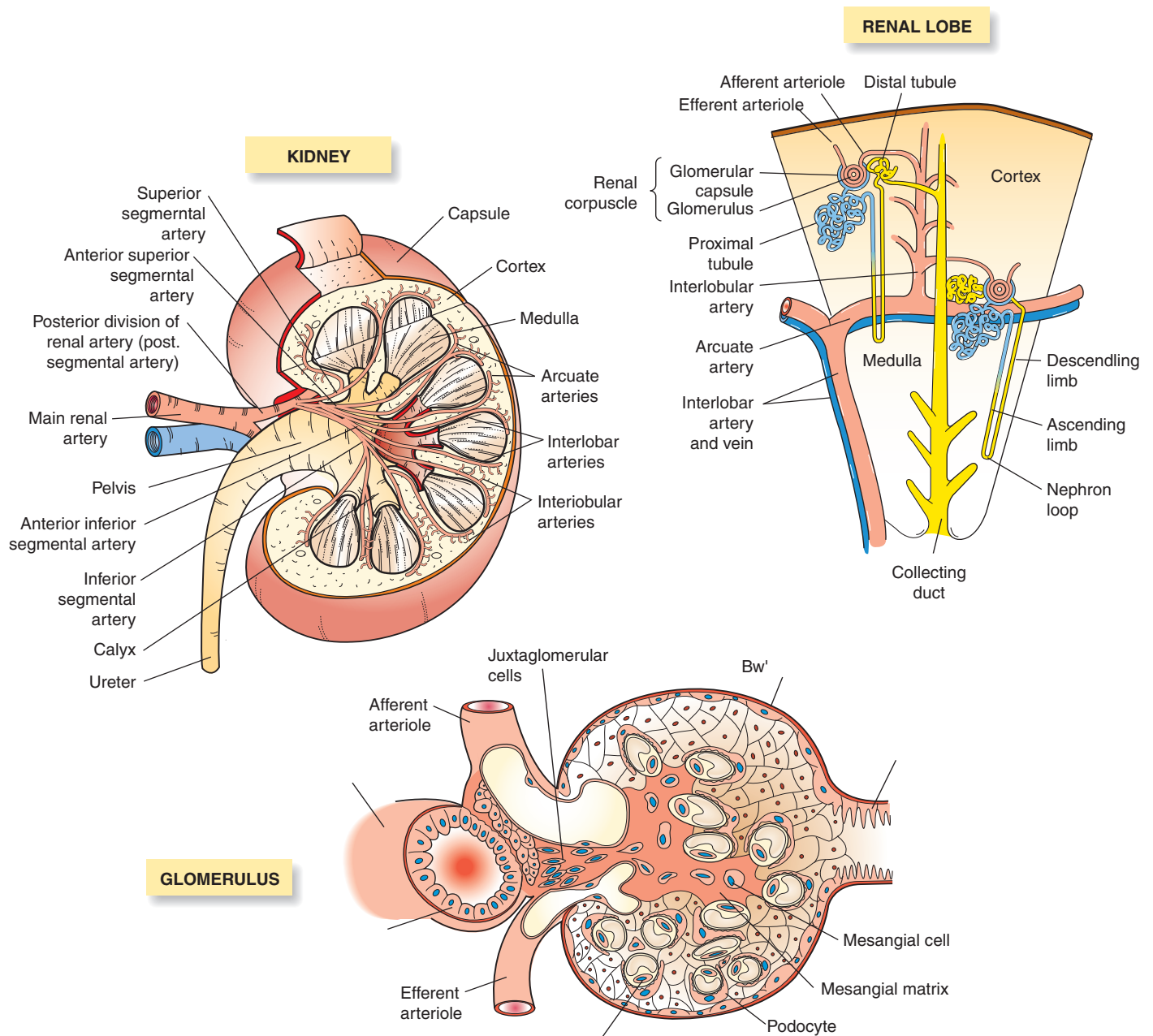


FIGURE 16-4.

The gross and microscopic anatomy of the kidney.

tails selected pathologic features of some of these diseases (discussed below).

Nephritic Syndrome Is an Inflammatory Disease

Nephritic syndrome is characterized by hematuria (either microscopic or visible grossly), variable degrees of proteinuria, and decreased glomerular filtration rate. It results in elevated blood urea nitrogen and serum creatinine, oliguria, salt and water retention, edema, and hypertension. The proteinuria and hematuria associated with the nephritic syndrome are caused by inflam-

matory changes in glomeruli, such as infiltration by leukocytes, hyperplasia of glomerular cells, damage to capillaries, and, in severe lesions, necrosis. The inflammatory damage may also impair glomerular flow and filtration, resulting in renal insufficiency, fluid retention, and hypertension. Nephritis may be characterized as:

- **Acute glomerulonephritis**, which develops rapidly and is irreversible
- **Rapidly progressive glomerulonephritis**, which may resolve with aggressive treatment

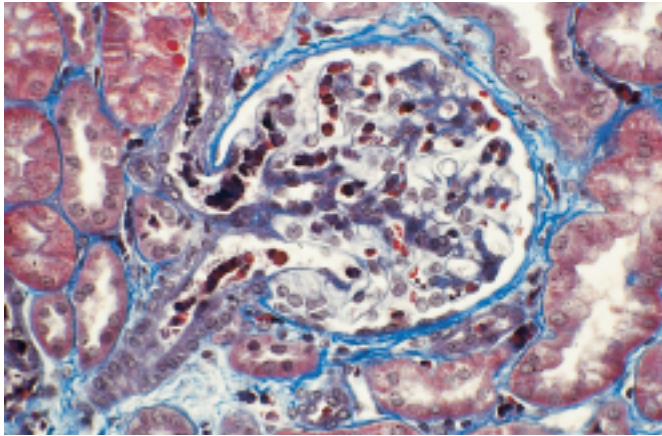


FIGURE 16-5. Normal glomerulus, light microscopy. The Masson trichrome stain shows a glomerular tuft with delicate blue capillary wall basement membranes, small amounts of blue matrix surrounding mesangial cells, and the hilum on the left. The afferent arteriole enters below and the efferent arteriole exits above.

- **Chronic glomerulonephritis**, which may persist for years and proceeds slowly to renal failure

With the possible exception of minimal-change glomerulopathy (which almost always causes the nephrotic syndrome), all glomerular diseases occasionally produce mixed nephritic and nephrotic manifestations that confound clinical diagnosis.

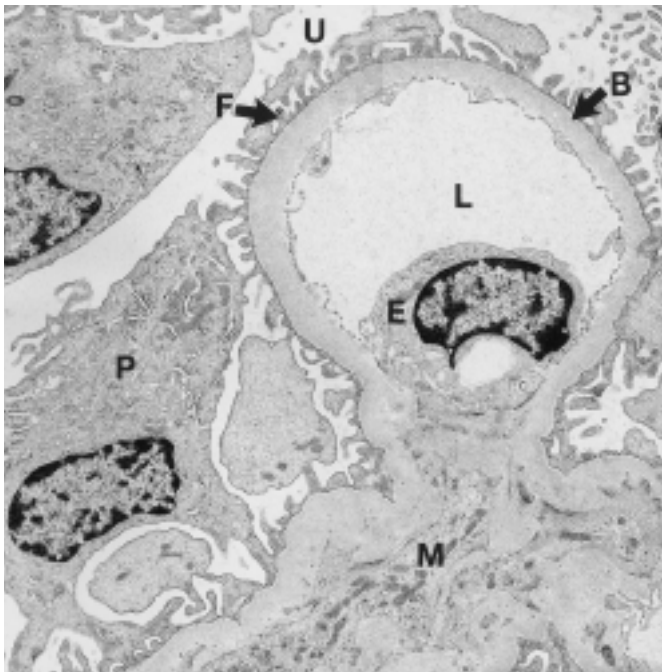


FIGURE 16-6. Normal glomerulus. In this electron micrograph of a single capillary loop and adjacent mesangium, the capillary wall portion of the lumen (L) is lined by a thin layer of fenestrated endothelial cytoplasm that extends out from the endothelial cell body (E). The endothelial cell body is in direct contact with the mesangium, which includes the mesangial cell (M) and adjacent matrix. The outer aspect of the basement membrane (B) is covered by foot processes (F) from the podocyte (P) that line the urinary space (U). Compare this figure with Figure 16-4.

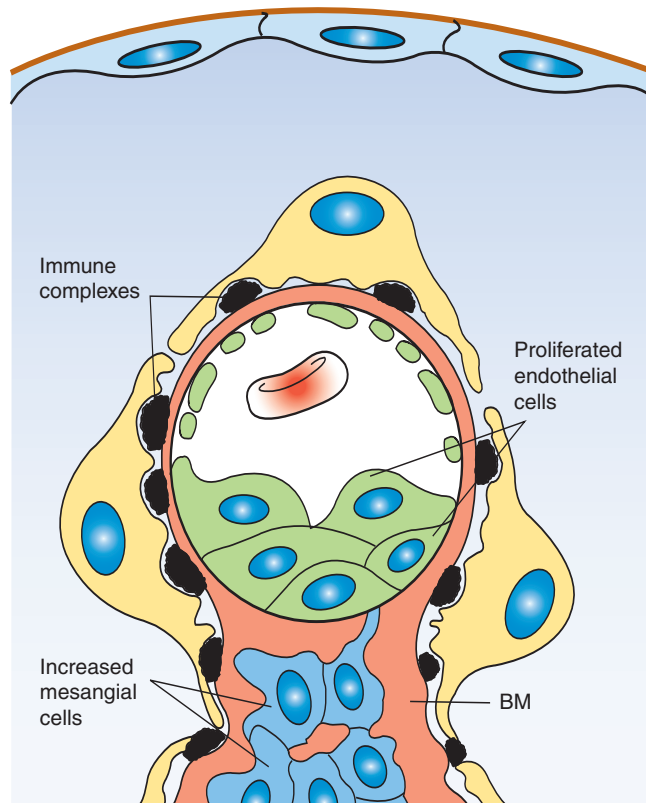


FIGURE 16-7. Normal glomerulus. The relationship of the different glomerular cell types to the basement membrane and mesangial matrix is illustrated using a single glomerular loop. The entire outer aspect of the glomerular basement membrane (BM) (peripheral loop and stalk) is covered by the visceral epithelial cell (podocyte) foot processes. The outer portions of the fenestrated endothelial cell are in contact with the inner surface of the basement membrane, whereas the central part is in contact with the mesangial cell and adjacent mesangial matrix. Compare this figure with Figure 16-3.

Glomerular Inflammation Is Most Frequently Mediated by Immune Mechanisms



PATHOGENESIS: Both antibody-mediated and cell-mediated types of immunity play roles in the production of glomerular inflammation. However, three mechanisms of antibody-induced inflammation have been incriminated as the major pathogenetic processes in most forms of glomerulonephritis (Fig. 16-9):

- **In situ immune complex formation** involves binding of circulating antibodies to intrinsic antigens or foreign antigens within glomeruli, resulting in inflammatory injury (see Chapter 4).
- **Deposition of circulating immune complexes** in glomeruli leads to inflammation similar to that produced by immune complex formation in situ.
- **Antineutrophil cytoplasmic autoantibodies (ANCA)** cause a severe glomerulonephritis that exhibits little or no glomerular deposition of im-

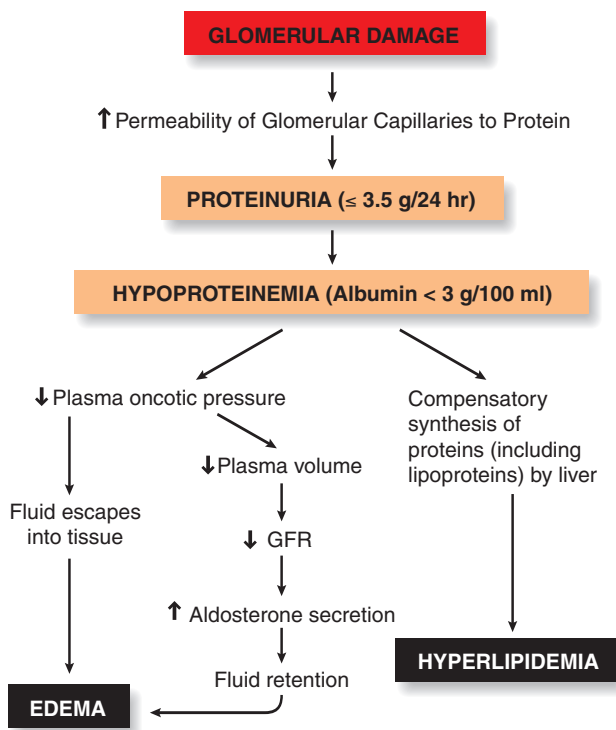


FIGURE 16-8. Pathophysiology of the nephrotic syndrome. GFR, glomerular filtration rate.

munoglobulins. These patients have a high frequency of circulating autoantibodies specific for antigens in the cytoplasm of neutrophils, which can mediate glomerular inflammation by activating neutrophils.



PATHOLOGY: Many specific glomerular diseases have distinctive pathologic features, as well as different natural histories and appropriate treatments. Accurate pathologic diagnosis of glomerular diseases requires evaluation of renal tissue by light, immunofluorescence, and electron microscopy, accompanied by integration of the findings with clinical information. Table 16-3 lists pathologic features that are useful for diagnosing glomerular diseases.

TABLE 16-1

Frequency of Causes for the Nephrotic Syndrome Induced by Primary Glomerular Diseases in Children and Adults

Cause	Children (%)	Adults (%)
Minimal-change glomerulopathy	75	15
Membranous glomerulopathy	5	30
Focal segmental glomerulosclerosis	10	30
Type I membranoproliferative glomerulonephritis	5	5
Other glomerular diseases*	5	20

*Includes many forms of mesangioproliferative and proliferative glomerulonephritis, such as immunoglobulin (Ig)A nephropathy, which often also cause nephritic features.

In general, the pathologic features of acute inflammation, such as endocapillary and extracapillary hypercellularity, leukocyte infiltration, and necrosis are more common in disorders that have predominantly nephritic features than in those with nephrotic attributes. **Glomerular crescent formation** (extracapillary epithelial cell proliferation) is not specific for a particular cause of glomerular inflammation. Crescent formation serves as a marker for severe rapidly progressing injury that has resulted in extensive rupture of capillary walls, allowing inflammatory mediators to enter Bowman's space and resulting in macrophage infiltration and epithelial proliferation.

Minimal-Change Glomerulopathy Causes Nephrotic Syndrome

Minimal-change glomerulopathy is a disorder that is clinically associated with the nephrotic syndrome. Pathologically, the disease is characterized by effacement of podocyte foot processes.



PATHOGENESIS: The pathogenesis of minimal-change glomerulopathy is unknown. Involvement of the immune system has been postulated because the disease frequently enters remission when treated with corticosteroids and because it may occur in association with an allergic disease or a lymphoid neoplasm such as Hodgkin disease. The heavy proteinuria of minimal-change glomerulopathy is accompanied by a loss of polyanionic sites on the glomerular basement membrane (GBM), which allows anionic proteins, particularly albumin, to pass more easily through the GBM.



PATHOLOGY: The light microscopic appearance of glomeruli in minimal-change glomerulopathy is essentially normal. Electron microscopy of glomeruli reveals total **effacement of visceral, epithelial cell foot processes**, an effect caused by their retraction into the parent epithelial cell bodies (compare Fig. 16-6 with Fig. 16-10). Such retraction (presumably resulting from cell swelling) is not specific for minimal-change glomerulopathy and occurs in association with virtually all cases of proteinuria in the nephrotic range. Loss of protein in the urine leads to hypoalbuminemia, and a compensatory increase in lipoprotein secretion by the liver results in hyperlipidemia. The loss of lipoproteins through the glomeruli causes lipid accumulation in the proximal tubular cells, which is reflected histologically as glassy (hyaline) droplets in tubular epithelial cytoplasm, a finding associated with any disease causing the nephrotic syndrome. Immunofluorescence microscopy for immunoglobulins and complement are most often negative, but there is occasional weak mesangial staining for IgM and the complement component C3.

TABLE 16-2

Pathologic Features of Important Causes of the Nephrotic Syndrome

	Minimal Change Glomerulopathy	Focal Segmental Glomerulosclerosis	Membranous Glomerulopathy	Membranoproliferative Glomerulonephritis
Light microscopy	No lesion	Focal and segmental glomerular consolidation	Diffuse global capillary wall thickening	Capillary wall thickening and endocapillary hypercellularity
Immuno-fluorescence microscopy	No immune deposits	No immune deposits	Diffuse capillary wall immunoglobulin	Diffuse capillary wall complement
Electron microscopy	No immune deposits	No immune deposits	Diffuse subepithelial dense deposits	Subendothelial (type I) or intramembranous (type II) dense deposits



CLINICAL FEATURES: Minimal-change glomerulopathy causes 90% of nephrotic syndrome cases in young children, 50% in older children, and 15% in adults. Proteinuria is generally more selective (albumin > globulins) than in the nephrotic syndrome caused by other diseases, but there is too much overlap for this selectivity to be used as a diagnostic criterion. More than 90% of children and fewer adults with minimal-change glomerulopathy have a complete remission of proteinuria within 8 weeks of the initiation of corticosteroid therapy. After withdrawal of corticosteroids, most patients suffer intermittent relapses for up to 10 years. In the absence of complications, the long-term outlook for patients with minimal-change glomerulopathy is no different from that of the general population

Focal Segmental Glomerulosclerosis (FSGS) is a Feature of Multiple Disease Processes

Focal segmental glomerulosclerosis (FSGS) is characterized by glomerular consolidation that affects some (focal), but not all, glomeruli and initially involves only part of an affected glomerular tuft (segmental). The consolidated segments often contain increased collagenous matrix (sclerosis). There are several primary and secondary forms of FSGS.



