**Figure 19-11** Pancreatic mucinous cystadenoma. *A*, Cross-section through a mucinous multiloculated cyst in the tail of the pancreas. The cysts are large and filled with tenacious mucin. *B*, The cysts are lined by columnar mucinous epithelium, and a dense "ovarian" stroma is noted.
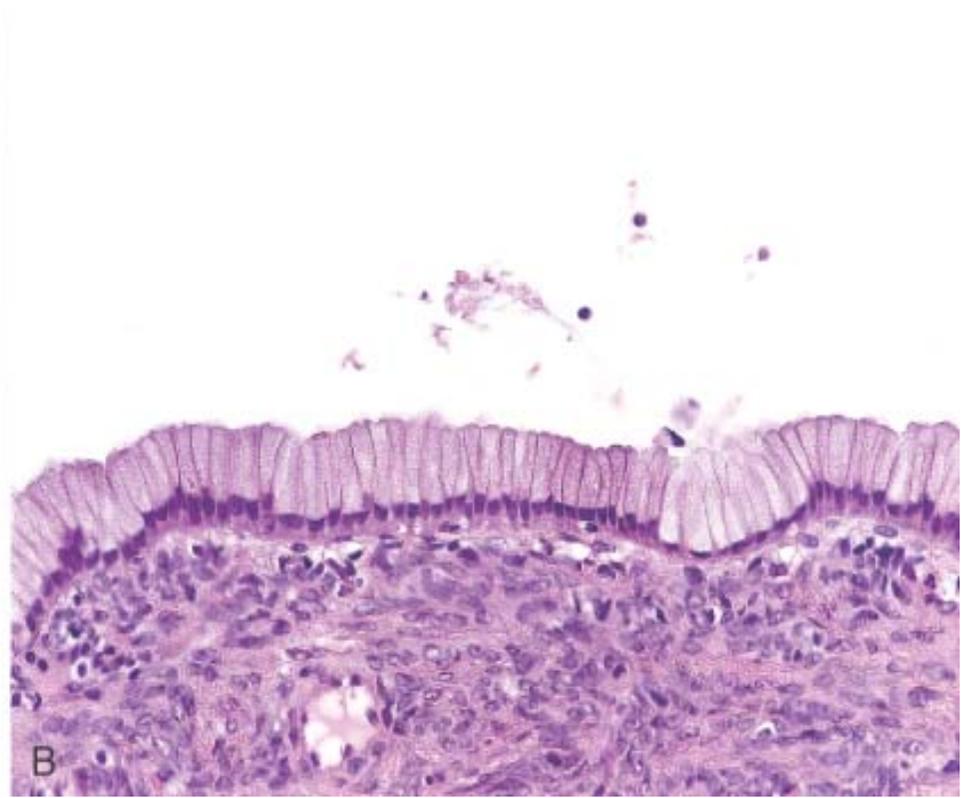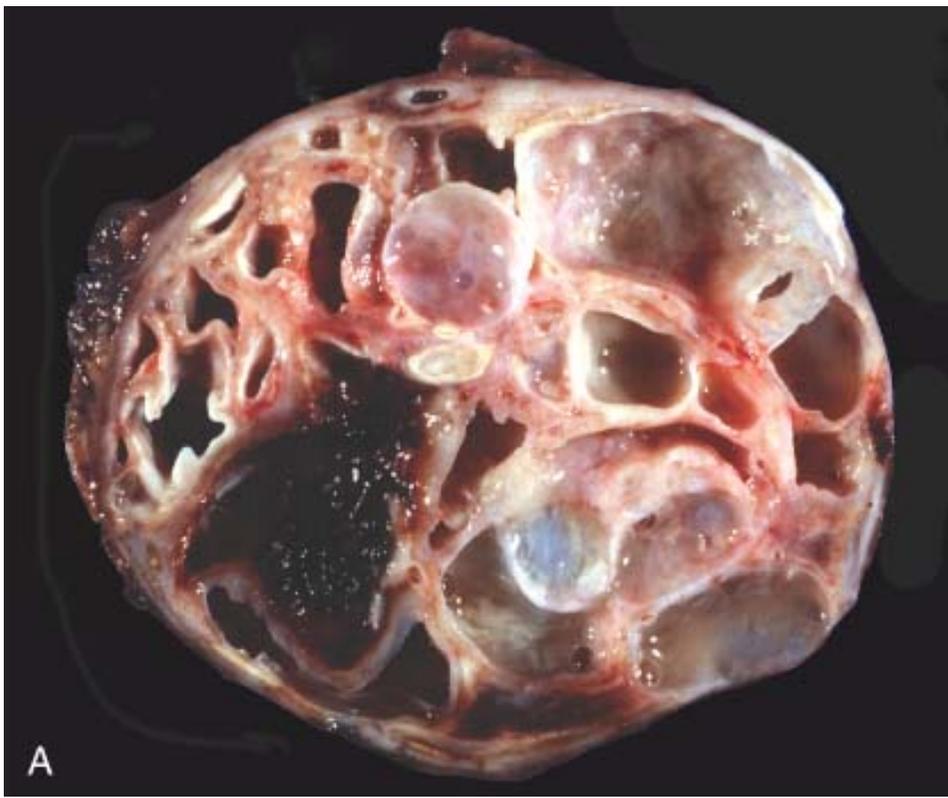
**Figure 19-12** Intraductal papillary mucinous neoplasm. *A*, Cross-section through the head of the pancreas showing a prominent papillary neoplasm distending the main pancreatic duct. *B*, The papillary mucinous neoplasm involved the main pancreatic duct (*left*) and extending down into the smaller ducts and ductules (*right*).
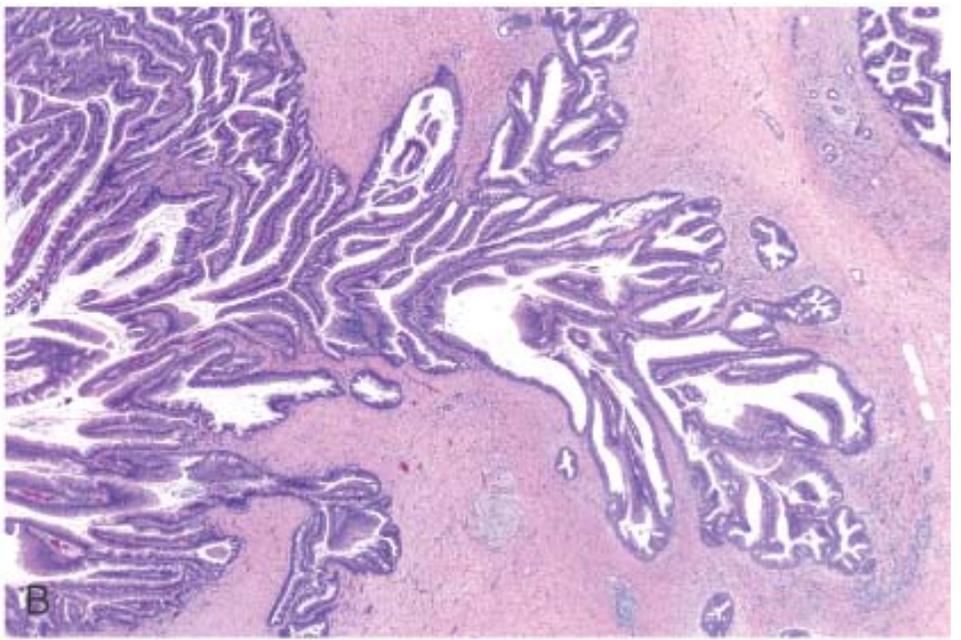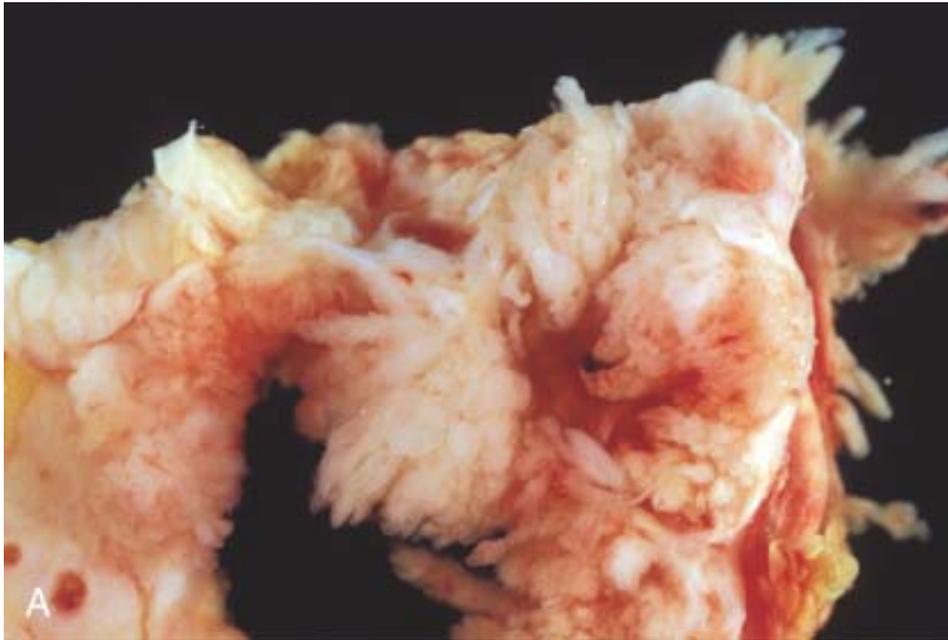
**Figure 19-13** Progression model for the development of pancreatic cancer. It is postulated that telomere-shortening, and mutations of the oncogene *K-RAS* occur at early stages, that inactivation of the *p16* tumor suppressor gene occurs at intermediate stages, and the inactivation of the *p53*, *SMAD4* (*DPC4*), and *BRCA2* tumor suppressor genes occur at late stages. It is important to note that while there is a general temporal sequence of changes, the accumulation of multiple mutations is more important than their occurrence in a specific order. *(Adapted from Wilentz RE, lacobuzio-Donahue CA, et al: Loss of expression of DPC4 in pancreatic intraepithelial neoplasia: evidence that DPC4 inactivation occurs late in neoplastic progression. Cancer Res 2000; 60:2002.)*