PATHOGENESIS: The term **FSGS** is applied to a heterogeneous group of glomerular diseases with different causes, pathologies, responses to treatment, and outcomes. FSGS occurs as an idiopathic (primary) process or secondary to a number of conditions. It is likely that multiple factors leading to podocyte damage may be common to all types of FSGS. FSGS has been associated with the following conditions likely to injure or stress podocytes:

- **Genetic abnormalities of podocyte proteins** such as podocin, α -actinin-4, and transient receptor potential cation channel 6.

- **Reductions in renal mass**, which may be congenital (unilateral agenesis) or acquired (reflux nephropathy, see below)
- **Functional overwork** associated with obesity or hypoxia (as in sickle cell disease or congenital cyanotic heart diseases)

Viruses, the drug pamidronate, and serum factors have also been implicated as causes of FSGS. Infection with HIV, especially in blacks, and intravenous drug abuse are associated with a variant of FSGS characterized by a collapsing pattern of sclerosis, possibly associated with viral injury to podocytes. A serum permeability factor has been detected in some patients with FSGS, which suggests a systemic cause for the glomerular injury. This concept is further supported by the recurrence of FSGS in renal transplants, especially in patients who have the permeability factor.



PATHOLOGY: By light microscopy, varying numbers of glomeruli show segmental obliteration of capillary loops by increased matrix or by the accumulation of cells, or both (Fig. 16-11). Insudation of plasma proteins and lipid into the lesions causes a glassy appearance, called **hyalinosis**. Adhesions to Bowman's capsule occur adjacent to the sclerotic lesions. Uninvolved glomeruli may appear entirely normal, although mild mesangial hypercellularity is occasionally present.

By electron microscopy, FSGS exhibits diffuse effacement of epithelial cell foot processes, with occasional focal detachment or loss of podocytes from the GBM. Increased matrix material, folding and thickening of the basement membranes, and capillary collapse are present in sclerotic segments.

Immunofluorescence microscopy demonstrates nonimmune trapping of IgM and C3 in the segmental areas of sclerosis and hyalinosis. IgG, C4, and C1q are less frequently found in sclerotic segments. Nonsclerotic segments have no staining or only trace mesangial staining, usually for IgM and C3.

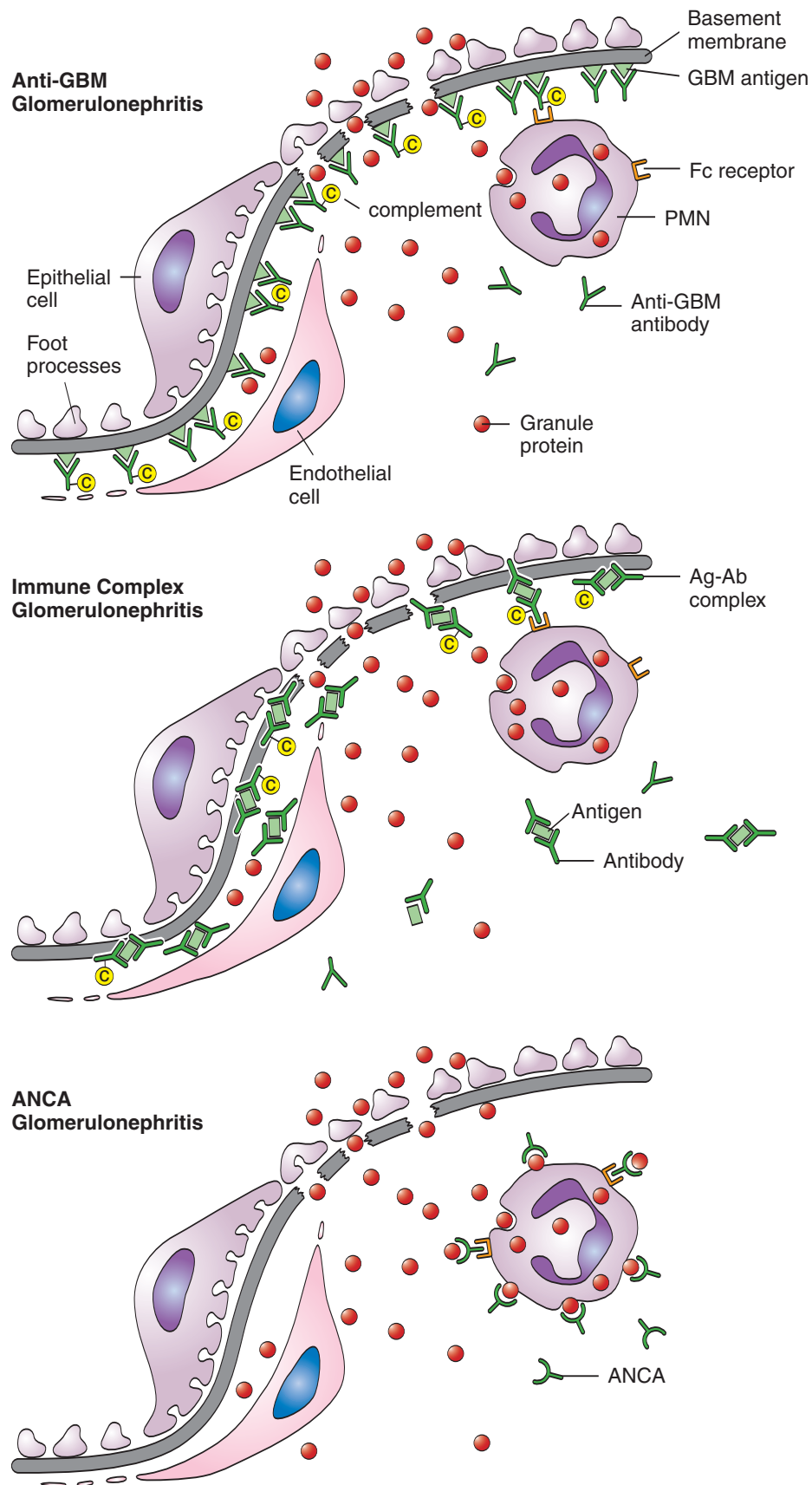


FIGURE 16-9. Antibody-mediated glomerulonephritis. (Top): Anti-glomerular basement membrane (GBM) antibodies cause glomerulonephritis by binding in situ to basement membrane antigens. This activates complement and recruits inflammatory cells. (Middle): Immune complexes that deposit from the circulation also activate complement and recruit inflammatory cells. (Bottom): Antineutrophil cytoplasmic antibodies (ANCA) cause inflammation by activating leukocytes by direct binding of the antibodies to the leukocytes and by Fc receptor engagement of ANCA bound to antigen. PMN, polymorphonuclear neutrophil; Ag-Ab complex, antigen-antibody complex.

TABLE 16-3
Diagnostic Features of Glomerular Diseases
I. Light Microscopic Features
A. Increased cellularity Infiltration by leukocytes (e.g., neutrophils, monocytes, macrophages) Proliferation of “endocapillary” cells (i.e., endothelial and mesangial cells) Proliferation of “extracapillary” cells (i.e., epithelial cells) (crescent formation)
B. Increased extracellular material Localization of immune complexes Thickening or replication of (GBM) Increases in collagenous matrix (sclerosis) Insudation of plasma proteins (hyalinosis) Fibrinoid necrosis Deposition of amyloid
II. Immunofluorescence Features
A. Linear staining of GBM Anti-GBM antibodies Multiple plasma proteins (e.g., in diabetic glomerulosclerosis) Monoclonal light chains
B. Granular immune complex staining Mesangium (e.g., IgA nephropathy) Capillary wall (e.g., membranous glomerulopathy) Mesangium and capillary wall (e.g., lupus glomerulonephritis)
C. Irregular (fluffy) staining Monoclonal light chains (AL amyloidosis) AA protein (AA amyloidosis)
III. Electron Microscopic Features
A. Electron-dense immune complex deposits Mesangial (e.g., IgA nephropathy) Subendothelial (e.g., lupus glomerulonephritis) Subepithelial (e.g., membranous glomerulopathy)
B. GBM thickening (e.g., diabetic glomerulosclerosis)
C. GBM replication (e.g., membranoproliferative glomerulonephritis)
D. Collagenous matrix expansion (e.g., focal segmental glomerulosclerosis)
E. Fibrillary deposits (e.g., amyloidosis)

IgA, immunoglobulin A; GBM, glomerular basement membrane.



CLINICAL FEATURES: FSGS is the cause of 30% of nephrotic syndrome in adults and 10% in children. It is more common in American blacks (where it is the leading cause of nephrotic syndrome) than in whites. For unknown reasons, its frequency has been increasing over the past few decades. The most common clinical presentation is an insidious onset of asymptomatic proteinuria, which frequently progresses to the nephrotic syndrome. Many patients are hypertensive, and microscopic hematuria is frequent.

Most individuals with FSGS show persistent proteinuria and a progressive decline in renal function. Many progress to end-stage renal disease after 5 to 20 years. Some, but not

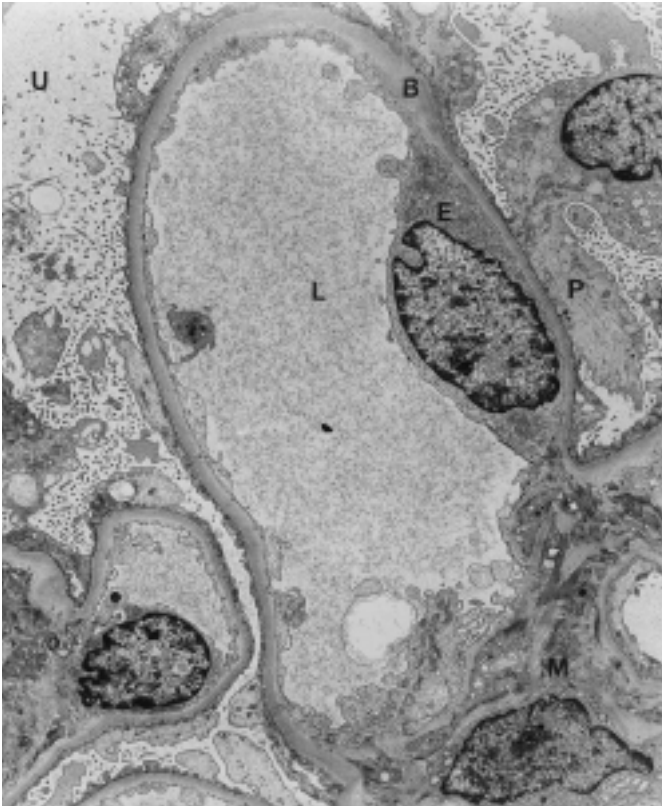


FIGURE 16-10. Minimal-change glomerulopathy. In this electron micrograph, the podocyte (P) displays extensive effacement of foot processes and numerous microvilli projecting into the urinary space (U). B, basement membrane; E, endothelial cell; L, lumen; M, mesangial cell.

all, patients appear to improve with corticosteroid therapy. Although renal transplantation is the preferred treatment for end-stage renal disease, FSGS recurs in half of transplanted kidneys. The collapsing variant has a particularly poor prognosis, and half of all patients reach end-stage disease within 2 years. Patients with FSGS secondary to obesity or reduced renal mass usually have a more indolent course that benefits from treatment with angiotensin-converting enzyme inhibitors.

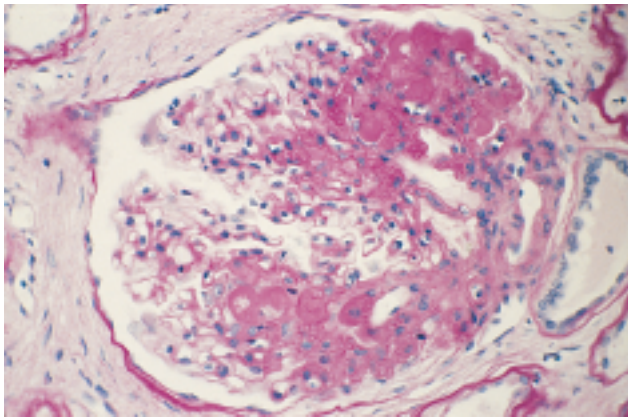


FIGURE 16-11. Focal segmental glomerulosclerosis. Periodic acid-Schiff (PAS) staining shows perihilar areas of segmental sclerosis and adjacent adhesions to Bowman's capsule.

Membranous Glomerulopathy Is an Immune Complex Disease

Membranous glomerulopathy is a frequent cause of the nephrotic syndrome in adults. It is caused by the accumulation of immune complexes in the subepithelial zone of glomerular capillaries.



PATHOGENESIS: Immune complexes localize in the **subepithelial zone** (between the visceral epithelial cell and the GBM), most likely as a result of immune complex formation in situ or possibly by the deposition of circulating immune complexes. The following are general causes of membranous glomerulopathy:

- Idiopathic (primary) membranous glomerulopathy
- Secondary membranous glomerulopathy
 - Autoimmune disease (systemic lupus erythematosus [SLE])
 - Infectious disease (hepatitis B)
 - Therapeutic agents (penicillamine)
 - Neoplasms (lung cancer)



PATHOLOGY: The glomeruli are normocellular. Depending on the duration of the disease, capillary walls are normal or thickened (Fig. 16-12). By electron microscopy, immune complexes appear in capillary walls as electron-dense deposits (Fig. 16-13). As the disease progresses, capillary lumina are narrowed, and glomerular sclerosis eventually ensues. Advanced lesions of membranous glomerulopathy cannot be distinguished from those in other forms of chronic glomerular disease. Atrophy of tubules and interstitial fibrosis parallel the degree of glomerular sclerosis.

Immunofluorescence microscopy reveals diffuse granular staining of capillary walls for IgG and C3 (Fig. 16-14). There is intense staining for terminal complement components, including the membrane attack complex, which participate in the induction of glomerular injury.



CLINICAL FEATURES: Membranous glomerulopathy is the most frequent primary glomerular cause of the nephrotic syndrome in white and Asian adults in the United States. (The most common secondary glomerular cause is diabetic glomerulosclerosis.) The course of membranous glomerulopathy is highly variable. Approximately 25% of patients have spontaneous remission within 20 years, 50% have persistent proteinuria and stable or only partial loss of renal function, and 25% develop renal failure. Patients with progressive renal failure are treated with corticosteroids or immunosuppressive drugs, or both. The prognosis is better in children because of a higher rate of permanent spontaneous remission.

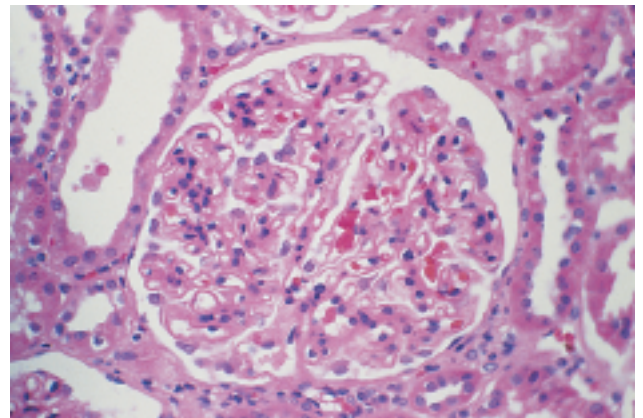


FIGURE 16-12. Membranous glomerulopathy. The glomerulus is slightly enlarged and shows diffuse thickening of the capillary walls. There is no hypercellularity.

Diabetic Glomerulosclerosis Results in Proteinuria and Progressive Renal Failure



PATHOGENESIS: Glomerulosclerosis is a part of diabetic vasculopathy that involves small vessels throughout the body (see Chapter 22). Diabetes is complicated by a generalized increase in synthesis of basement membrane material by the microvasculature. Less than half of patients with diabetes develop glomerulosclerosis, suggesting that additional factors are contributory in some, but not all, diabetic patients.