NORMAL    PanIN-1A    PanIN-1B    PanIN-2    PanIN-3    INVASIVE CARCINOMA

Telomere shortening

Mutations of K-*RAS*

Inactivation of *p16*

Inactivation of *p53*
SMAD4
BRCA2
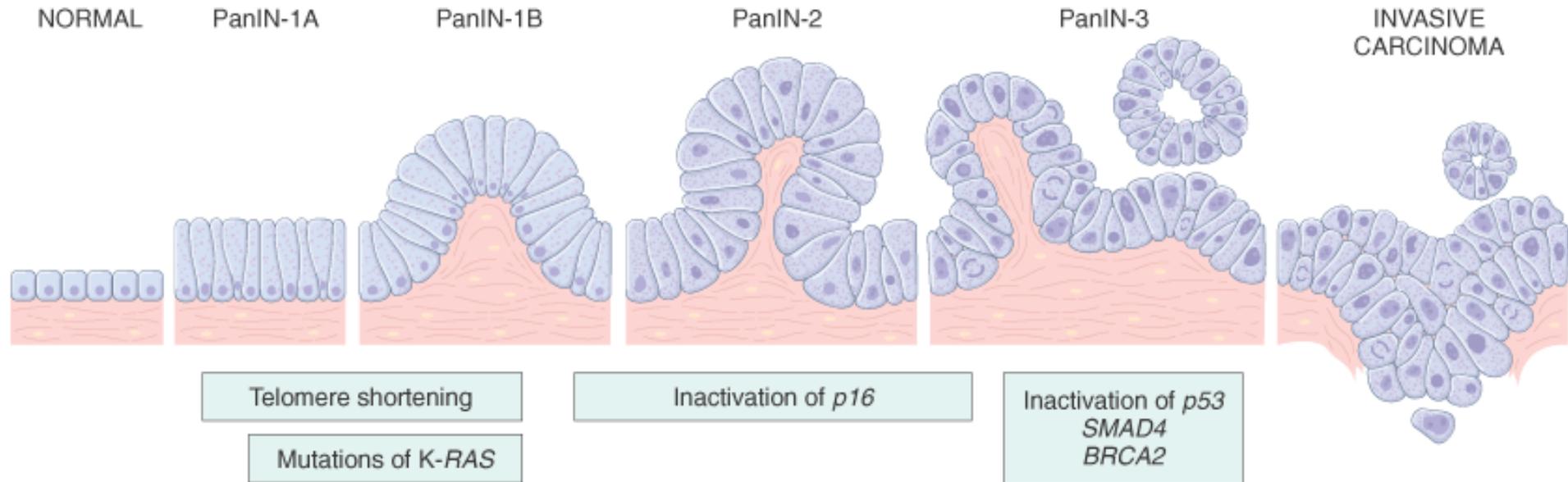
**TABLE 19-2** -- Molecular Alterations in Invasive Pancreatic Adenocarcinoma

| Gene (Chromosomal Region) | Percent of Tumors with Genetic Alteration |
|---|---|
| K-*ras* (12p) | >90% |
| *p16 CDKN2A* (9p) | >95% |
| *p53* (17p) | 50–70% |
| *SMAD4* (18q) | 55% |
| *AKT2* (19q) | 10–20% |
| *MYB* (6q) | 10% |
| *AIB1* (20q) | 10% |
| *BRCA2* (13q) | 7–10% |
| *LKB1/STK11* (19p) | <5% |
| *MKK4* (17p) | <5% |
| *TGFβ-R1* (9q) or *TGFβ-R2* (3p) | <5% |

| *RB1* (13q) | <5% |
|---|---|

**K-RAS.**

The *K-RAS* gene (chromosome 12p) is the most frequently altered oncogene in pancreatic cancer. This oncogene is activated by point mutation in 80% to 90% of pancreatic cancers. These point mutations impair the intrinsic GTPase activity of the K-*ras* gene product, resulting in a protein that is constitutively active. Ras in turn activates several intracellular signal transduction pathways that, among other effects, culminate in the activation of the transcription factors fos and jun.

**p16.**

The *p16* gene (chromosome 9p) is the most frequently inactivated tumor suppressor gene in pancreatic cancer.[62] It is inactivated in 95% of cases. The *p16* gene product, p16, plays a critical role in the control of the cell cycle, and inactivation of p16 abrogates an important cell cycle checkpoint.

**SMAD4.**

The *SMAD4* tumor suppressor gene (chromosome 18q) is inactivated in 55% of pancreatic cancers.[63] *SMAD4*, also known as *DPC4*, codes for a protein that plays an important role in signal transduction from the transforming growth factor-β (TGF-β) family of cell-surface receptors. The normal function of *SMAD4* is most likely to suppress growth and promote apoptosis. Loss of *SMAD4* therefore abrogates two important controls on cell population. *SMAD4* is only rarely inactivated in other cancer types.

**p53.**

Inactivation of the *p53* tumor suppressor gene (chromosome 17p) is seen in 50% to 70% of pancreatic cancers.[64] The *p53* gene product is a nuclear DNA-binding protein that acts both as a cell cycle checkpoint and as an inducer of cell death (apoptosis).

**Other Genes.**

A growing number of less common, but nonetheless important, genetic loci have been reported to be damaged in pancreatic cancer ( Table 19-2 ). For example, the *AKT2* gene (chromosome 19q) is amplified in 10% to 20%, the *MYB* gene (6q) in 10%, and the *AIB1* gene (chromosome 20q) in 10%. The *BRCA2* (chromosome 13q), *LKB1/STK11* (chromosome 19p), *MKK4* (chromosome 17p), *TGFβ-R1* (chromosome 9q), *TGFβ-R2* (chromosome 3p), and *RB1* (chromosome 13q) tumor suppressor genes are inactivated in fewer than 10% of pancreatic cancers.

**Methylation Abnormalities.**

A number of methylation abnormalities also occur in pancreatic cancer. Hypermethylation of the promoter of a number of tumor suppressor genes is associated with transcriptional silencing of the genes.

**Gene Expression.**

In addition to DNA alterations, global analyses of gene expression have identified a number of genes that are highly overexpressed in pancreatic cancers. [65] [66] These overexpressed genes are potential targets for novel therapeutics and may form the basis of future screening tests. For example the hedgehog signaling pathway has recently been shown to be activated in pancreatic cancer. Inhibition of this pathway with the drug cyclopamine blocks growth of pancreatic cancers in experimental systems. [67]

**Epidemiology, Etiology, and Pathogenesis.**

Unlike other cancers of the alimentary tract, little is known about the cause of pancreatic cancer. Pancreatic cancer is primarily a disease in the elderly, 80% of cases occurring between the ages of 60 and 80.[68] It is more common in blacks than in whites, and it is slightly more common in individuals of Jewish decent.

The strongest environmental influence is *smoking*, which is believed to double the risk of pancreatic cancer.[68] Even though the magnitude of this increased risk is not great, the impact of smoking on pancreatic cancer is significant because of the large number of people who smoke. Consumption of a diet rich in fats has also been implicated but less consistently. Chronic pancreatitis and diabetes mellitus have both been associated with an increased risk of pancreatic cancer. Pancreatic cancer arises with greater frequency in patients with chronic pancreatitis, [50] but a causal role for pancreatitis, with the exception of hereditary pancreatitis, is not well established. Smoking and alcohol use in patients with chronic pancreatitis may underlie some of the association.[50] It is also hard to sort out whether chronic pancreatitis is the cause of pancreatic cancer or an effect of the disease, since small pancreatic cancers may block the pancreatic duct and produce chronic pancreatitis. A similar argument applies to the association of diabetes mellitus with pancreatic cancer, since diabetes may develop as a consequence of pancreatic cancer.

Familial clustering of pancreatic cancer has been reported, and a growing number of inherited genetic syndromes are now recognized that increase pancreatic cancer risk ( Table 19-3 ). [69]

**Morphology.**

Approximately 60% of cancers of the pancreas arise in the head of the gland, 15% in the body, and 5% in the tail; in 20%, the neoplasm diffusely involves the entire gland. Carcinomas of the pancreas are usually hard, stellate, gray-white, poorly defined masses ( Fig. 19-14*A* ).

The vast majority of carcinomas are ductal adenocarcinomas that recapitulate to some degree the normal ductal epithelium by forming glands and secreting mucin. Two features are characteristic of pancreatic cancer: It is highly invasive (even "early" invasive pancreatic cancers extensively invade peripancreatic tissues), and it elicits an intense non-neoplastic host reaction composed of fibroblasts, lymphocytes, and extracellular matrix (called a "desmoplastic response").

Most carcinomas of the head of the pancreas obstruct the distal common bile duct as it courses

**TABLE 19-3** -- Familial Syndromes Predisposing to Pancreatic Cancer

| Disorder | Gene (Chromosome Location) | Increased Risk of Pancreatic Cancer |
|---|---|---|
| Hereditary nonpolyposis colorectal cancer (Lynch II variant) | *hMSH2* (2p22), *hMLH1* (3p21) | ? |
| Hereditary breast and ovarian cancer | *BRCA2* (13q12-q13) | 4–10X |
| Familial atypical multiple mole melanoma syndrome (FAMMM) | *p16* (9p21) | 20–35X |
| Hereditary pancreatitis | *PRSS1* (7q35) | 50–80X |

| Peutz-Jeghers syndrome | *STK11/LKB1* (19p13) | 130X |

through the head of the pancreas. As a consequence, there is marked distention of the biliary tree in about 50% of patients with carcinoma of the head of the pancreas, and most develop jaundice. In marked contrast, **carcinomas of the body and tail of the pancreas do not impinge on the biliary tract and hence remain silent for some time. They may be quite large and widely disseminated by the time they are discovered**. Pancreatic cancers often extend through the retroperitoneal space, entrapping adjacent nerves, and occasionally invade the spleen, adrenals, vertebral column, transverse colon, and stomach. Peripancreatic, gastric, mesenteric, omental, and portahepatic lymph nodes are frequently involved, and the liver is often enlarged owing to metastatic deposits. Distant metastases occur, principally to the lungs and bones.