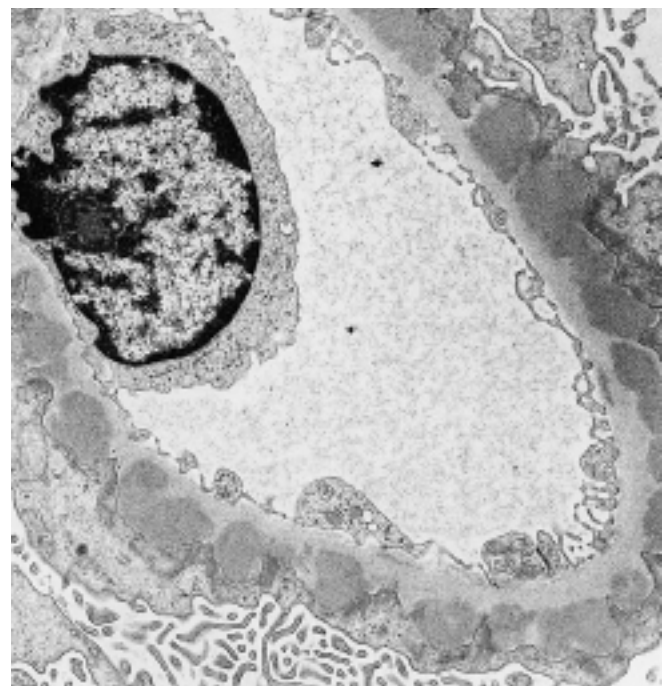


FIGURE 16-13. Stage II membranous glomerulopathy. An electron micrograph shows deposits of electron-dense material, with intervening delicate projections of basement membrane material.

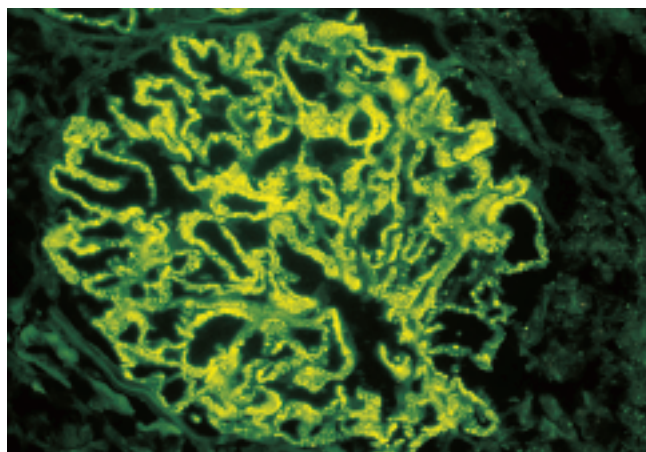


FIGURE 16-14. Membranous glomerulopathy. Immunofluorescence microscopy shows granular deposits of IgG outlining the glomerular capillary loops.



PATHOLOGY: The earliest lesions of diabetic glomerulosclerosis are glomerular enlargement, GBM thickening, and mesangial matrix expansion. Mild mesangial hypercellularity may also be present. With progressive disease, GBM thickening, and especially expansion of the mesangial matrix, result in changes that can be seen by light microscopy. Overt diabetic glomerulosclerosis is characterized by diffuse global thickening of GBMs and diffuse mesangial matrix expansion, accompanied by sclerotic lesions termed **Kimmelstiel-Wilson nodules** (Fig. 16-15). Tubular basement membranes are thickened. Sclerosing and insudative changes also occur in afferent and efferent arterioles, causing hyaline arteriosclerosis. Generalized arteriosclerosis is usually present in the kidney. Vascular narrowing and reduced blood flow to the medulla predisposes to papillary necrosis and pyelonephritis.

Electron microscopy shows up to 5- to 10-fold widening of the basement membrane lamina densa. Mesangial matrix is increased, particularly in nodular lesions. The insudative lesions appear as electron-dense masses that contain lipid debris. Immunofluorescence microscopy demonstrates diffuse nonimmune linear trapping of IgG, albumin, fibrinogen, and other plasma proteins in the GBM.



CLINICAL FEATURES: Diabetic glomerulosclerosis is the leading cause of end-stage renal disease in the United States, accounting for one-third of all patients with chronic renal failure. It occurs in type 1 and type 2 diabetes mellitus. The earliest manifestation is microalbuminuria (slightly increased proteinuria). Overt proteinuria occurs between 10 and 15 years after the onset of diabetes and often becomes severe enough to cause the nephrotic syndrome. In time, diabetic glomerulosclerosis progresses to renal failure. Strict control of blood glucose reduces the incidence of diabetic glomerulosclerosis and retards progression once it develops. Control of hypertension

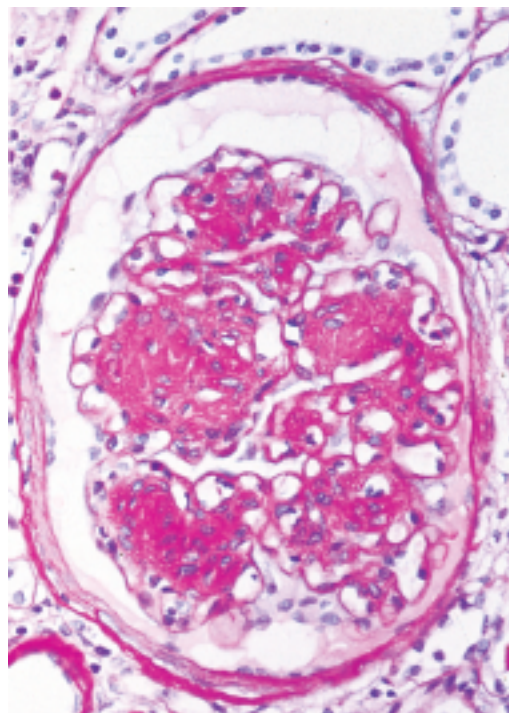


FIGURE 16-15. Diabetic glomerulosclerosis. Periodic acid-Schiff (PAS) staining reveals a prominent increase in the mesangial matrix, forming several nodular lesions. Dilatation of glomerular capillaries is evident, and some capillary basement membranes are thickened.

and restriction of dietary protein also slow progression of the disease.

Amyloidosis Leads to Nephrotic Syndrome and Renal Failure

Renal disease is a frequent complication of primary (AL) and secondary (AA) amyloidosis (see Chapter 23 for details of the pathogenesis of amyloid formation).



PATHOLOGY: Histologically, amyloid is an eosinophilic, amorphous material (Fig. 16-16) that has a characteristic apple-green color in sections stained with Congo red and examined by polarized light microscopy. Acidophilic deposits initially are most apparent in the mesangium but later extend into capillary walls and may destroy capillary lumina (see Fig. 16-16). Glomerular structure is completely obliterated in advanced amyloidosis, and glomeruli appear as large eosinophilic spheres.

Amyloid is composed of nonbranching fibrils, approximately 10 nm in diameter. These fibrils are most prominent in the mesangium but often extend into capillary walls, especially in advanced cases. The epithelial foot processes overlying the GBM are effaced.



CLINICAL FEATURES: Renal involvement is prominent in most cases of systemic AL and AA amyloidosis. Proteinuria is often the initial mani-

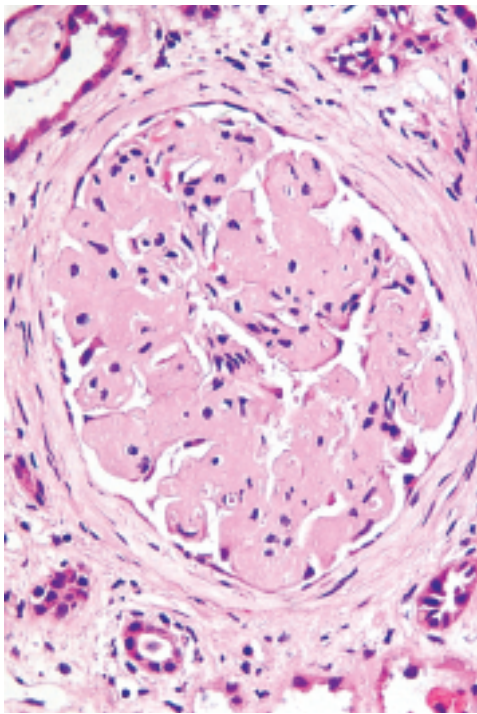


FIGURE 16-16. Amyloid nephropathy. Amorphous acellular material expands the mesangial areas and obstructs the glomerular capillaries. The deposits of amyloid may take on a nodular appearance, somewhat resembling those of diabetic glomerulosclerosis (see Fig. 16-26). However, amyloid deposits are not periodic acid-Schiff–positive and are identifiable by Congo red staining.

festation. It is nonselective (i.e., both albumin and globulins appear in the urine) and produces nephrotic syndrome in 60% of patients. Eventually, severe infiltration of the glomeruli and blood vessels by amyloid results in renal failure. AL amyloidosis is treated with chemotherapy analogous to that used for multiple myeloma. AA amyloidosis, especially when caused by familial Mediterranean fever, is ameliorated by colchicine therapy.

Hereditary Nephritis (Alport Syndrome) Reflects Abnormal Type IV Collagen in GBMs

Hereditary nephritis is a proliferative and sclerosing glomerular disease, often accompanied by defects of the ears or the eye, which is caused by mutations in type IV collagen. Alport syndrome is accompanied by a hearing deficit.



PATHOGENESIS: A variety of genetic mutations cause molecular defects in the GBM that produce the renal lesions of hereditary nephritis. The most common defect accounting for 85% of hereditary nephritis is X-linked and is caused by a mutation in the gene for the $\alpha 5$ chain of type IV collagen (COL4A5 gene).



PATHOLOGY: Early glomerular lesions of hereditary nephritis show mild mesangial hypercellularity and matrix expansion. Renal disease progression is associated with increasing focal and eventually diffuse glomerular sclerosis. Advanced glomerular lesions are accompanied by tubular atrophy, interstitial fibrosis, and the presence of foam cells in the tubules and interstitium. The most diagnostic morphologic lesion is seen only by electron microscopy as an irregularly thickened GBM, with splitting of the lamina densa into interlacing lamellae that surround electron-lucent areas.



CLINICAL FEATURES: Males with X-linked hereditary nephritis develop microscopic hematuria early in childhood, usually followed by proteinuria, and progressive renal failure during the second to fourth decades of life. Females with X-linked (heterozygous) disease generally have a milder form. The slower progression of symptoms varies substantially among patients, possibly related to the degree of random inactivation of the mutated X chromosome. Sensorineural, high-frequency hearing loss affects half of males with X-linked disease.

Thin Glomerular Basement Membrane Nephropathy Is a Benign Cause of Hematuria

Thin basement membrane nephropathy, also termed benign familial hematuria, is a common hereditary GBM disorder that typically manifests as asymptomatic microscopic hematuria, and occasionally with intermittent gross hematuria. This disease and IgA nephropathy are the two major diagnostic considerations in patients with asymptomatic glomerular hematuria. Patients with thin basement membrane nephropathy usually do not develop renal failure or substantial proteinuria. By light microscopy, glomeruli are unremarkable. Electron microscopy reveals a reduced thickness of the GBM (150 to 300 nm, compared with the normal 350 to 450 nm). The most common mode of inheritance is autosomal dominant. Heterozygous mutations in the COL4A3 and COL4A4 genes lead to thin basement membrane disease, and homozygous mutations lead to a recessive variant of Alport syndrome.

Acute Postinfectious Glomerulonephritis Is an Immune Complex Disease of Childhood

Acute postinfectious glomerulonephritis usually occurs after infection with group A (β -hemolytic) streptococci and is caused by deposition of immune complexes in glomeruli.



PATHOGENESIS: Acute postinfectious glomerulonephritis is most often caused by certain nephritogenic strains of group A (β -hemolytic) streptococci. Occasional examples are caused by staphylococcal

infection (e.g., acute staphylococcal endocarditis, staphylococcal abscess), and rare cases result from viral (e.g., hepatitis B) or parasitic (e.g., malaria) infections. The exact mechanism by which infection causes the characteristic inflammatory changes in the glomeruli is not completely understood. It is likely that postinfectious glomerulonephritis is caused by glomerular localization of immune complexes composed of antibody plus bacterial, viral, or parasitic antigens. Poststreptococcal glomerulonephritis has a latent period of 9 to 14 days between the time of exposure to the infectious agent and the occurrence of glomerulonephritis. Immune complexes could localize in glomeruli by deposition from the circulation or formation in situ as bacterial antigens trapped in the glomeruli bind circulating antibodies. The specific nephritogenic streptococcal antigens have not been conclusively identified. Immune complexes within glomeruli initiate inflammation by activating complement, as well as other humoral and cellular inflammatory mediators.



PATHOLOGY: The acute phase of postinfectious glomerulonephritis is characterized by diffuse glomerular enlargement and hypercellularity, which defines acute diffuse proliferative glomerulonephritis. Hypercellularity reflects proliferation of both endothelial and mesangial cells (Fig. 16-17) as well as infiltration by neutrophils and monocytes. Crescents are uncommon. Interstitial edema and mild infiltration of mononuclear leukocytes occur in parallel with the glomerular changes.

The acute phase begins 1 or 2 weeks after the onset of the nephritogenic infection and resolves in more than 90% of patients after several weeks. All histologic changes resolve completely in most patients after several months.

The most distinctive ultrastructural features of acute postinfectious glomerulonephritis are **subepithelial dense deposits** that are shaped like “**humps**” (see Fig. 16-17). These deposits are invariably accompanied by mesangial and subendothelial deposits, which may be more difficult to find but are probably more important in pathogenesis because of their proximity to the inflammatory mediator systems in the blood. In the first few weeks of disease, immunofluorescence microscopy typically reveals granular deposits corresponding to IgG and C3 along the basement membrane, in locations corresponding to the humps. Later in the disease, C3 is present without IgG, possibly because immune complexes containing IgG no longer accumulate in the glomeruli after the infection clears (Fig. 16-18).



CLINICAL FEATURES: Acute poststreptococcal glomerulonephritis is less common than in the past but remains one of the most common childhood renal diseases. The nephritic syndrome begins

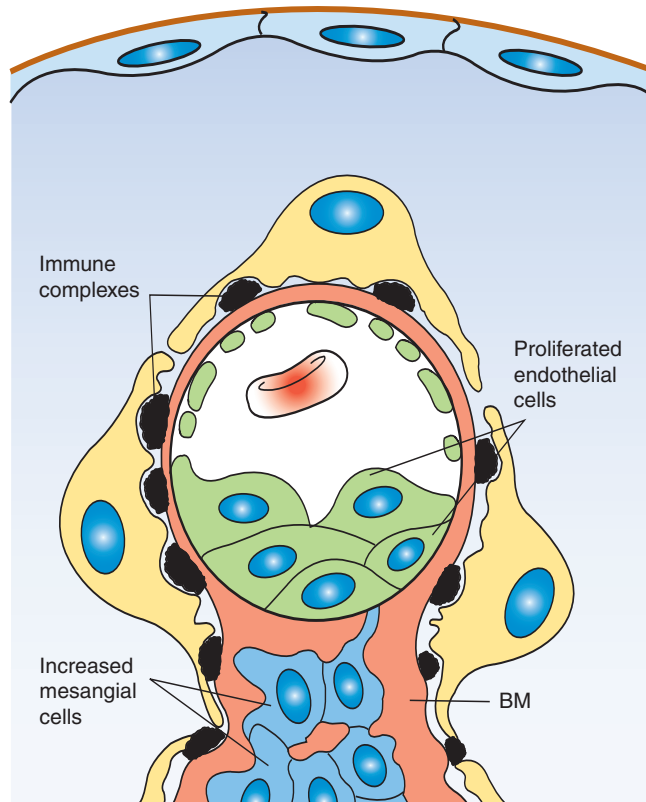


FIGURE 16-17. Postinfectious glomerulonephritis. Accumulation of numerous subepithelial immune complexes as hump-like structures is a characteristic feature. Less prominent subendothelial immune complexes are associated with endothelial cell proliferation and are related to increased capillary permeability and narrowing of the lumen. Frequently, proliferation of mesangial cells and a thickened mesangial matrix (BM) result in widening of the stalk and conspicuous trapping of immune complexes.

abruptly with oliguria, hematuria, facial edema, and hypertension. Serum C3 levels are lower during the acute syndrome but return to normal within 1 to 2 weeks. Overt nephritis resolves after several weeks, although hematuria and especially proteinuria may persist for several months. A

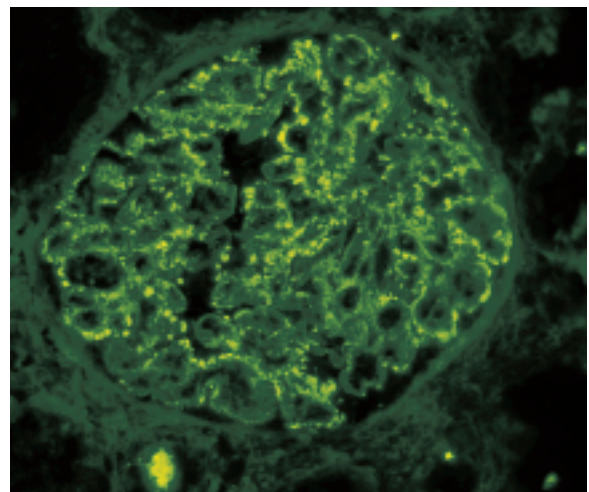


FIGURE 16-18. Acute postinfectious glomerulonephritis. An immunofluorescence micrograph demonstrates granular staining for C3 in capillary walls and the mesangium.

few patients have abnormal urinary sediment for years after the acute episode, and rare patients (particularly adults) develop progressive renal failure.

Type I Membranoproliferative Glomerulonephritis Is a Chronic Immune-Complex Disease

Type I membranoproliferative glomerulonephritis is characterized by hypercellularity and capillary wall thickening. Deposition of mesangial and subendothelial immune complexes causes mesangial proliferation and extension into the subendothelial zone.



PATHOGENESIS: Type I membranoproliferative glomerulonephritis, also called **mesangiocapillary glomerulonephritis**, is caused by localization of immune complexes to the mesangium and the subendothelial zone of capillary walls. In most patients, the origin of nephritogenic antigen is unknown, but some have associated conditions that are the apparent source of the antigen. Elimination of disorders such as bacterial endocarditis or osteomyelitis leads to the resolution of glomerulonephritis, which supports a causal relationship between the two. Agents that are responsible for type I membranoproliferative glomerulonephritis cause persistent, indolent infections that are associated with chronic antigenemia. This condition leads to chronic localization of immune complexes in glomeruli and resultant hypercellularity and matrix remodeling.



PATHOLOGY: Glomeruli in type I membranoproliferative glomerulonephritis are diffusely enlarged, with conspicuous mesangial cell proliferation resulting in lobular distortion (“hypersegmentation”) of the glomeruli (Fig. 16-19). Twenty percent of patients will have crescents, usually involving only a minority of glomeruli. Capillary walls are thickened, and silver stains show a doubling or complex replication of GBMs.

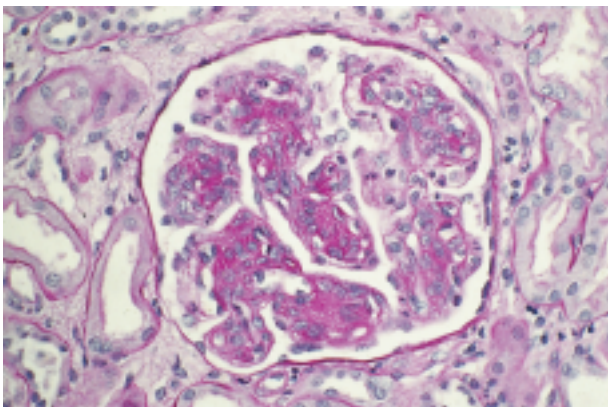


FIGURE 16-19. Type I membranoproliferative glomerulonephritis. The glomerular lobulation is accentuated. Increased cells and matrix in the mesangium and thickening of capillary walls are noted.

Electron microscopy shows that the capillary wall thickening and replication of GBMs are a consequence of the marked mesangial expansion, with extension of mesangial cytoplasm into the subendothelial zone and deposition of new basement membrane material between the mesangial cytoplasm and endothelial cell (Fig. 16-20 and Fig. 16-21). Subendothelial and mesangial electron-dense deposits, corresponding to immune complexes, are the likely stimuli for the mesangial response. Variable numbers of subepithelial dense deposits may also be seen. Immunofluorescence microscopy shows granular deposition of immunoglobulins and complement in glomerular capillary loops and mesangium.



CLINICAL FEATURES: Type I membranoproliferative glomerulonephritis is most frequent in older children and young adults. It may manifest as either nephrotic or nephritic syndrome or a combination of both. Type I disease accounts for 5% of nephrotic syn-

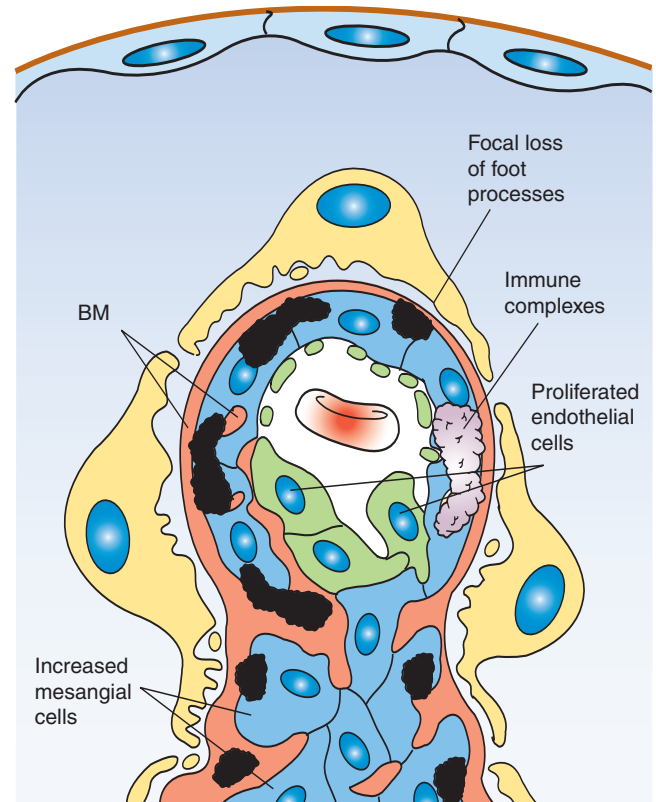


FIGURE 16-20. Membranoproliferative glomerulonephritis, type I. In this disease, the glomeruli are enlarged. Hypercellular tufts and narrowing or obstruction of the capillary lumen are seen. Large subendothelial deposits of immune complexes extend along the inner border of the basement membrane. The mesangial cells proliferate and migrate peripherally into the capillary. Basement membrane (BM) material accumulates in a linear fashion parallel to the BM in a subendothelial position. The interposition of mesangial cells and basement membrane between the endothelial cells and the original BM creates a double-contour effect. The accumulation of mesangial cells and stroma in the tufts narrows the capillary lumen. The proliferation of mesangial cells and the accumulation of BM material also widen the mesangium. The entire process leads progressively to lobulation of the glomerulus. Note the proliferation of endothelial cells and focal effacement of foot processes.

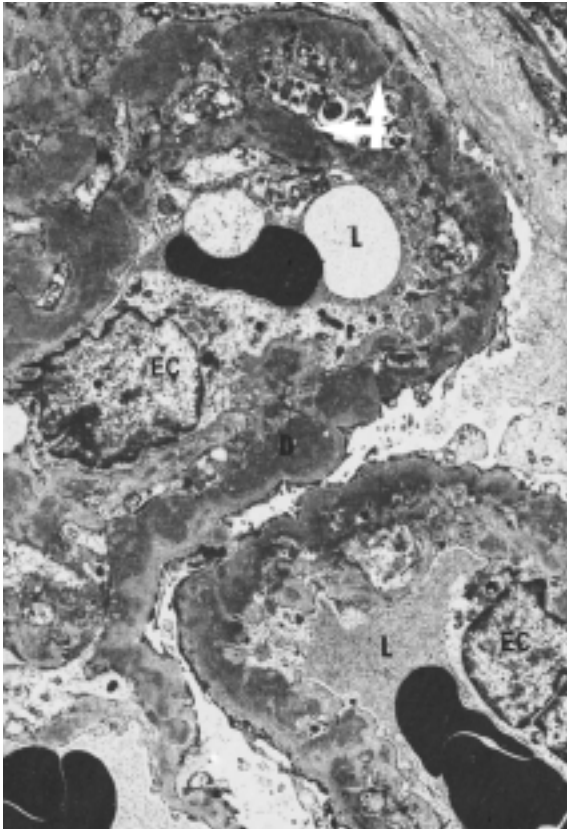


FIGURE 16-21. Type I membranoproliferative glomerulonephritis. An electron micrograph demonstrates a double-contour basement membrane (arrow) with mesangial interposition and prominent subendothelial deposits. EN, endothelial cell; L, capillary lumen.

drome in children and adults in the United States. It is much more common in developing countries that have a high prevalence of chronic infections. Type I membranoproliferative glomerulonephritis is usually a persistent but slowly progressive disease. Half of patients reach end-stage renal disease after 10 years.

Type II Membranoproliferative Glomerulonephritis (Dense Deposit Disease) Features Complement Deposition

Type II membranoproliferative glomerulonephritis is characterized by a pathognomonic electron-dense transformation of GBMs and extensive complement deposition.



PATHOGENESIS: The extensive localization of complement in the GBMs and mesangial matrix, in the absence of significant immunoglobulin deposition, suggests that complement activation via the alternate pathway is a major mediator of the structural and functional abnormalities associated with the disease. A deficiency of, and mutations in, regulatory factors of the alternative complement

pathway (e.g., factor H), and the presence in most patients of a serum IgG autoantibody termed **C3 nephritic factor** (which results in the prolongation of C3 cleaving activity), implicate dysregulation of the alternate complement pathway in disease pathogenesis.



PATHOLOGY: The histologic appearance of type II membranoproliferative glomerulonephritis may be similar to that of type I, with capillary wall thickening and some degree of hypercellularity. The distinctive ribbon-like zone of increased density in the center of a thickened GBM and in the mesangial matrix justifies the alternative name **dense deposit disease**. Immunofluorescence microscopy shows linear staining of capillary walls for C3, with little or no staining for immunoglobulins.



CLINICAL FEATURES: Type II membranoproliferative glomerulonephritis is rare. It resembles type I disease in clinical presentation and course, except that hypocomplementemia is more common, and the prognosis is slightly worse. No effective treatment has been identified.

Lupus Glomerulonephritis Is Associated With Many Autoantibodies

SLE is an autoimmune disease characterized by a generalized dysregulation and hyperactivity of B cells, with production of autoantibodies to a variety of nuclear and nonnuclear antigens, including DNA, RNA, nucleoproteins, and phospholipids (see Chapter 4). Nephritis is one of the most common complications of SLE, with a wide range of patterns of immune complex deposition seen in the glomerulus. Mesangial deposition of immune complexes causes less inflammation than subendothelial deposits, which are more exposed to the circulation. Subepithelial localization causes proteinuria but not overt glomerular inflammation.



PATHOGENESIS: Immune complexes may localize in glomeruli by deposition from the circulation or formation in situ (involving antigens such as DNA bound to GBM or mesangium by charge interaction). Glomerular immune complexes activate complement and initiate inflammatory injury. Immune complexes deposited in other renal compartments may be involved in the tubulointerstitial inflammation seen in patients with lupus nephritis.



PATHOLOGY: The pathologic and clinical manifestations of lupus nephritis are highly variable because of variable patterns of immune complex accumulation in different patients and in the same patient over time.

- **Class I (minimal mesangial lupus nephritis):** Immune complexes are confined to the mesangium and cause no changes by light microscopy.
- **Class II (mesangial proliferative lupus nephritis):** Immune complexes are confined to the mesangium and produce varying degrees of mesangial hypercellularity and matrix expansion (Fig. 16-22).
- **Class III (focal proliferative lupus nephritis):** Immune complex accumulation in the subendothelial zone and the mesangium stimulates inflammation, with proliferation of mesangial and endothelial cells and the influx of neutrophils and monocytes.
- **Class IV (diffuse proliferative lupus nephritis):** This type is similar to class III but involves more than 50% of glomeruli.
- **Class V (membranous lupus nephritis):** Immune complexes are mostly in the subepithelial zone, but concurrent class III or IV injury may also occur.
- **Class VI (advanced sclerosing lupus nephritis):** This category is the most severe chronic disease.

Electron microscopy demonstrates the varied locations of immune-complex dense deposits in mesangial, subendothelial, and subepithelial locations. About 80% of specimens have **tubuloreticular inclusions** in endothelial cells. Lupus nephritis and HIV-associated nephropathy are the only renal diseases with a high frequency of these structures.

By immunofluorescence, the subepithelial complexes are granular, and the subendothelial deposits appear granular or band-like. The immune complexes often stain most intensely for IgG, but IgA and IgM are also almost always present, as are C3, C1q, and other complement components. Granular staining along tubular basement membranes and interstitial vessels is present in more than 50% of patients.

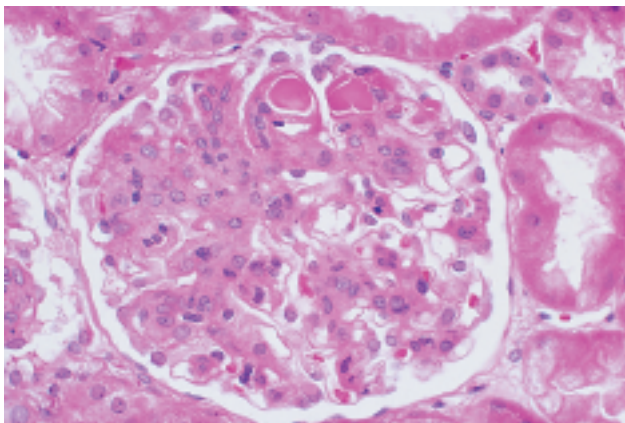


FIGURE 16-22. Proliferative lupus glomerulonephritis. Segmental endocapillary hypercellularity and thickening of capillary walls are present.



CLINICAL FEATURES: Seventy percent of all patients with SLE develop renal disease, which is the major cause for morbidity and mortality in many patients. SLE and associated renal disease is most common in black women. The clinical manifestations and prognosis of renal dysfunction are varied and depend on the pathologic nature of the underlying renal disease. Class III and class IV lupus nephritis have the poorest prognosis and are treated most aggressively, usually with high doses of corticosteroids and other immunosuppressive drugs. Currently, less than 25% of patients with class IV disease reach end-stage renal failure within 5 years.

IgA Nephropathy (Berger Disease) Is Caused by Immune Complexes of IgA



PATHOGENESIS: Although the deposition of IgA-dominant immune complexes is the cause of IgA nephropathy, the constituent antigens and mechanism of accumulation are not known. Patients with IgA nephropathy often have elevated blood levels of IgA, and circulating IgA-containing immune complexes have been detected. *Exacerbations of IgA nephropathy are often initiated by respiratory or gastrointestinal infections.* There is evidence for MHC-linked susceptibility to IgA nephropathy, possibly mediated via dysregulation of IgA immune responses. Abnormal glycosylation of the hinge region of IgA appears to be an important predisposing factor in many patients with IgA nephropathy.

IgA-containing immune complexes within the mesangium most likely activate the alternative complement pathway. This concept is supported by the demonstration of C3 and properdin, but not C1q and C4, in the IgA deposits.



PATHOLOGY: Immunofluorescence microscopy is essential for diagnosis of IgA nephropathy. The diagnostic finding is mesangial staining for IgA more intense than, or equivalent to, staining for IgG or IgM. This is almost always accompanied by staining for C3.

Depending on the severity and duration of glomerular inflammation, IgA nephropathy manifests a continuum of histologic appearances, ranging from (1) no discernible light microscopic changes, to (2) focal or diffuse mesangial hypercellularity, to (3) focal or diffuse proliferative glomerulonephritis, to (4) chronic sclerosing glomerulonephritis. This spectrum of pathologic changes is analogous to that seen with lupus nephritis but tends to be less severe.



CLINICAL FEATURES: IgA nephropathy (Berger disease) is the most common form of glomerulonephritis in the world. It accounts for 10% of cases in the United States, has a high frequency in Native Americans, and is rare in blacks. It is most common in young men, with a peak age of 15 to 30 years at diagnosis. The clinical presentations are varied, which reflects the varied pathologic severity. The disease rarely resolves completely, but has a slowly progressive course with 20% of patients reaching end-stage renal failure after 10 years.

Anti-Glomerular Basement Membrane Glomerulonephritis Is Often Associated With Pulmonary Hemorrhage

Anti-GBM antibody glomerulonephritis is an uncommon but aggressive form of glomerulonephritis that occurs as a renal-limited disease or is combined with pulmonary hemorrhage (Goodpasture syndrome).



PATHOGENESIS: Anti-GBM glomerulonephritis is mediated by an autoimmune response against a component of the GBM within the globular noncollagenous domain of the $\alpha 3$ type of collagen IV. Because the target antigen is also expressed on pulmonary alveolar capillary basement membranes, half of patients also have pulmonary hemorrhages and hemoptysis, sometimes severe enough to be life-threatening. If both lungs and kidneys are involved, the eponym **Goodpasture syndrome** is used. Anti-GBM antibodies, anti-GBM T cells, or both may mediate the injury. Genetic susceptibility to anti-GBM disease is associated with *HLA-DR2* genes. Disease onset often follows viral upper-respiratory tract infections. Pulmonary involvement appears to require prior exposure to other injurious agents, such as cigarette smoke.



PATHOLOGY: The pathologic hallmark of anti-GBM glomerulonephritis is diffuse linear staining of GBMs for IgG, which indicates autoantibodies bound to the basement membrane (Fig. 16-23). More than 90% of patients with anti-GBM glomerulonephritis have glomerular crescents (**crescentic glomerulonephritis**) (Fig. 16-24 and Fig. 16-25).



CLINICAL FEATURES: Anti-GBM glomerulonephritis typically presents with rapidly progressive renal failure and nephritic signs and symptoms. It accounts for 10% to 20% of rapidly progressive (crescentic) glomerulonephritis. Treatment consists of high-dose immunosuppressive therapy and plasma exchange. If end-stage renal failure develops, renal transplantation is frequently successful, with little risk of loss of the allograft to recurrent glomerulonephritis.