Microscopically, there is no difference between carcinomas of the head of the pancreas and those of the body and tail of the pancreas. The appearance is usually that of a **moderately to poorly differentiated adenocarcinoma forming abortive tubular structures or cell clusters and exhibiting an aggressive, deeply infiltrative growth pattern** ( Fig. 19-14*B* ). Dense stromal fibrosis accompanies tumor invasion, and there is a proclivity for perineural invasion within and beyond the organ. Lymphatic invasion is also commonly seen. The malignant glands are atypical, irregular, small, and bizarre and are usually lined by

**Figure 19-14** Carcinoma of the pancreas. *A*, A cross-section through the head of the pancreas and adjacent common bile duct showing both an ill-defined mass in the pancreatic substance (*arrowheads*) and the green discoloration of the duct resulting from total obstruction of bile flow. *B*, Poorly formed glands are present in densely fibrotic stroma within the pancreatic substance; there are some inflammatory cells.
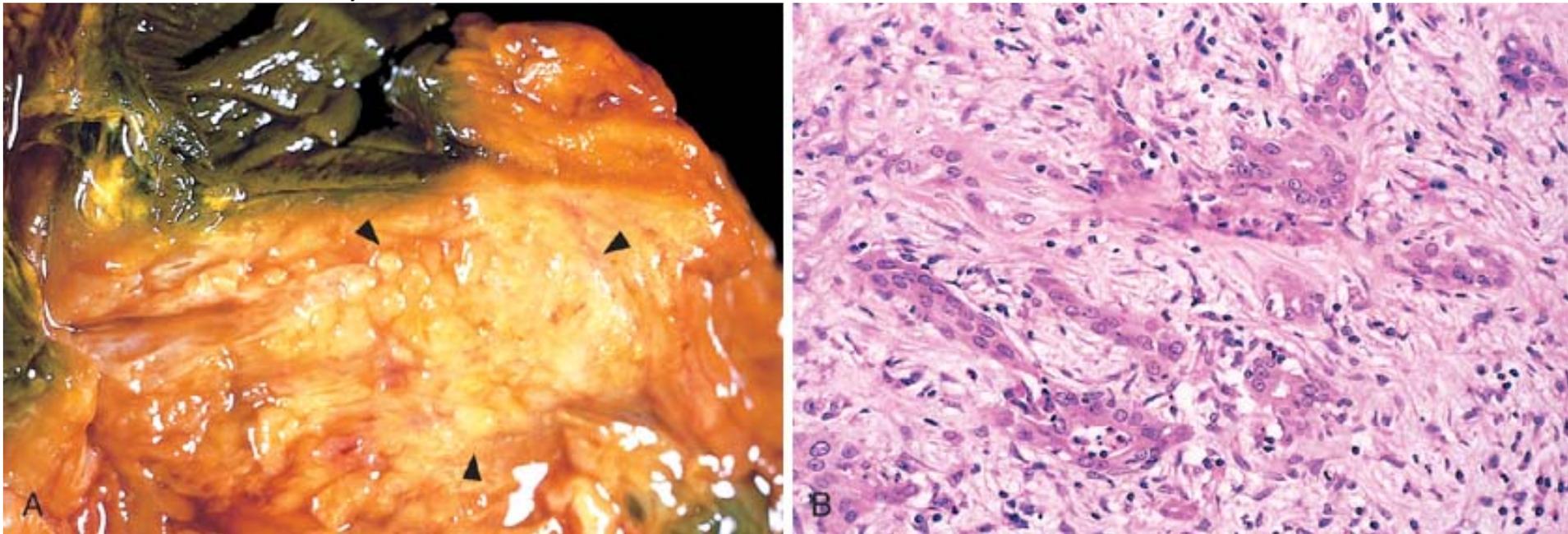


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**954**

**955**

# Chapter 20 - The Kidney

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**956**

**Normal**

What is a human but an ingenious machine designed to turn, with "infinite artfulness, the red wine of Shiraz into urine"? So said the storyteller in Isak Dinesen's *Seven Gothic Tales*.[1] More accurately but less poetically, human kidneys serve to convert more than 1700 liters of blood per day into about 1 liter of a highly specialized concentrated fluid called urine. In so doing, the kidney excretes the waste products of metabolism, precisely regulates the body's concentration of water and salt, maintains the appropriate acid balance of plasma, and serves as an endocrine organ, secreting such hormones as erythropoietin, renin, and prostaglandins. The physiologic mechanisms that the kidney has evolved to carry out these functions require a high degree of structural complexity.

Each human adult kidney weighs about 150 gm. As the ureter enters the kidney at the hilum, it dilates into a funnel-shaped cavity, the *pelvis*, from which derive two or three main branches, the *major calyces*; each of these subdivides again into three or four *minor calyces*. There are about 12 minor calyces in the human kidney. On the cut surface, the kidney is made up of a *cortex* and a *medulla*, the former 1.2 to 1.5 cm in thickness. The medulla consists of *renal pyramids*, the apices of which are called *papillae*, each related to a calyx. Cortical tissue extends into spaces between adjacent pyramids as the *renal columns of Bertin*. From the standpoint of its diseases, the kidney can be divided into four components: blood vessels, glomeruli, tubules, and interstitium.

**Blood Vessels.**

The kidney is richly supplied by blood vessels, and although both kidneys make up only 0.5% of the total body weight, they receive about 25% of the cardiac output. The cortex is by far the most richly vascularized part of the kidney, receiving 90% of the total renal blood supply. The main renal artery divides into anterior and posterior sections at the hilum. From these, *interlobar arteries* emerge, course between lobes, and give rise to the *arcuate arteries*, which arch between cortex and medulla, in turn giving rise to the *interlobular arteries*. From the interlobular arteries, *afferent arterioles* enter the glomerular tuft, where they progressively subdivide into 20 to 40 capillary loops arranged in several units or lobules architecturally centered by a supporting mesangial stalk. Capillary loops merge to exit from the glomerulus as *efferent arterioles*. In general, efferent arterioles from superficial nephrons form a rich vascular network that encircles cortical tubules (*peritubular vascular network*), and deeper juxtamedullary glomeruli give rise to the *vasa recta*, which descend as straight vessels to supply the outer and inner medulla. These descending arterial vasa recta then make several loops in the inner medulla and ascend as the *venous vasa recta*.

The anatomy of renal vessels has several important implications. First, because the arteries are largely end-arteries, *occlusion of any branch usually results in infarction of the specific area it supplies*. Glomerular disease that interferes with blood flow through the glomerular capillaries has profound effects on the tubules, within both the cortex and the medulla, because *all tubular capillary beds are derived from the efferent arterioles*. The peculiarities of the blood supply to the renal medulla render them especially vulnerable to ischemia; *the medulla does not have its own arterial blood supply but is dependent on the blood emanating from the glomerular efferent arterioles*. The blood in the capillary loops in the medulla has a remarkably low level of oxygenation. Thus, minor interference with the blood supply of the medulla may result in medullary necrosis from ischemia.

**Glomeruli.**

The glomerulus consists of an anastomosing network of capillaries lined by fenestrated endothelium invested by two layers of epithelium ( Fig. 20-1 ). The visceral epithelium is incorporated into and becomes an intrinsic part of the capillary wall, separated from endothelial cells by a basement membrane. The parietal epithelium, situated on Bowman's capsule, lines the urinary space, the cavity in which plasma filtrate first collects.