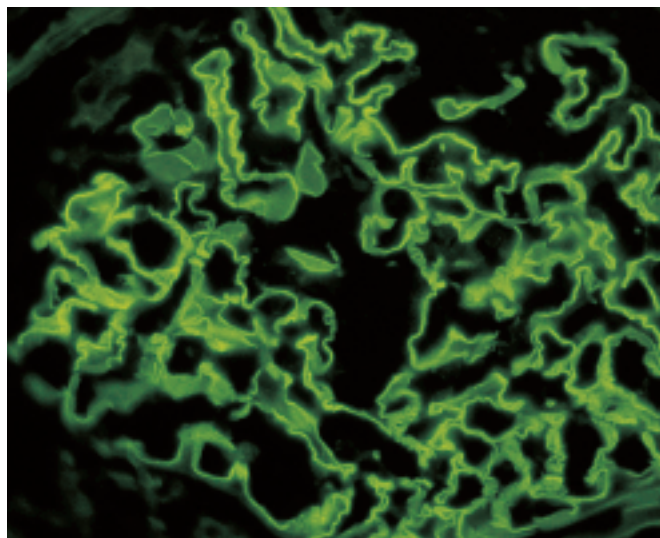


FIGURE 16-23. Anti-glomerular basement membrane (GBM) glomerulonephritis. Linear immunofluorescence for immunoglobulin G is seen along the GBM. Compare this linear pattern of staining with the granular pattern of immunofluorescence typical for most types of immune complex deposition within capillary walls (see Fig. 16-36).

ANCA Glomerulonephritis Features Neutrophil-Induced Injury

ANCA glomerulonephritis is an aggressive, neutrophil-mediated disease that is characterized by glomerular necrosis and crescents.



PATHOGENESIS: ANCA glomerulonephritis was once called *idiopathic crescentic glomerulonephritis* because immunofluorescence microscopy did not demonstrate evidence of glomerular deposition of anti-GBM antibodies or immune complexes. The discovery that 90% of patients with this pat-

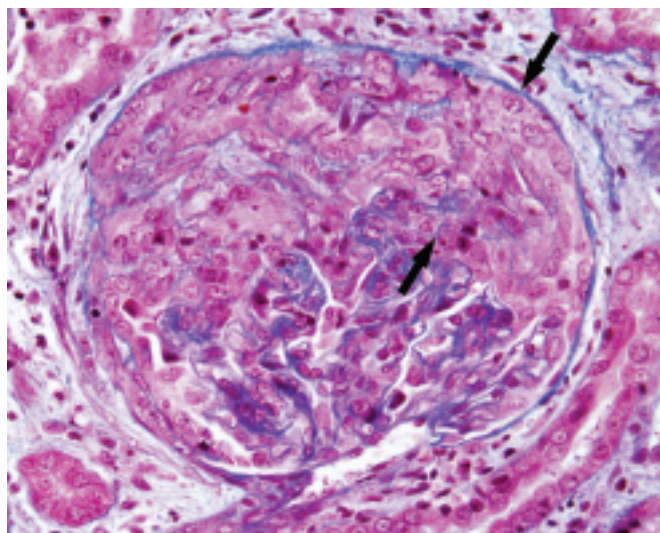


FIGURE 16-24. Crescentic anti-glomerular basement membrane glomerulonephritis. Bowman's space is filled by a cellular crescent (between arrows). The injured glomerular tuft is at the bottom (Masson trichrome stain).

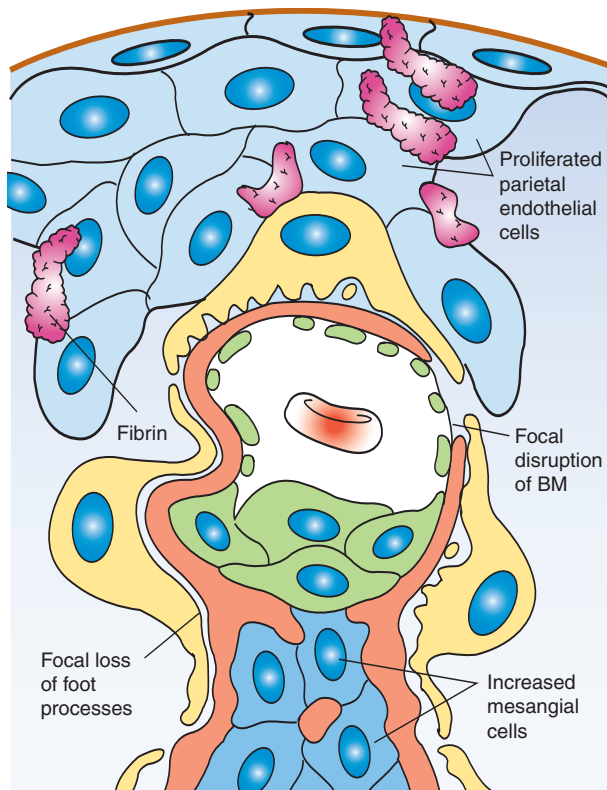


FIGURE 16-25. Crescentic (rapidly progressive) glomerulonephritis. A variety of different pathogenic mechanisms cause crescent formation by disrupting glomerular capillary walls. This allows plasma constituents into Bowman's space, including coagulation factors and inflammatory mediators. Fibrin forms, and there is proliferation of parietal epithelial cells and influx of macrophages, resulting in crescent formation.

tern of glomerular injury have circulating ANCAs led to the demonstration that these autoantibodies cause the disease. *ANCAs are specific for proteins in the cytoplasm of neutrophils and monocytes, usually MPO-ANCA or PR3-ANCA.*



PATHOLOGY: More than 90% of patients with ANCA glomerulonephritis have focal glomerular necrosis (Fig. 16-26) and crescent formation. In many patients, more than 50% of glomeruli exhibit crescents. Nonnecrotic segments may appear normal or have slight neutrophil infiltration or mild endocapillary hypercellularity. Immunofluorescence microscopy demonstrates an absence or paucity of staining for immunoglobulins and complement.



CLINICAL FEATURES: The most common clinical presentation for ANCA glomerulonephritis is rapidly progressive renal failure, with nephritic signs and symptoms. The disease accounts for 75% of rapidly progressive (crescentic) glomerulonephritis in patients over 60 years of age, 45% in middle-aged adults, and 30% in

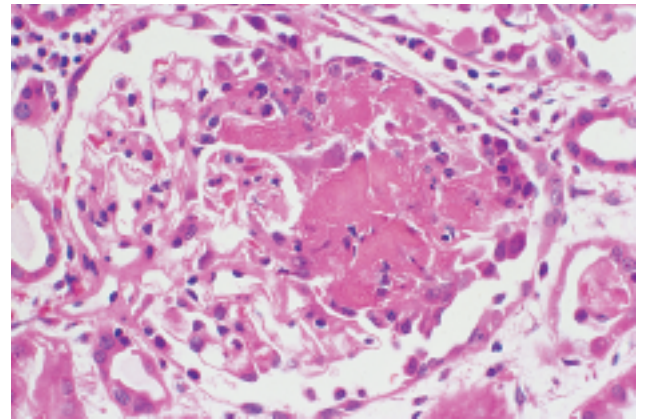


FIGURE 16-26. Antineutrophil cytoplasmic autoantibody glomerulonephritis. Segmental fibrinoid necrosis is illustrated. In time, this lesion stimulates crescent formation.

young adults and children. *Three quarters of patients with ANCA glomerulonephritis have systemic small-vessel vasculitis (see below), which has many manifestations, including pulmonary hemorrhage, a much more frequent cause of pulmonary-renal vasculitic syndrome than is Goodpasture syndrome.* Without treatment, more than 80% of patients with ANCA glomerulonephritis develop end-stage renal disease within 5 years. Immunosuppressive therapy decreases the development of end-stage disease at 5 years to less than 25%.

VASCULAR DISEASES

Renal Vasculitis May Affect Vessels of All Sizes

The kidney is involved in many types of systemic vasculitis (Table 16-4). *In a sense, glomerulonephritis is a local form of vasculitis that affects glomerular capillaries.* The glomeruli may be the only site of vascular inflammation, or the renal disease may be a component of a systemic vasculitis.

Small-Vessel Vasculitis

Small-vessel vasculitis affects small arteries, arterioles, capillaries, and venules. Glomerulonephritis, purpura, arthralgias, myalgias, peripheral neuropathy, and pulmonary hemorrhage are common components of the small-vessel vasculitides. Additional details of extrarenal disease may be found in Chapter 10.

Henoch-Schönlein purpura is the most common type of childhood vasculitis. It is caused by vascular localization of immune complexes containing mostly IgA. The glomerular lesion is identical with that to IgA nephropathy.

Cryoglobulinemic vasculitis causes proliferative glomerulonephritis, usually type I membranoproliferative glomerulonephritis. By light microscopy, aggregates of cryoglobulins ("hyaline thrombi") are often seen within capillary lumina.

TABLE 16-4

Types of Vasculitis That Involve the Kidneys

Type of Vasculitis	Major Target Vessels in Kidney	Major Renal Manifestations
Small-vessel vasculitis		
Immune-complex vasculitis		
Henoch-Schönlein purpura	Glomeruli	Nephritis
Cryoglobulinemic vasculitis	Glomeruli	Nephritis
Anti-GBM vasculitis		
Goodpasture syndrome	Glomeruli	Nephritis
ANCA-vasculitis		
Wegener granulomatosis	Glomeruli, arterioles, interlobular arteries	Nephritis
Microscopic polyangiitis	Glomeruli, arterioles, interlobular arteries	Nephritis
Churg-Strauss syndrome	Glomeruli, arterioles, interlobular arteries	Nephritis
Medium-sized vessel vasculitis		
Polyarteritis nodosa	Interlobar and arcuate arteries	Infarcts and hemorrhage
Kawasaki disease	Interlobar and arcuate arteries	Infarcts and hemorrhage
Large-vessel vasculitis		
Giant cell arteritis	Main renal artery	Renovascular hypertension
Takayasu arteritis	Main renal artery	Renovascular hypertension

ANCA, antineutrophil cytoplasmic autoantibody; GBM, glomerular basement membrane.

ANCA vasculitis involves vessels outside the kidneys in 75% of patients with ANCA glomerulonephritis (see Chapter 10). In addition to causing necrotizing and crescentic glomerulonephritis, the ANCA vasculitides often display necrotizing inflammation in other renal vessels, such as arteries, arterioles, and medullary peritubular capillaries.

Medium-Sized and Large-Vessel Vasculitis

Medium-sized vessel vasculitides such as **polyarteritis nodosa** (in adults) and **Kawasaki disease** (primarily in children) affect arteries, but not arterioles, capillaries, or venules. Large-vessel vasculitides, such as **giant cell arteritis** and **Takayasu arteritis**, affect the aorta and its major branches and may cause renovascular hypertension by involving the main renal arteries or their aortic origin (see Chapter 10).

Hypertensive Nephrosclerosis (Benign Nephrosclerosis) Leads to Obliteration of Glomeruli



PATHOGENESIS: Sustained systolic pressures over 140 mm Hg and diastolic pressures over 90 mm are generally considered to represent hypertension (see Chapter 10). Mild-to-moderate hypertension causes typical hypertensive nephrosclerosis in approximately 15% of patients and thus is not truly benign.



PATHOLOGY: The kidneys are smaller than normal (atrophic) and are usually affected bilaterally. The cortical surfaces have a fine granularity (Fig. 16-27), but coarser scars are occasionally present. On cut

section, the cortex is thinned. Microscopically, many glomeruli appear normal; others show varying degrees of ischemic change. Initially, glomerular capillaries demonstrate thickening, wrinkling, and collapse of GBMs. Cells of the glomerular tuft are progressively lost, and collagen and matrix material are deposited within Bowman's space. Eventually, the glomerular tuft is obliterated by a dense, eosinophilic globular mass within a scar. Tubular atrophy, a consequence of glomerular loss, is associated with interstitial fibrosis and infiltration by chronic inflammatory cells.



FIGURE 16-27. Hypertensive nephrosclerosis. The kidney is reduced in size, and the cortical surface exhibits fine granularity.

Sclerotic glomeruli and surrounding atrophic tubules are often clustered in focal subcapsular zones, with adjacent areas of preserved glomeruli and tubules (Fig. 16-28), the basis for the granular surfaces of nephrosclerotic kidneys.

The pattern of change in the renal blood vessels depends on the size of the vessel. Arteries down to the size of the arcuate arteries have fibrotic thickening of the intima, with replication of the elastica-like lamina and partial replacement of the muscularis with fibrous tissue. Interlobular arteries and arterioles may develop medial hyperplasia. Arterioles exhibit concentric hyaline thickening of the wall, often with the loss of smooth muscle cells or their displacement to the periphery. This arteriolar change is termed **hyaline arteriosclerosis**.

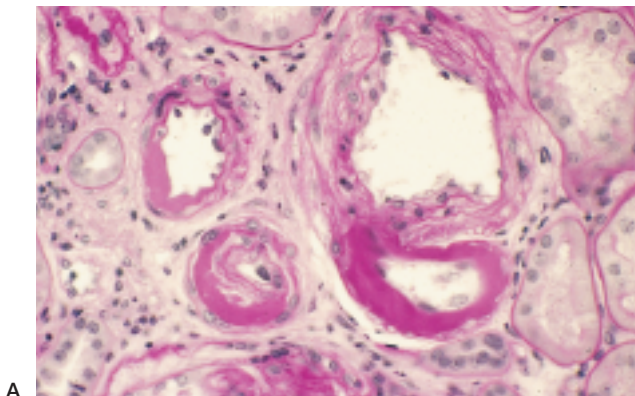


CLINICAL FEATURES: Although hypertensive nephrosclerosis does not usually lead to significant renal function abnormalities, a few of the many persons with “benign” hypertension develop progressive renal failure, which may terminate in end-stage renal disease. Benign nephrosclerosis is most prevalent and aggressive among blacks. *In fact, among blacks in the United States, hypertension without any evidence of a malignant phase is the leading cause of end-stage renal disease.*

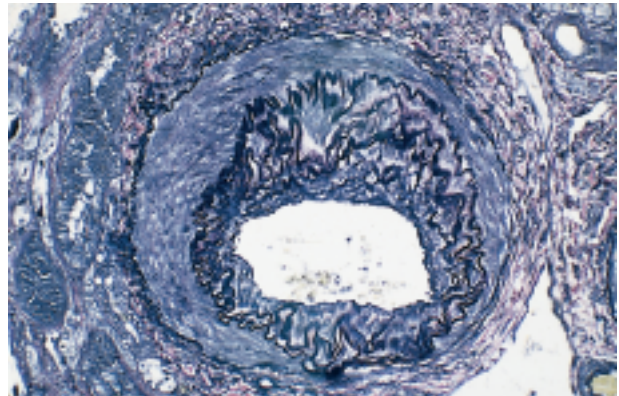
Malignant Hypertensive Nephropathy Is a Potentially Fatal Renal Disease



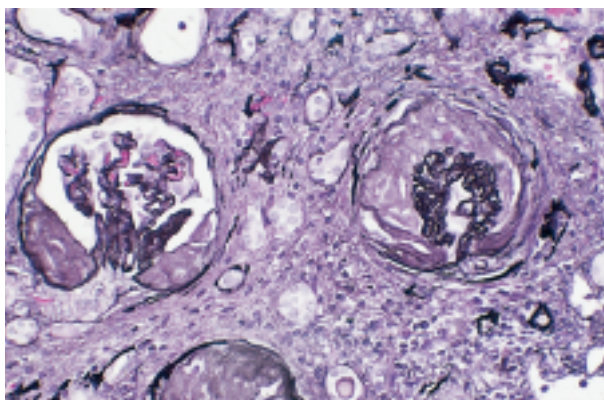
PATHOGENESIS: No specific blood pressure defines malignant hypertension, but diastolic pressures over 130 mm Hg, retinal vascular changes, papilledema, and renal functional impairment are usual criteria. About half of patients have prior histories of benign hypertension, and many others have a background of chronic renal injury caused by many different diseases. Occasionally, malignant hypertension arises *de novo* in apparently healthy persons, particularly young black men. The pathogenesis of the vascular injury is unclear, but it may result from endothelial damage as the blood slams into the narrowed small vessels. At sites of vascular injury, plasma constituents leak into injured walls of arterioles (resulting in fibrinoid necrosis), into intima of arteries (causing edematous intimal thickening), and into the subendothelial zone of glomerular capillaries (leading to glomerular consolidation). At these sites of vascular injury, thrombosis can result in focal renal cortical necrosis (infarcts).



A



B



C

FIGURE 16-28. Hypertensive nephrosclerosis. **A.** Three arterioles with hyaline sclerosis (periodic acid-Schiff stain). **B.** Arcuate artery with fibrotic intimal thickening causing narrowing of the lumen (silver stain). **C.** One glomerulus with global sclerosis and one with segmental sclerosis. Note also the tubular atrophy, interstitial fibrosis, and chronic inflammation (silver stain).



PATHOLOGY: The size of the kidneys in malignant hypertensive nephropathy varies from small to enlarged, depending on the duration of pre-existing benign hypertension. The cut surface is mottled red and yellow and occasionally exhibits small cortical infarcts. Microscopically, malignant hypertensive nephropathy is often superimposed on a background of hypertensive nephrosclerosis, with edematous (myxoid, mucoid) intimal expansion in arteries and fibrinoid necrosis of arterioles. Variable glomerular changes range from capillary congestion to consolidation to necrosis (Fig. 16-29). Severe cases show thrombosis and focal ischemic cortical necrosis (infarction). These pathologic changes are identical to those observed in other forms of thrombotic microangiopathy (see below).



CLINICAL FEATURES: Malignant hypertension occurs more often in men than in women, typically around the age of 40 years. Patients suffer from headaches, dizziness, and visual disturbances and may develop overt encephalopathy. Hematuria and proteinuria are frequent. Progressive deterioration of renal function develops if the malignant hypertension persists. Aggressive antihypertensive therapy often controls the disease.

Renovascular Hypertension Follows Narrowing of a Renal Artery



PATHOGENESIS: In patients with renal artery stenosis, hypertension reflects increased production of renin, angiotensin II, and aldosterone. Most (95%) cases are caused by atherosclerosis, which explains why this disorder is twice as common in men as in women and is seen primarily in older age groups. **Fibromuscular dysplasia**, characterized by fibrous and muscular stenosis of the renal artery and vasculitis are less common causes overall but are the most frequent ones in children.

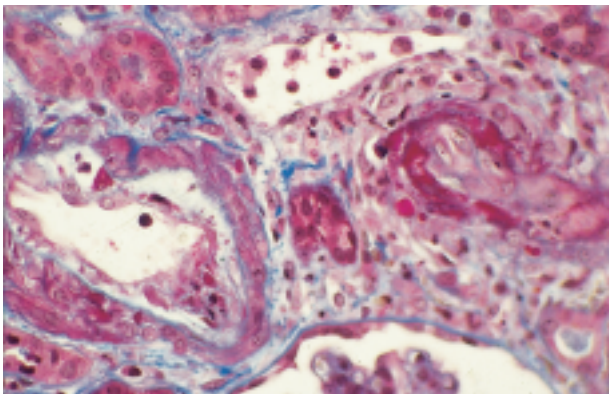


FIGURE 16-29. Malignant hypertensive nephropathy. Red fibrinoid necrosis in the wall of the arteriole on the right and clear edematous expansion in the intima of the interlobular artery on the left from a patient with malignant hypertension (Masson trichrome stain).



PATHOLOGY: No matter what the cause of renal artery stenosis is, the kidney parenchymal changes are the same. The size of the involved kidney is reduced. Glomeruli appear normal but are closer to each other than expected, because the intervening tubules show marked ischemic atrophy without extensive interstitial fibrosis. Many glomeruli lose their attachment to the proximal tubule. The juxtaglomerular apparatus is prominent and reveals hyperplasia and increased granularity.



CLINICAL FEATURES: Renovascular hypertension is characterized by mild-to-moderate blood pressure elevations. A bruit may be heard over the renal artery. In more than half of patients, surgical revascularization, angioplasty, or nephrectomy cures hypertension.

Thrombotic Microangiopathy Refers to Systemic Diseases With Similar Renal Lesions



PATHOGENESIS: Thrombotic microangiopathy has a variety of causes, all leading to endothelial damage that initiates a final common pathway of vascular changes, which result in narrowing of vessel lumina and ischemia. The injured endothelial surfaces promote thrombosis, which worsens ischemia and may cause focal ischemic necrosis. The passage of blood through the injured vessels leads to a nonimmune (Coombs negative) hemolytic anemia, characterized by misshapen and disrupted erythrocytes (schistocytes) and thrombocytopenia. This hematologic syndrome is termed **microangiopathic hemolytic anemia** (See Chapter 20). The kidneys are ubiquitous targets of thrombotic microangiopathies, but other organs may also be injured.



PATHOLOGY: The renal pathologic changes are comparable to those in malignant hypertensive nephropathy, which is a form of thrombotic microangiopathy.



CLINICAL FEATURES: Various clinical presentations and causes allow recognition of different categories of thrombotic microangiopathy. The various clinical disorders share (1) microangiopathic hemolytic anemia, (2) thrombocytopenia, (3) hypertension, and (4) renal failure, although these features are expressed to different degrees.

Hemolytic-Uremic Syndrome

Hemolytic-uremic syndrome (HUS) features microangiopathic hemolytic anemia and acute renal failure, with little or no evidence for significant vascular disease outside the kidneys. *HUS is the most common cause of acute renal failure in*

children. Major causes for HUS are Shiga toxin-producing strains of *E coli*, which are ingested in contaminated food such as poorly cooked hamburger or contaminated vegetable products. The toxin injures endothelial cells, setting in motion the sequence of events described above and resulting in thrombotic microangiopathy. Patients present with hemorrhagic diarrhea and rapidly progressive renal failure.

Thrombotic Thrombocytopenic Purpura

Thrombotic thrombocytopenic purpura displays systemic microvascular thrombosis and is characterized clinically by thrombocytopenia, purpura, fever, and changes in mental status. Unlike HUS, renal involvement is often absent or less important than other organ disease (See Chapter 20 for details).

Cortical Necrosis Is Secondary to Severe Ischemia and Sparing the Medulla

Cortical necrosis affects part or all of the renal cortex. The term **infarct** is used when there is one area (or a few areas) of necrosis caused by occlusion of arteries, whereas **cortical necrosis** implies more widespread ischemic necrosis.



PATHOGENESIS: Vasa recta that supply arterial blood to the medulla arise from juxtamedullary efferent arterioles, proximal to vessels supplying the outer cortex. Thus, occlusion of outer cortical vessels, for example by vasospasm, thrombi, or thrombotic microangiopathy, leads to cortical necrosis and sparing of the medulla. Historically, the most common cause for renal cortical necrosis was premature separation of the placenta (abruptio placentae) in the third trimester of pregnancy. However, renal cortical necrosis can complicate any clinical condition associated with hypovolemic or endotoxic shock. Because all forms of shock are associated with acute tubular necrosis (ATN), it is not surprising that there is an overlap between that condition and cortical necrosis, both clinically and pathologically.



PATHOLOGY: The extent of cortical necrosis varies from patchy to confluent (Fig. 16-30). In the most severely involved areas, all parenchymal elements exhibit coagulative necrosis. The proximal convoluted tubules are invariably necrotic, as are most of the distal tubules. In the adjacent viable portions of the cortex, the glomeruli and distal convoluted tubules are usually unaffected, but many of the proximal convoluted tubules have features of ischemic injury, such as epithelial flattening or necrosis.

With extensive necrosis, the cortex has a marked pallor. The cortex is diffusely necrotic, except for thin rims of vi-



FIGURE 16-30. Renal cortical necrosis. The cortex of the kidney is pale yellow and soft due to diffuse cortical necrosis.

able tissue immediately beneath the capsule and at the corticomedullary junction, which are supplied by capsular and medullary collateral blood vessels, respectively. Patients who survive cortical necrosis may develop striking dystrophic calcification of the necrotic areas.



CLINICAL FEATURES: Severe cortical necrosis manifests as acute renal failure, which initially may be indistinguishable from that produced by ATN. Recovery is determined by the extent of the disease, but there is a significant incidence of hypertension among survivors.

DISEASES OF TUBULES AND INTERSTITIUM

ATN Causes Acute Renal Failure

ATN is a severe, but potentially reversible, renal failure due to impairment of tubular epithelial function caused by ischemia or toxic injury. Because necrosis often is not a prominent feature of ATN, this process is also called acute renal injury.



PATHOGENESIS: Ischemic ATN results from reduced renal perfusion, usually associated with hypotension. Tubular epithelial cells, with their high rate of energy-consuming metabolic activity and numerous organelles, are particularly sensitive to hypoxia and anoxia. Tubular epithelial cells

may be simplified (flattened) but not necrotic in some patients with typical clinical ATN.

Nephrotoxic ATN is caused by chemically induced injury to epithelial cells. Tubular epithelial cells are preferred targets because they absorb and concentrate toxins. The high rate of energy consumption by epithelial cells also makes them susceptible to injury by toxins that perturb oxidative or other metabolic pathways. Hemoglobin and myoglobin can be considered endogenous toxins that can induce ATN (**pigment nephropathy**) when they are present in the urine in high concentrations.

The pathophysiology of ATN appears to involve some or all of the perturbations outlined in Figure 16-31, various combinations of which result in a reduced glomerular filtration rate and tubular epithelial dysfunction.



PATHOLOGY: Ischemic ATN is characterized by swollen kidneys that have a pale cortex and a congested medulla. No pathologic changes are seen in glomeruli or blood vessels. Tubular injury is focal and is most pronounced in the proximal tubules and the thick limbs of the loop of Henle in the outer medulla. The proximal tubules display focal flattening of the epithelium,

with dilation of the lumina and loss of the brush border (epithelial simplification). This results in part from sloughing of the apical cytoplasm, which appears in the distal tubular lumina and urine as brown granular casts. A characteristic feature of **ischemic** ATN is the absence of widespread necrosis of tubular epithelial cells, individual necrotic cells being found within some proximal or distal tubules. These single necrotic cells as well as a few viable cells are shed into the tubular lumen, with resulting focal denudation of tubular basement membrane (Fig. 16-32). Interstitial edema is common. The vasa recta of the outer medulla are congested and frequently contain nucleated cells, which are predominantly mononuclear leukocytes.

Toxic ATN shows more extensive necrosis of tubular epithelium than is usually caused by ischemic ATN (compare Fig. 16-32 and Fig. 16-33). In most cases, however, necrosis is limited to certain tubular segments that are most sensitive to the particular toxin. The most common site of injury is the proximal tubule. ATN due to hemoglobin or myoglobin also has many red-brown tubular casts that are colored by heme pigments.

During the recovery phase of ATN, the tubular epithelium regenerates, with mitoses, increased size of cells and nuclei, and cell crowding. Survivors eventually display complete restoration of normal renal architecture.

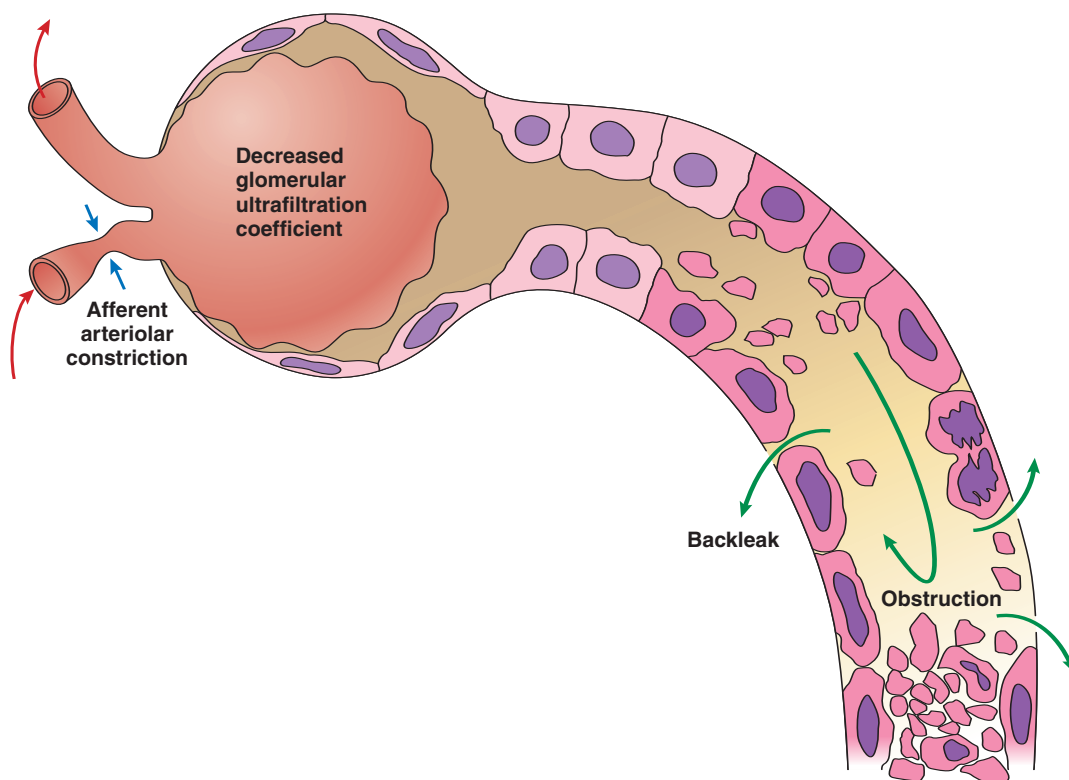


FIGURE 16-31.

Pathogenesis of acute tubular necrosis. Sloughing and necrosis of epithelial cells result in cast formation. The presence of casts leads to obstruction and increased intraluminal pressure, which reduces glomerular filtration. Afferent arteriolar vasoconstriction, caused in part by tubuloglomerular feedback, results in decreased glomerular capillary filtration pressure. Tubular injury and increased intraluminal pressure cause fluid back leakage from the lumen into the interstitium.

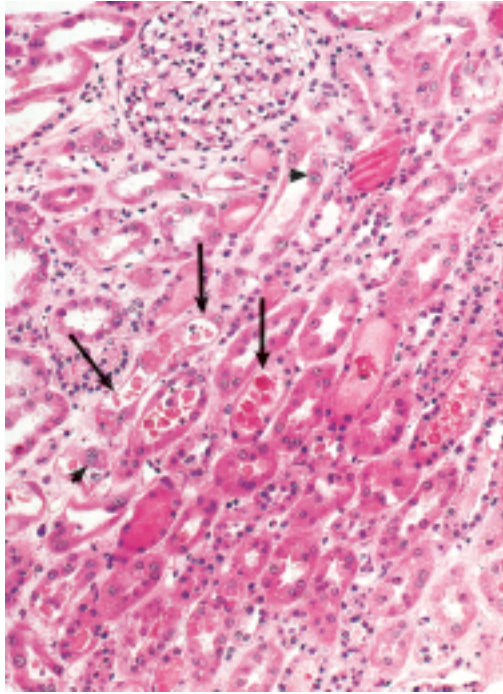


FIGURE 16-32. Ischemic acute tubular necrosis. Necrosis of individual tubular epithelial cells is evident both from focal denudation of the tubular basement membrane (arrows) and from the individual necrotic epithelial cells present in some tubular lumina. Some enlarged, regenerative-appearing epithelial cells are also present (arrowheads). Note the lack of significant interstitial inflammation.



CLINICAL FEATURES: *ATN is the leading cause of acute renal failure.* It manifests as a rapidly rising serum creatinine level, usually associated with decreased urine output (oliguria). Urinalysis demonstrates degenerating epithelial cells and **“dirty brown” granular casts** (acute renal failure casts) with cellular debris rich in cytochrome pigments.

The duration of renal failure in patients with ATN depends on many factors, especially the nature and reversibility of the cause. If the cause is immediately removed after the initiation of the injury, renal function often recovers within 1 to 2 weeks, although it may be delayed for months.

Pyelonephritis Refers to Bacterial Infection of the Kidney

Acute Pyelonephritis



PATHOGENESIS: Gram-negative bacteria from the feces, most commonly *E. coli*, cause 80% of acute pyelonephritis. Infection reaches the kidney by ascending through the urinary tract, a process that depends on several factors:

- Bacterial urinary infection
- Reflux of infected urine up the ureters into the renal pelvis and calyces

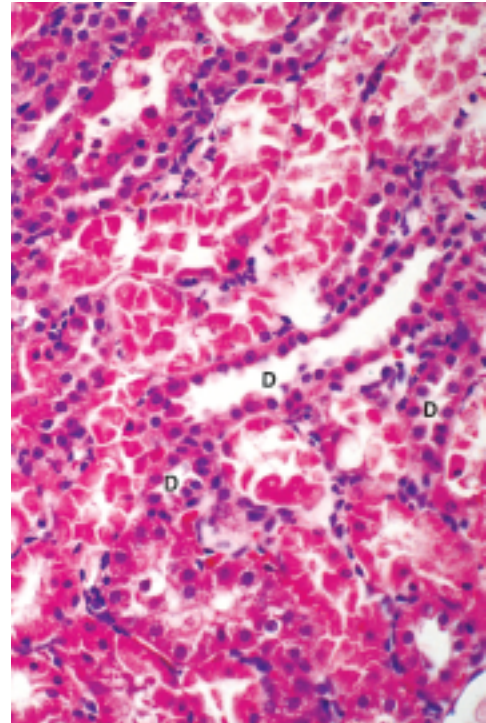


FIGURE 16-33. Toxic acute tubular necrosis due to mercury poisoning. There is widespread necrosis of proximal tubular epithelial cells, with sparing of distal and collecting tubules (D). Interstitial inflammation is minimal.