The glomerular capillary wall is the filtering membrane and consists of the following structures[2] ( Fig. 20-2 ):

- A thin layer of fenestrated *endothelial cells*, each fenestrum being about 70 to 100 nm in diameter.
- A *glomerular basement membrane* (GBM) with a thick electron-dense central layer, the *lamina densa*, and thinner electron-lucent peripheral layers, the *lamina rara interna* and *lamina rara externa*. The GBM consists of collagen (mostly type IV), laminin, polyanionic proteoglycans (mostly heparan sulfate), fibronectin, entactin, and several other glycoproteins. Type IV collagen forms a network

suprastructure to which other glycoproteins attach. The building block (monomer) of this network is a triple-helical molecule made up of three $\alpha$-chains, composed of one or more of six types of $\alpha$-chains ($\alpha_1$ to $\alpha_6$ or COL4A1 to COL4A6), the most common consisting of $\alpha_1$, $\alpha_2$, $\alpha_1$ ( Fig. 20-3). [3]Each molecule consists of a 7S domain at the amino terminus, a triple-helical domain in the middle, and a globular noncollagenous domain (NC1) at the carboxyl terminus. The NC1 domain is important for helix formation and for assembly of collagen monomers into the basement membrane suprastructure. Glycoproteins (laminin, entactin) and acidic proteoglycans (heparan sulfate, perlecan) attach to the collagenous suprastructure[3][4][5]( Fig. 20-4). *These biochemical determinants are critical to understanding glomerular diseases.*For example, as we shall see, the antigens in the NC1 domain are the targets of antibodies in anti-GBM nephritis; genetic defects in the $\alpha$-chains underlie some forms of hereditary nephritis; and the acidic porous nature of the GBM determines its permeability characteristics.

- The *visceral epithelial cells* (podocytes), are structurally complex cells that possess interdigitating processes embedded in and adherent to the lamina rara externa of the basement membrane. Adjacent *foot processes* (pedicels) are separated by 20- to 30-nm-wide *filtration slits*, which are bridged by a thin diaphragm (see Fig. 20-2 ).
- The entire glomerular tuft is supported by *mesangial cells* lying between the capillaries. Basement membrane-like *mesangial matrix* forms a meshwork through which the mesangial cells are centered ( Fig. 20-1 ). These cells, of mesenchymal origin, are contractile, phagocytic, and capable of proliferation, of laying down both matrix and collagen, and of secreting a number of biologically active mediators. Biologically, they are most akin to vascular smooth muscle cells and pericytes. They are, as we shall see, important players in many forms of human glomerulonephritis.

**Figure 20-1** *A*, Low-power electron micrograph of renal glomerulus. CL, capillary lumen; MES, mesangium; END, endothelium; EP, visceral epithelial cells with foot processes. *(Courtesy of Dr. Vicki Kelley, Brigham and Women's Hospital, Boston, MA.) B*, Schematic representation of a glomerular lobe.