- Bacterial entry through the papillae into the renal parenchyma

Bladder infection precedes acute pyelonephritis. It is more common in females because of a short urethra, lack of antibacterial prostatic secretions, and facilitation of bacterial migration by sexual intercourse.

Under some circumstances, the residual urine volume (normally 2 to 3 mL) is increased (e.g., in prostatic obstruction or in an atonic bladder). As a result, the bladder contents are not sufficiently diluted with sterile urine from the kidneys to prevent bacterial accumulation. Diabetic glycosuria also predisposes to infection by providing a rich medium for bacterial growth.

Bacteria in bladder urine usually do not gain access to the kidneys. The ureter commonly inserts into the bladder wall at a steep angle (Fig. 16-34) and in its most distal portion courses parallel to the bladder wall between the mucosa and muscularis. The intravesicular pressure produced by micturition occludes the distal ureteral lumen, preventing urinary reflux. In many individuals who are particularly susceptible to pyelonephritis, an abnormally short passage of the ureter within the bladder wall is associated with an angle of insertion that is more perpendicular to the mucosal surface of the bladder. Thus, on micturition, rather than occluding the lumen, intravesicular pressure forces urine into the patent ureter. This reflux is powerful enough to force the urine into the renal pelvis and calyces.

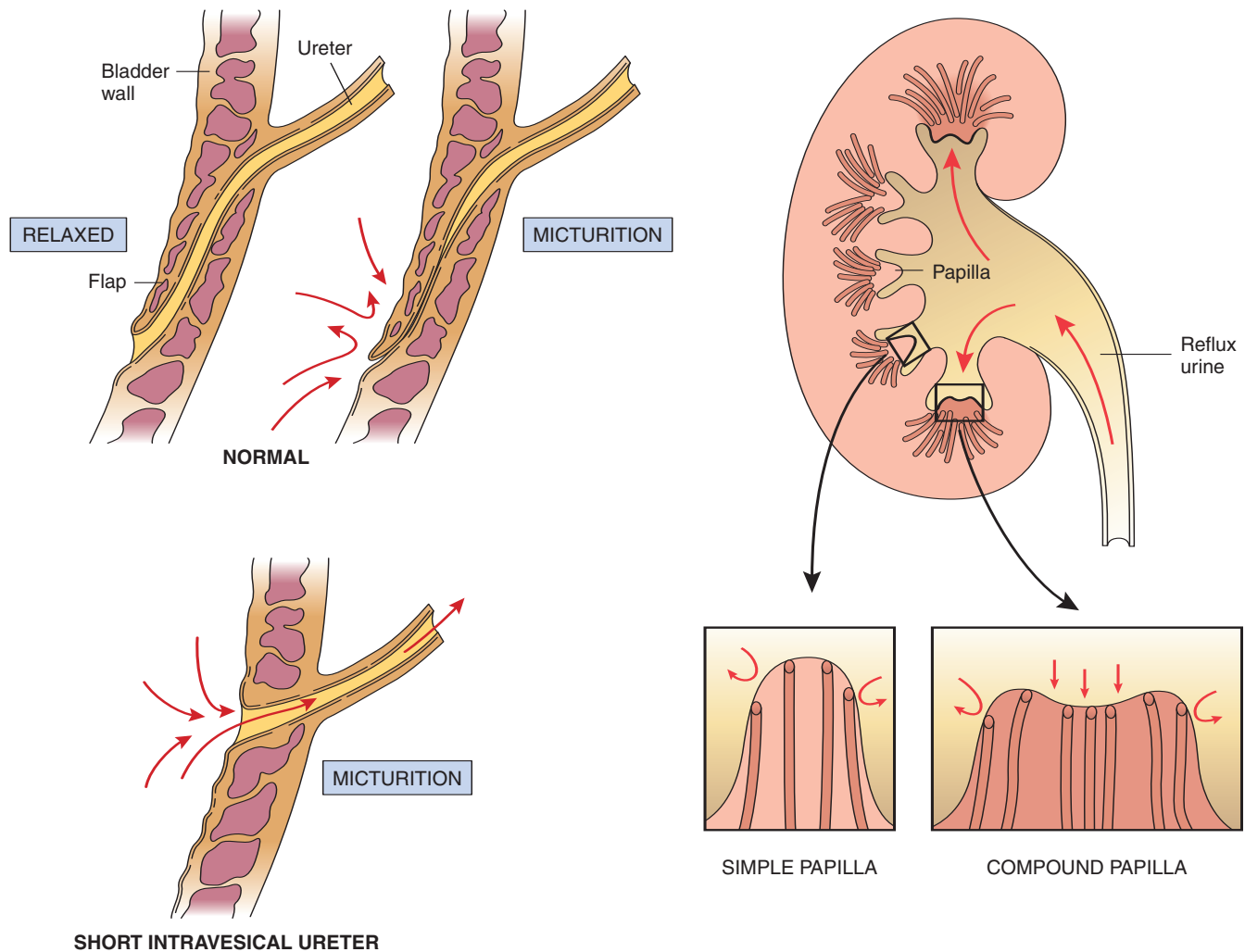


FIGURE 16-34. Anatomical features of the bladder and kidney in pyelonephritis caused by ureterovesical reflux. In the normal bladder, the distal portion of the intravesical ureter courses between the mucosa and the muscularis, forming a mucosal flap. On micturition, the elevated intravesicular pressure compresses the flap against the bladder wall, thereby occluding the lumen. Persons with a congenitally short intravesical ureter have no mucosal flap, because the angle of entry of the ureter into the bladder approaches a right angle. Thus, micturition forces urine into the ureter. In the renal pelvis, simple papillae of the central calyces are convex and do not readily allow reflux of urine. By contrast, the peripheral compound papillae are concave and permit entry of refluxed urine.

The simple papillae of the central calyces are convex and do not readily admit reflux urine (see Fig. 16-34). By contrast, the concave shapes of peripheral compound papillae allow easier access to the collecting system. However, if the pressure is prolonged, as in obstructive uropathy, even simple papillae are eventually vulnerable to the retrograde entry of urine. From the collecting tubules, bacteria gain access to the interstitial tissue and other tubules of the kidney.

In addition to ascending through urine, bacteria and other pathogens can gain access to renal parenchyma through the circulation. For example, gram-positive organisms, such as staphylococci, can disseminate from an infected valve in bacterial endocarditis and establish a focus of infection in the kidney. The kidney is commonly involved in miliary tuberculosis. Fungi, such as *Aspergillus*, can seed the kidney in an immunocompromised host. Hematogenous infections of the kidney preferentially affect the cortex.



PATHOLOGY: The kidneys of acute pyelonephritis have small white abscesses on the subcapsular surface and on cut surfaces. Pelvic and calyceal urothelium may be hyperemic and covered by purulent exudate. *Acute pyelonephritis is often focal, and much of the kidney may appear normal.* Most infections involve only a few papillary systems. Microscopically, the parenchyma, particularly the cortex, typically shows extensive focal destruction by the inflammatory process, although vessels and glomeruli often are preferentially preserved. Inflammatory infiltrates mainly contain neutrophils, which often fill tubules and especially collecting ducts (Fig. 16-35). In severe cases of acute pyelonephritis, necrosis of the papillary tips may occur or infection may extend beyond the renal capsule to cause a perinephric abscess.

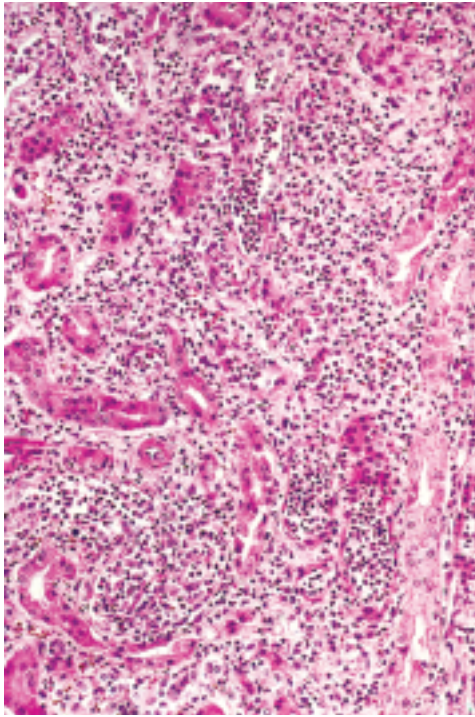


FIGURE 16-35. Acute pyelonephritis. An extensive infiltrate of neutrophils is present in the collecting tubules and interstitial tissue.

CLINICAL FEATURES: Symptoms of acute pyelonephritis include fever, chills, sweats, malaise, flank pain, and costovertebral angle tenderness. Leukocytosis with neutrophilia is common. Differentiating upper from lower urinary tract infection is

often clinically difficult, but the finding of **leukocyte casts** in the urine supports a diagnosis of pyelonephritis.

Chronic Pyelonephritis



PATHOGENESIS: Chronic pyelonephritis is caused by recurrent and persistent bacterial infection secondary to urinary tract obstruction, urine reflux, or both. In chronic pyelonephritis caused by reflux or obstruction, the medullary tissue and overlying cortex are preferentially injured by recurrent acute and chronic inflammation. Progressive atrophy and scarring ensue, with resultant contraction of the involved papillary tip (or sloughing if there is papillary necrosis) and thinning of the overlying cortex. *This process results in the distinctive gross appearance of a broad depressed area of cortical fibrosis and atrophy overlying a dilated calyx (caliectasis) (Fig. 16-36).*



PATHOLOGY: Chronic pyelonephritis is one of many causes of the microscopic pattern of injury termed **chronic tubulointerstitial nephritis**. The gross appearance of chronic pyelonephritis is more distinctive. *Only chronic pyelonephritis and analgesic nephropathy produce a combination of caliectasis with overlying corticomedullary scarring.* Microscopically, the scars have atrophic dilated tubules surrounded by interstitial fibrosis and infiltrates of chronic inflammatory cells (Fig. 16-37). The most characteristic (but not specific) tubular change is severe epithelial atrophy, with diffuse, eosinophilic, hyaline casts. Such

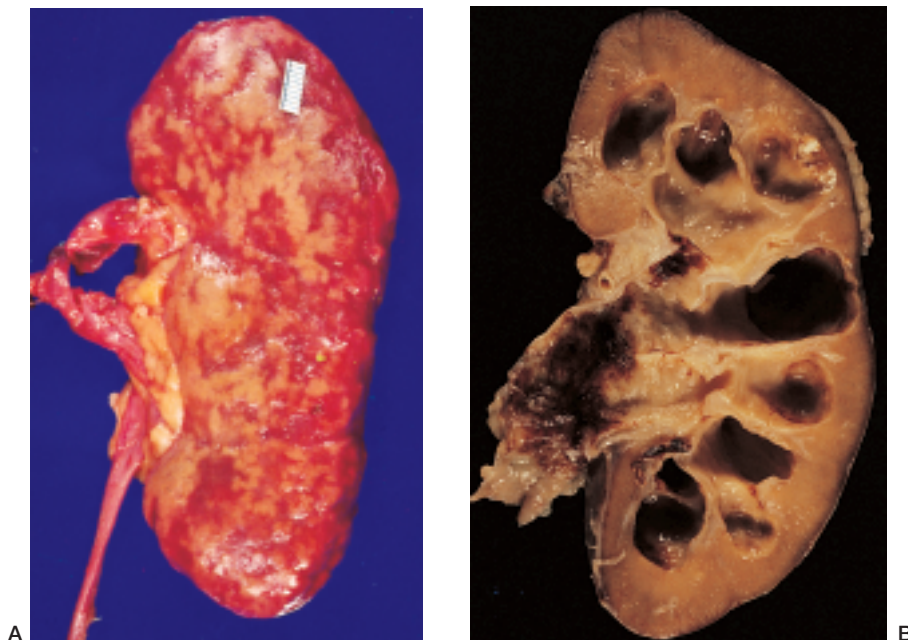


FIGURE 16-36. Chronic pyelonephritis. **A.** The cortical surface contains many irregular, depressed scars (reddish areas). **B.** There is marked dilation of calyces (caliectasis) caused by inflammatory destruction of papillae, with atrophy and scarring of the overlying cortex.

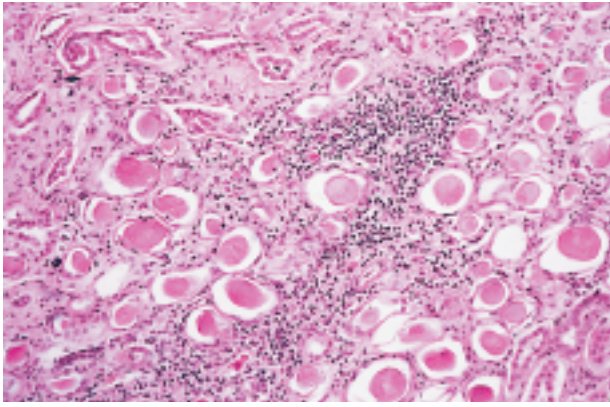


FIGURE 16-37. A light micrograph shows tubular dilation and atrophy, with many tubules containing eosinophilic hyaline casts resembling the colloid of thyroid follicles (so-called thyroidization). The interstitium is scarred and contains a chronic inflammatory cell infiltrate.

tubules, which are “pinched-off” spherical segments, resemble colloid-containing thyroid follicles, a pattern called “thyroidization.” Glomeruli may be completely uninvolved, may show periglomerular fibrosis, or may be sclerotic.

CLINICAL FEATURES: Most patients with chronic pyelonephritis have episodic symptoms of urinary tract infection or acute pyelonephritis, such as recurrent fever and flank pain. Some patients have a silent course until end-stage renal disease develops. Urinalysis shows leukocytes, and imaging studies reveal caliectasis and cortical scarring.

Analgesic Nephropathy Results From Chronic Overdosage of Drugs

Patients with analgesic nephropathy typically have consumed more than 2 kg of analgesic compounds, often in combinations, such as aspirin and acetaminophen. Acetaminophen poses a higher risk for inducing nephropathy than aspirin or nonsteroidal anti-inflammatory drugs. The basis for analgesic nephropathy is not clear. Possibilities include direct nephrotoxicity or ischemic damage as a result of drug-induced vascular changes, or both.

PATHOLOGY: Medullary injury with papillary necrosis appears to be the earliest event in analgesic nephropathy, followed by atrophy, chronic inflammation, and scarring of the overlying cortex. Early parenchymal changes are confined to the papillae and inner medulla and consist of focal thickening of tubular and capillary basement membranes, interstitial fibrosis, and focal coagulative necrosis. Eventually, the entire papilla becomes necrotic (**papillary necrosis**), often remaining in place as a structureless mass. Dystrophic calcification of such necrotic papillae is common. There is secondary tubular atrophy, interstitial fibrosis, and chronic inflammation in the overlying cortex.



CLINICAL FEATURES: Signs and symptoms occur only in the late stages of analgesic nephropathy and include an inability to concentrate the urine, distal tubular acidosis, hematuria, hypertension, and anemia. Sloughing of necrotic papillary tips into the renal pelvis may result in colic as they pass through the ureters. Progressive renal failure often develops and may lead to end-stage renal disease.

Drug-Induced (Hypersensitivity) Acute Tubulointerstitial Nephritis Is a Cell-Mediated Immune Response



PATHOGENESIS: Acute, drug-induced, tubulointerstitial nephritis is characterized histologically by infiltrates of activated T lymphocytes and eosinophils, a pattern that indicates a type IV cell-mediated immune reaction. Drugs most commonly implicated include nonsteroidal anti-inflammatory drugs, diuretics and certain antibiotics, especially β -lactam antibiotics, such as synthetic penicillins and cephalosporins.



PATHOLOGY: Microscopically, there is patchy infiltration of the cortex and (to a much lesser extent) medulla by lymphocytes and a small number of eosinophils (5% to 10% of the total leukocytes in the tissue). Neutrophils are rare, and their presence should raise suspicion of pyelonephritis or hematogenous bacterial infection. Foci of granulomatous inflammation may be present, especially in the later phase of the disease. Proximal and distal tubules are focally invaded by white blood cells (“tubulitis”). Glomeruli and vessels are not inflamed.



CLINICAL FEATURES: Acute tubulointerstitial nephritis usually manifests as acute renal failure, typically about 2 weeks after drug administration is started. The urine contains erythrocytes, leukocytes (including eosinophils), and sometimes leukocyte casts. Tubular defects are common, including sodium wasting, glucosuria, aminoaciduria, and renal tubular acidosis. Systemic allergic symptoms such as fever and rash may also be present. Most patients recover fully within several weeks or months if the drug is discontinued.

Light-Chain Cast Nephropathy May Complicate Multiple Myeloma

Light-chain cast nephropathy is renal injury caused by monoclonal immunoglobulin light chains in the urine, which produce tubular epithelial injury and numerous tubular casts.



PATHOGENESIS: Light-chain cast nephropathy is the most common form of renal disease associated with multiple myeloma and is caused by glomerular filtering of circulating light chains. At the acidic pH typical of urine, the light chains bind to Tamm-Horsfall glycoproteins, which are secreted by distal tubular epithelial cells and form casts. Renal dysfunction results from the toxic effects of free light chains on tubular epithelial cells and obstruction from the casts. The molecular structure of light chains determines whether they will induce disease by causing light-chain cast nephropathy, AL amyloidosis, or light-chain deposition disease. Occasional patients show several of these renal diseases.



PATHOLOGY: The characteristic tubular lesion exhibits numerous dense, hyaline casts in the distal tubules and collecting ducts. These casts are brightly eosinophilic and glassy (hyaline) and often have fractures and angular borders. They may even have a crystalline appearance. Casts may elicit foreign body reactions, with macrophages and multinucleated giant cells. Interstitial chronic inflammatory infiltrates, as well as interstitial edema, typically accompany the tubular lesions.



CLINICAL FEATURES: Light-chain cast nephropathy may manifest as either acute or chronic renal failure. Proteinuria is usually present, although not necessarily in the nephrotic range and most often consists predominantly of immunoglobulin light chains. If a patient has nephrotic-range proteinuria with multiple myeloma, AL amyloidosis or light-chain deposition disease is more likely to occur than light-chain cast nephropathy.

Urate Nephropathy Displays Urate Crystals in the Tubules and Interstitium

Any condition with elevated blood levels of uric acid may cause urate nephropathy. The classic chronic disease in this category is primary gout (see Chapter 26).



PATHOGENESIS: Chronic urate nephropathy caused by gout is characterized by tubular and interstitial deposition of crystalline monosodium urate. **Acute urate nephropathy** can be caused by increased cell turnover. For example, chemotherapy for malignant neoplasms results in a sudden increase in blood uric acid because of the massive necrosis of cancer cells (**tumor lysis syndrome**). Acute renal failure reflects the obstruction of the collecting ducts by precipitated crystals of uric acid, a re-

sult of increased concentrations of uric acid in the acidic pH of the urine. Conditions that interfere with excretion of uric acid can also result in hyperuricemia (e.g., chronic intake of certain diuretics).



PATHOLOGY: In acute urate nephropathy, the precipitated uric acid in the collecting ducts is seen grossly as yellow streaks in the papillae. Histologically, the tubular deposits appear amorphous, but in frozen sections, birefringent crystals are apparent. The tubules proximal to the obstruction are dilated. Penetration of collecting ducts by uric acid crystals may provoke a foreign-body giant cell reaction.

The basic disease process of chronic urate nephropathy is similar to that of the acute form, but the prolonged course results in more substantial deposition of urate crystals in the interstitium, interstitial fibrosis, and cortical atrophy.



CLINICAL FEATURES: Acute urate nephropathy manifests as acute renal failure, whereas chronic urate nephropathy causes chronic renal tubular defects. Although histologic renal lesions are found in most persons with chronic gout, fewer than half show significant compromise of renal function.

RENAL STONES (NEPHROLITHIASIS AND UROLITHIASIS)

*Nephrolithiasis and urolithiasis are stones within the collecting system of the kidney (**nephrolithiasis**) or elsewhere in the collecting system of the urinary tract (**urolithiasis**).* Renal pelvis and calyces are common sites for calculi to form and accumulate. For unknown reasons, renal stones are more common in men than in women. They vary in size from gravel (<1 mm in diameter) to large stones that dilate the entire renal pelvis.

- **Calcium stones:** Most (75%) kidney stones contain calcium complexed with oxalate or phosphate or a mixture of these anions.
- **Infection stones:** About 15% of stones are caused by infection. Such stones are the most likely to be associated with clinical symptoms. In the presence of urea-splitting bacteria, usually *Proteus* or *Providencia* species, the resulting alkaline urine favors precipitation of magnesium ammonium phosphate (**struvite**) and calcium phosphate (**apatite**). These stones vary from hard to soft and friable. Infection stones occasionally fill the pelvis and calyces to form a cast of these spaces, referred to as a **staghorn calculus** (Fig. 16-38).



FIGURE 16-38. Staghorn calculi. The kidney shows hydronephrosis and stones that are casts of the dilated calyces.

- **Uric acid stones:** These stones occur in 25% of patients with hyperuricemia and gout, but most patients with uric acid stones do not have either condition (**idiopathic urate lithiasis**).
- **Cystine stones:** Only 1% of stones overall are of this type, but they represent a significant proportion of childhood calculi and occur exclusively with hereditary cystinuria.

Kidney stones may be well tolerated, but in some cases, they lead to severe hydronephrosis and pyelonephritis. Moreover, they can erode the mucosa and cause hematuria. Passage of a stone into the ureter causes excruciating flank pain, termed **renal colic**.

OBSTRUCTIVE UROPATHY AND HYDRONEPHROSIS

Obstructive uropathy is caused by structural or functional abnormalities in the urinary tract that impede urine flow, which may cause renal dysfunction (obstructive nephropathy) and dilation of the collecting system (hydronephrosis). The causes of urinary tract obstruction are discussed in detail in Chapter 17.



PATHOLOGY: The most prominent microscopic finding in early hydronephrosis is dilation of the collecting ducts, followed by dilation of proximal and distal convoluted tubules. Eventually, the proximal tubules become widely dilated, and loss of tubules is com-

mon. Glomeruli are usually spared. Grossly, progressive dilation of the renal pelvis and calyces occurs, and atrophy of the renal parenchyma ensues (Fig. 16-39). In the presence of hydronephrosis, the kidney is more susceptible to pyelonephritis, which causes additional injury.



CLINICAL FEATURES: Bilateral acute urinary tract obstruction results in acute renal failure (**postrenal acute renal failure**). Unilateral obstruction is frequently asymptomatic. Left untreated, an obstructed kidney undergoes atrophy. In the case of bilateral obstruction, chronic renal failure ensues.

RENAL TRANSPLANTATION

Renal transplantation is the treatment of choice for most patients with end-stage renal disease. The major obstacle is immunologic rejection, but recurrence of the disease that destroyed the native kidneys and nephrotoxicity from immunosuppressive drugs also injure the renal allograft. For additional details see Chapter 4. The same disease that led to renal failure in native kidneys can recur in a renal transplant.

MALIGNANT TUMORS OF THE KIDNEY

Wilms' Tumor (Nephroblastoma) Is Composed of Embryonal Elements

Wilms' tumor is a malignant neoplasm of embryonal nephrogenic elements composed of mixtures of blastemal, stromal, and epithelial tissue. It is the most frequent abdominal solid tumor in children, with a prevalence of 1 in 10,000.



PATHOGENESIS: In most (90%) cases, Wilms' tumor is sporadic and unilateral. About 10% of sporadic cases of Wilms' tumor

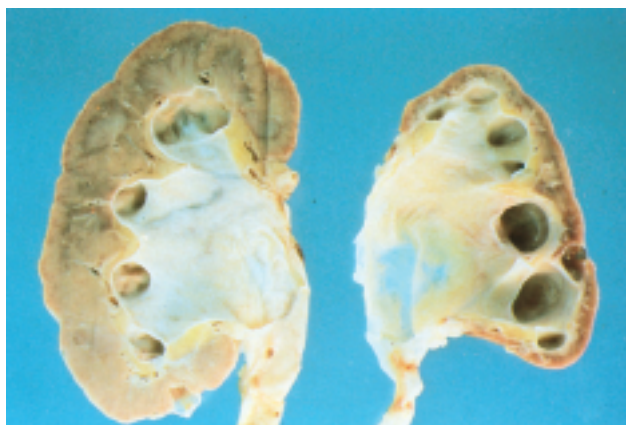


FIGURE 16-39. Hydronephrosis. Bilateral urinary tract obstruction has led to conspicuous dilation of the ureters, pelvis, and calyces. The kidney on the right shows severe parenchymal atrophy.

are associated with defects of **WT1**, the Wilms' tumor gene located on chromosome 11 (11p13). WT1 is a tumor-suppressor gene that regulates transcription of several other genes, including IGF-2 and PDGF. WT1 protein also forms a complex with the p53 protein. Presumably the presence of a germline mutation and loss of heterozygosity at the WT1 locus are associated with tumor formation in a manner similar to the pathogenesis of hereditary retinoblastoma (see Chapter 5). Two uncommon congenital syndromes associated with Wilms' tumor and other developmental defects—WAGR (**W**ilms **A**niridia, **G**enitourinary anomalies, and mental **R**etardation) and Denys-Drash syndrome are also associated respectively with either a deletion of one allele of WT1 or specific mutations within the gene having a dominant negative effect.

Less than 10% of sporadic Wilms' tumors exhibit abnormalities at the WT1 locus suggesting that other genes play a role in their genesis. A second gene, WT2, close to, but distinct from the WT1 locus is implicated in some sporadic tumors. Another uncommon congenital disease, Beckwith-Wiedemann Syndrome also features Wilms' tumor and other abnormalities and is also associated with defects at the WT2 locus. The genetics of defects at the locus is complex and is likely to involve genomic imprinting. Some cases of Beckwith-Wiedemann Syndrome have demonstrated paternal uniparental isodisomy (see Chapter 6).



PATHOLOGY: Wilms' tumor tends to be large when detected, with a bulging, pale tan, cut surface enclosed within a thin rim of renal cortex and capsule (Fig. 16-40). Histologically, the tumor is composed of elements that resemble normal fetal tissue (Fig. 16-41), including (1) metanephric blastema, (2) immature stroma (mesenchymal tissue), and (3) immature epithelial elements.

Although most Wilms' tumors contain all three elements in varying proportions, occasionally they contain only two elements or even only one. The component corresponding to blastema is composed of small ovoid cells with scanty cytoplasm, growing in nests and trabeculae. The epithelial component appears as small tubular structures. In some cases, tissues resembling immature glomeruli are found. The stroma between the other elements is composed of spindle cells, which are mostly undifferentiated but occasionally display smooth muscle or fibroblast differentiation.



CLINICAL FEATURES: Wilms' tumor usually presents between 1 and 3 years of age, and 98% of cases occur before 10 years of age. Most often, the diagnosis is made after recognition of an abdominal mass.

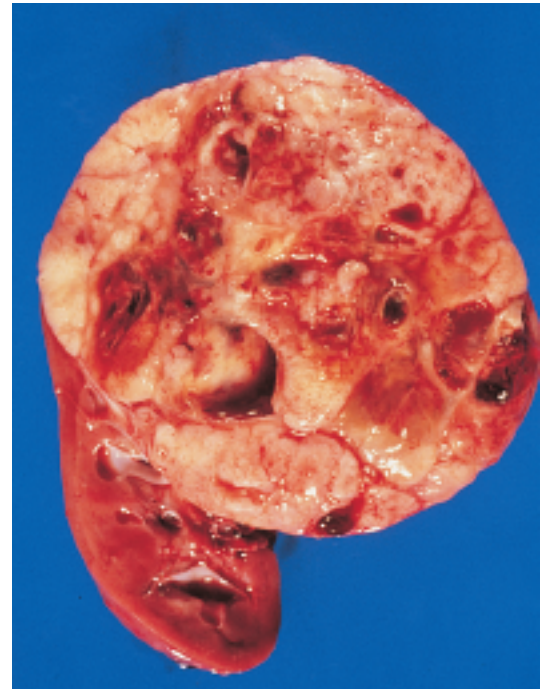


FIGURE 16-40. Wilms' tumor. A cross-section of a pale tan neoplasm attached to a residual portion of the kidney.

Additional manifestations include abdominal pain, intestinal obstruction, hypertension, hematuria, and symptoms of traumatic tumor rupture.

A number of histologic and clinical parameters have been used with varying success to predict the behavior of

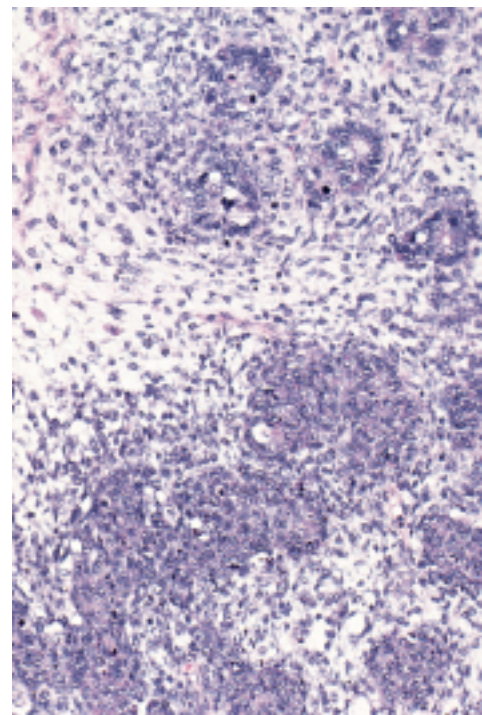


FIGURE 16-41. Wilms' tumor (nephroblastoma). This photomicrograph of the tumor shows highly cellular areas composed of undifferentiated blastema, loose stroma containing undifferentiated mesenchymal cells, and immature tubules.

Wilms' tumors. Patients younger than 2 years of age tend to have a better prognosis. Chemotherapy and radiation therapy, combined with surgical resection, have dramatically improved the outlook of patients with this tumor, and a long-term survival rate of 90% is reported.

Renal Cell Carcinoma (RCC) Is the Most Common Primary Cancer of the Kidney

Renal cell carcinoma (RCC) is a malignant neoplasm of renal tubular or ductal epithelial cells. It accounts for 80% of all renal cancers and more than 30,000 cases per year in the United States.



PATHOGENESIS: Most cases of RCC are sporadic, and virtually all such cases are associated with loss of heterozygosity of the tumor suppressor gene VHL, which is located on chromosome 3p. Mutations in VHL are found in more than half of such sporadic RCC tumors. Two uncommon forms of hereditary RCC, **autosomal dominant RCC** and **von Hippel-Lindau disease** (VHL, an autosomal dominant cancer syndrome) are associated with chromosomal translocations involving 3p. The latter disease has mutations in the above-mentioned VHL gene itself. A third uncommon form of hereditary RCC, **hereditary papillary RCC**, shows no association with the VHL gene.

Tobacco smoking or chewing is associated with an increased risk of RCC, and one third of these tumors are linked to tobacco use. Both inherited and acquired cystic diseases of the kidney may be complicated by development of RCC, especially papillary RCC. The cancer has also been tied to analgesic nephropathy.



FIGURE 16-42. Clear cell renal cell carcinoma. The kidney contains a large irregular neoplasm with a variegated cut surface. Yellow areas correspond to lipid-containing cells.

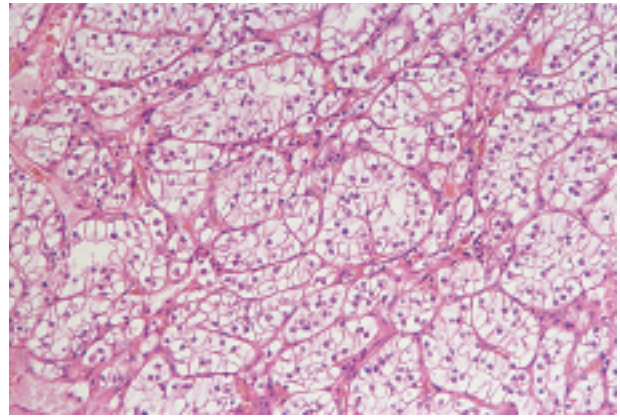


FIGURE 16-43. Clear cell renal cell carcinoma. Photomicrograph showing islands of neoplastic cells with abundant clear cytoplasm.



PATHOLOGY: There are pathologic variants of RCC that reflect differences in histogenesis and predict different outcomes.

Clear cell RCC is the most common type and arises from proximal tubular epithelial cells. It is typically yellow-orange and often shows conspicuous focal hemorrhage and necrosis (Fig. 16-42). The tumors are solid or focally cystic. The clear cytoplasm of the neoplastic cells (Fig. 16-43) reflects the removal of abundant cytoplasmic lipids and glycogen during tissue processing. The cells are often arranged in round or elongated collections demarcated by a network of delicate vessels, and little cellular or nuclear pleomorphism is present.



CLINICAL FEATURES: The incidence of RCC peaks in the sixth decade and is twice as frequent in men as in women. *The classic clinical triad of hematuria, flank pain, and a palpable abdominal mass occurs in less than 10% of patients. Hematuria is the single most common presenting sign.* Often, a patient with RCC initially presents with symptoms due to a metastasis. RCC is a potential source of ectopic hormone production and is frequently associated with fever and paraneoplastic symptoms.

The prognosis for RCC is influenced by many factors, including tumor size, extent of invasion and metastasis, histologic type, and nuclear grade. The 1-year overall survival rate after nephrectomy for clear cell RCC is 50%. Tumor stage is the most important prognostic factor. The 5-year survival rate is 90% if the RCC has not extended beyond the renal capsule, survival drops to 30% if there are distant metastases. The tumor spreads most frequently to the lungs and bones.

Transitional Cell Carcinoma

Between 5% and 10% of primary neoplasms of the kidney are transitional cell carcinomas of the renal pelvis or calyces (see Chapter 17).

AQ1: Author: Please confirm all cross-referencing in the chapter (cross-referenced chapters and figures).