**GLOMERULUS**

Capillary loops

Urinary space

Mesangium

Red cell

Parietal epithelium

Proximal tubule

Urinary space

Mesangial cell

Mesangial matrix

Fenestrae in endothelium

Capillary lumen

Parietal epithelium

Basement membrane

Visceral epithelium

Foot processes    Basement     Endothelium
                  membrane

B                            Red cell    Foot processes
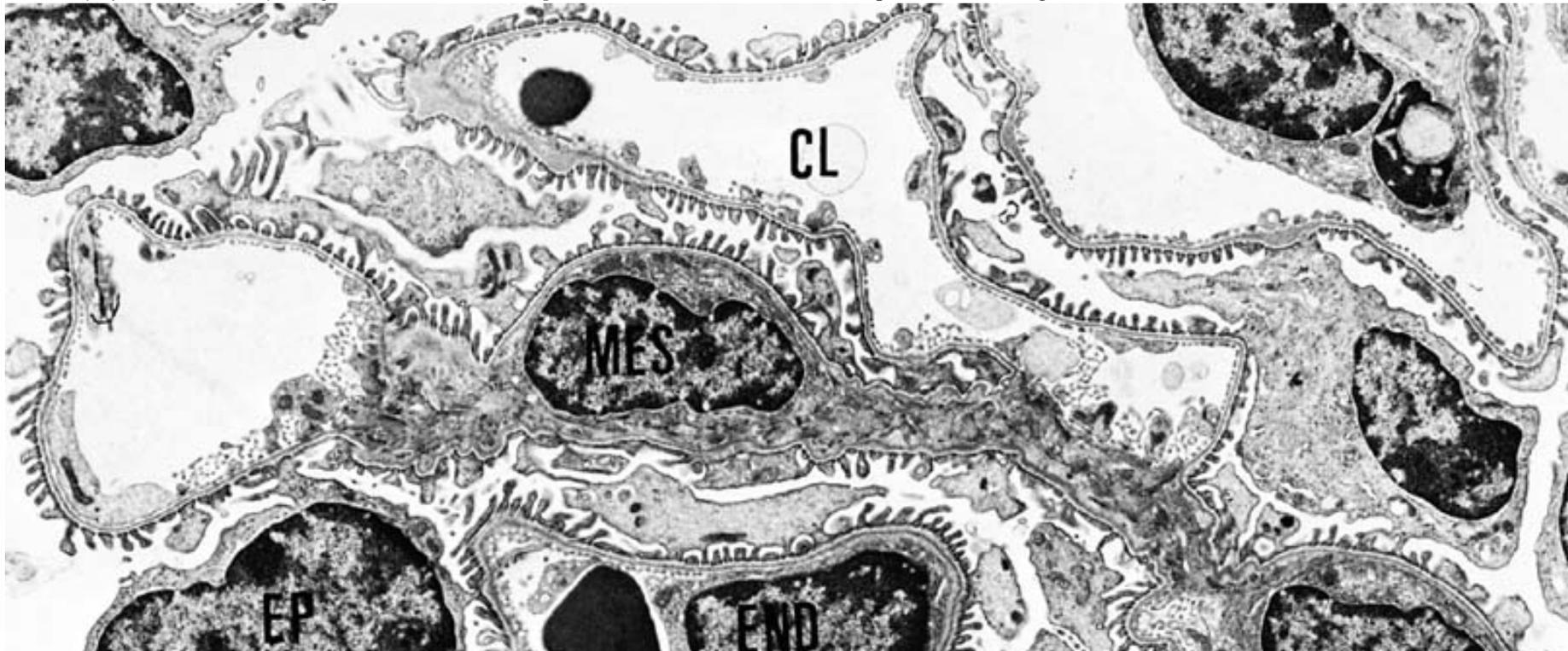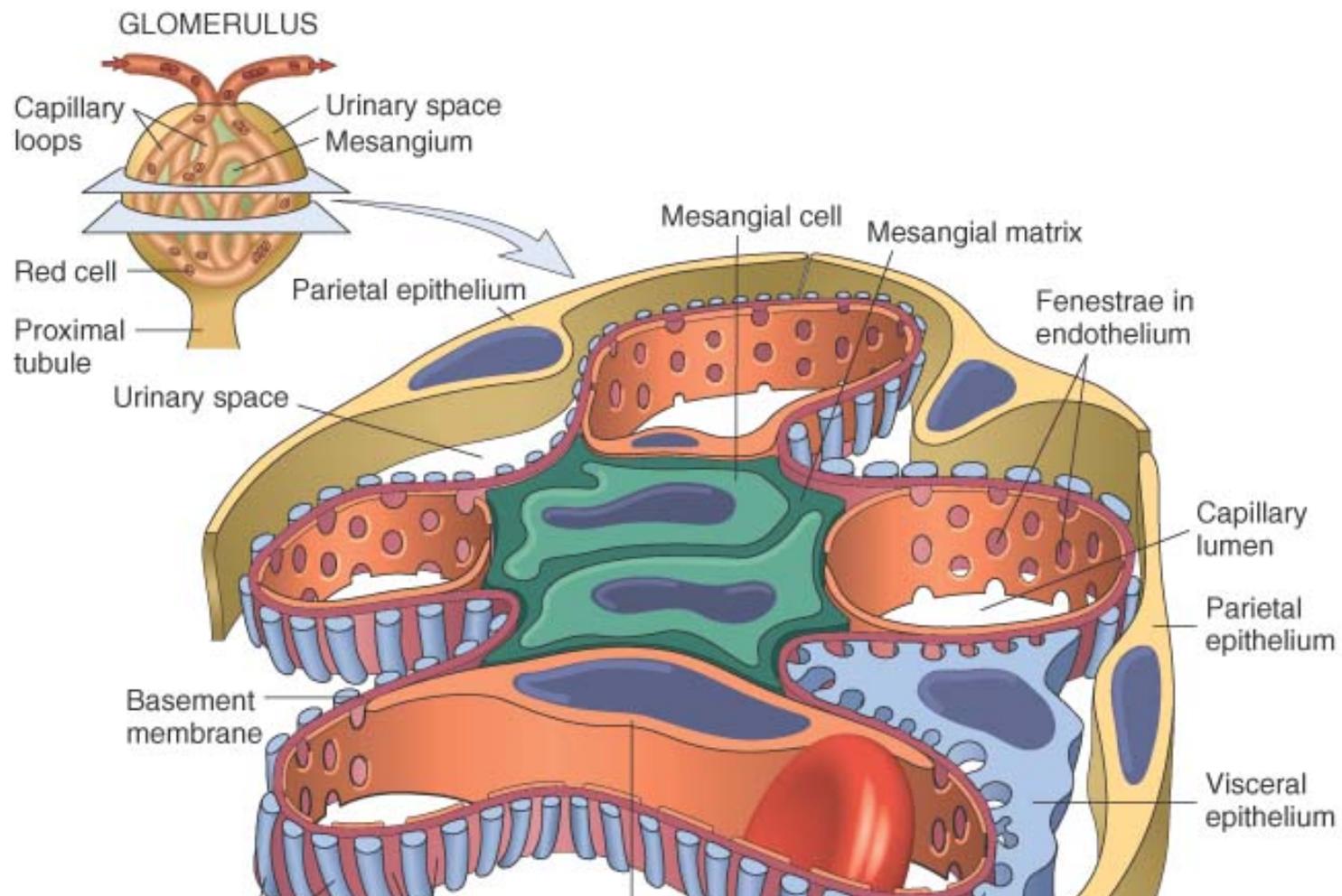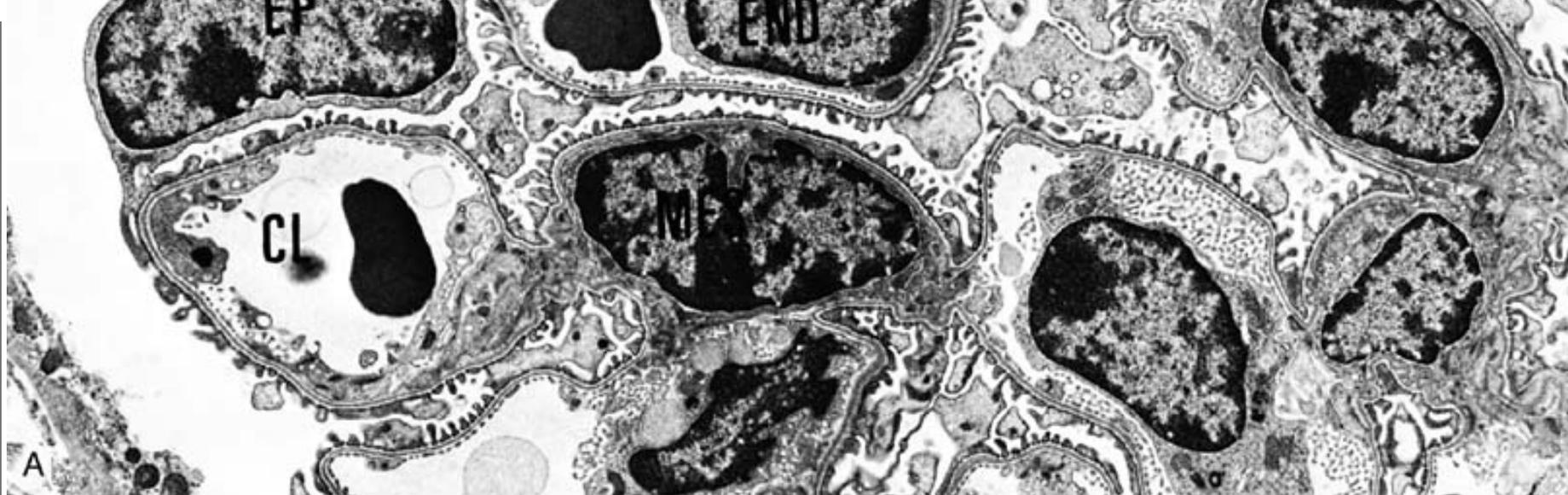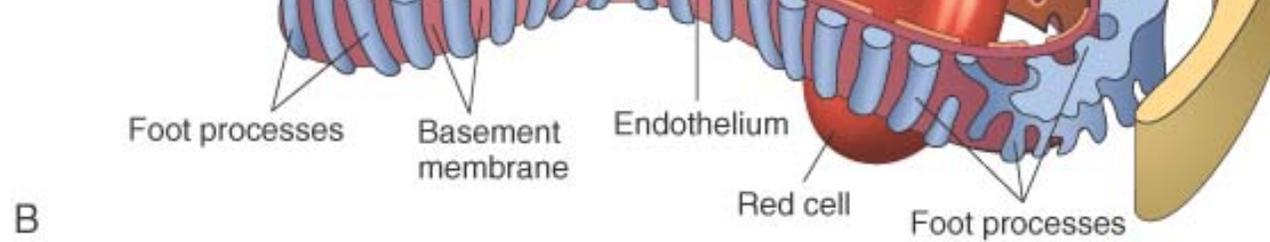
**Figure 20-2** Glomerular filter consisting, from bottom to top, of fenestrated endothelium, basement membrane, and foot processes of epithelial cells. Note the filtration slits (*arrows*) and diaphragm. Note also that the basement membrane consists of a central lamina densa, sandwiched between two looser layers, the lamina rara interna and lamina rara externa. *(Courtesy of Dr. Helmut Rennke, Brigham and Women's Hospital, Boston, MA.)*



**Figure 20-3** Schematic illustration of type IV collagen supramolecular network assembly. *A*, Six genetically distinct α-chains (α1 to α6) assemble into three distinct protomers. The protomers are characterized by a long central collagen triple helix, the 7S domain at the N terminus, and a globular NC1 trimer at the C terminus. *B*, NC1 domains provide specificity for chain association, alignment, registration, and propagation from the C- to N-terminal direction. This sequence of events, shown for the α1, α2 protomer, is true for other protomers also. *(Courtesy of Dr. Billy Hudson, Vanderbilt University, Nashville, TN, reprinted with permission.)*

A. TYPE IV COLLAGEN CHAINS

1

2

3

4

5

6

B. PROTOMER ASSEMBLY

1
2
1

1
2
1

NC1 trimer

1
2
1

α1, α2, α1
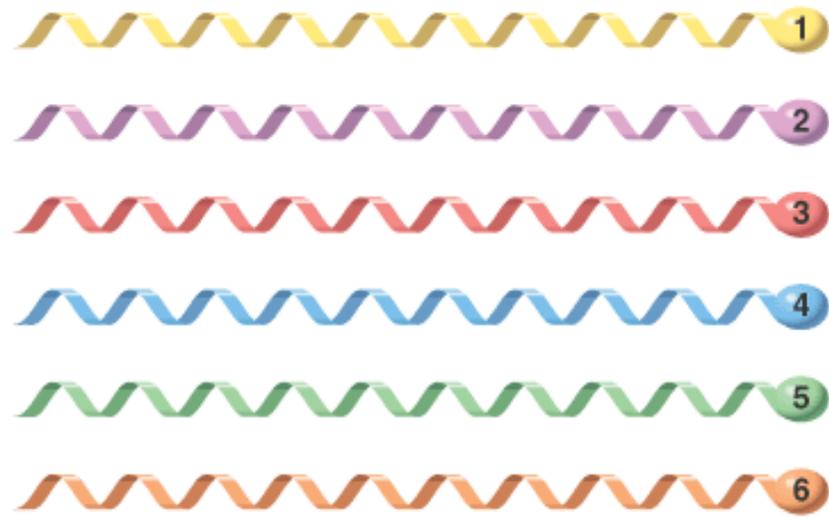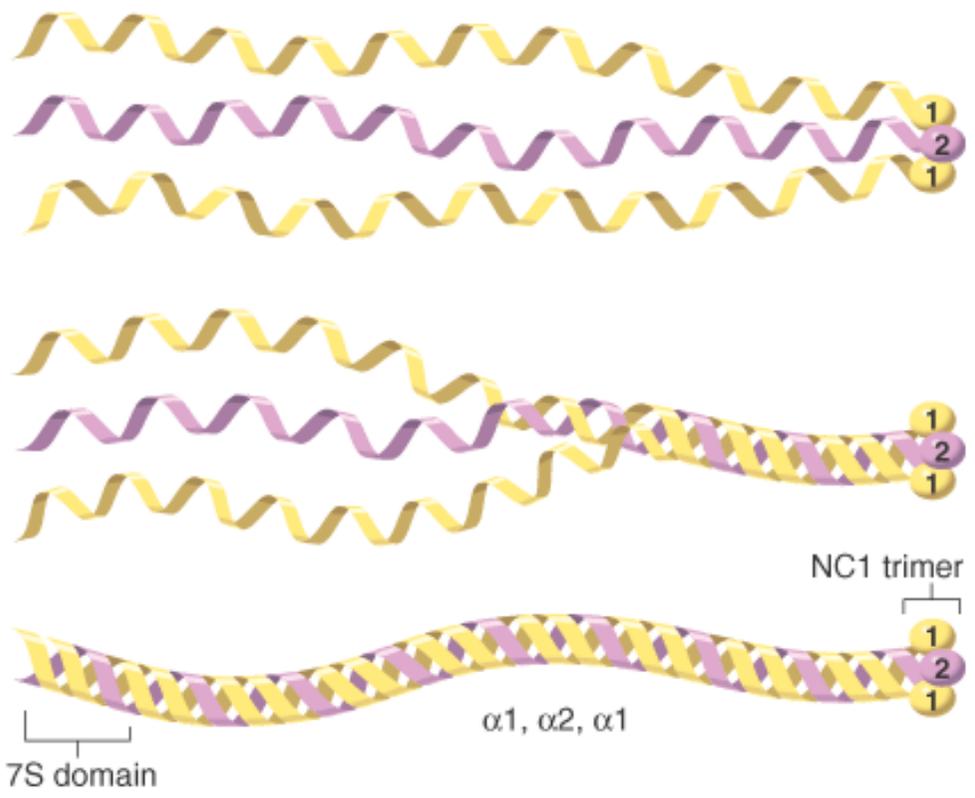
7S domain

**Figure 20-4** A proposed model of the GBM molecular architecture in which type IV collagen monomers (*gray*) form a stable network through their NC1 domains (dimeric interactions, gray spheres) and 7S domains (tetrameric interactions) and intertwine along the triple-helical domains. Laminin monomers (*red*) separately form a reversible meshwork. Entactin (*green*) connects laminin to the collagen network and binds to perlecan (*blue*), an anionic heparan sulfate proteoglycan. This anionic suprastructure determines the charged porous nature of the GBM. *(Courtesy of Dr. Peter Yurchenco, Robert W. Johnson Medical School, Piscataway, NJ.)*
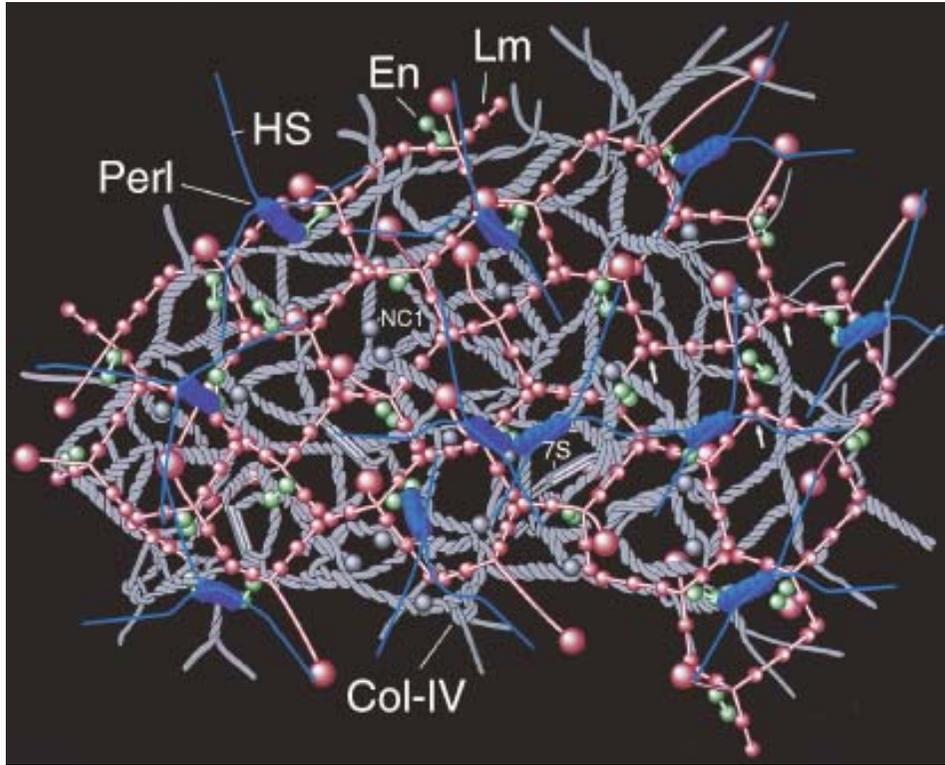


**Figure 20-5** Schematic diagram of the proteins of the glomerular slit diaphragm. CD2AP, CD2-associated protein.

Podocyte foot processes

Actin filaments

CD2AP

Nephrin molecules

Podocin

Slit diaphragm

Basement membrane

Endothelium (fenestrated)
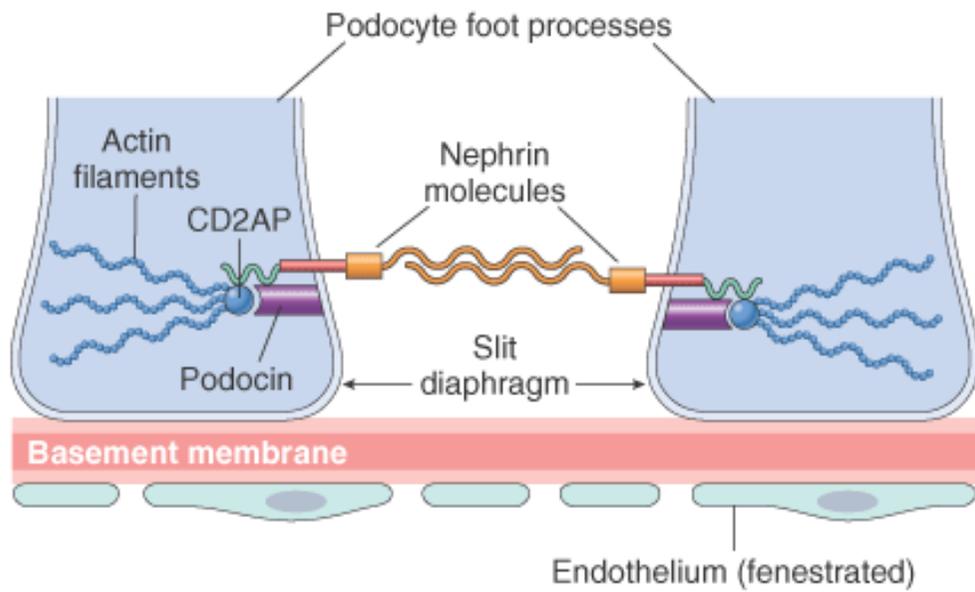
**TABLE 20-1** -- Principal Systemic Manifestations of Chronic Renal Failure and Uremia

| *Fluid and Electrolytes* |
| Dehydration |
| Edema |
| Hyperkalemia |
| Metabolic acidosis |
| *Calcium Phosphate and Bone* |
| Hyperphosphatemia |
| Hypocalcemia |
| Secondary hyperparathyroidism |
| Renal osteodystrophy |
| *Hematologic* |
| Anemia |
| Bleeding diathesis |
| *Cardiopulmonary* |
| Hypertension |
| Congestive heart failure |

| | |
|---|---|
| Pulmonary edema | |
| Uremic pericarditis | |
| *Gastrointestinal* | |
| Nausea and vomiting | |
| Bleeding | |
| Esophagitis, gastritis, colitis | |
| *Neuromuscular* | |
| Myopathy | |
| Peripheral neuropathy | |
| Encephalopathy | |
| *Dermatologic* | |
| Sallow color | |
| Pruritus | |
| Dermatitis | |

## Congenital Anomalies

About 10% of all people are born with potentially significant malformations of the urinary system. Renal dysplasias and hypoplasias account for 20% of chronic renal failure in children. Autosomal-dominant polycystic kidney disease, a congenital anomaly that becomes apparent in adults, is responsible for about 10% of chronic renal failure in humans.

Congenital renal disease can be hereditary but is most often the result of an acquired developmental defect that arises during gestation. As was discussed in Chapter 10 , defects in genes involved in development, including the Wilms tumor (WT1)-associated genes, cause urogenital anomalies. As a rule, developmental abnormalities involve structural components of the kidney and urinary tract. However, genetic abnormalities also cause enzymatic or metabolic defects in tubular transport, such as cystinuria and renal tubular acidosis. Here, we restrict the discussion to structural anomalies involving primarily the kidney. All except horseshoe kidney are uncommon. Anomalies of the lower urinary tract are discussed in Chapter 21 .

### Agenesis of the Kidney.

Total bilateral agenesis, which is incompatible with life, is usually encountered in stillborn infants. It is often associated with many other congenital disorders (e.g., limb defects, hypoplastic lungs) and leads to early death. Unilateral agenesis is an uncommon anomaly that is compatible with normal life if no other abnormalities exist. The opposite kidney is usually enlarged as a result of compensatory hypertrophy. Some patients eventually develop progressive glomerular sclerosis in the remaining kidney as a result of the adaptive changes in hypertrophied nephrons, discussed later in the chapter, and in time, chronic renal failure ensues.

### Hypoplasia.

Renal hypoplasia refers to failure of the kidneys to develop to a normal size. This anomaly may occur bilaterally, resulting in renal failure in early childhood, but it is more commonly encountered as a unilateral defect. True renal hypoplasia is extremely rare; most cases reported probably represent acquired scarring due to vascular, infectious, or other parenchymal diseases rather than an underlying developmental failure. Differentiation between congenital and acquired atrophic kidneys may be impossible, but *a truly hypoplastic kidney shows no*

*scars and has a reduced number of renal lobes and pyramids*, usually six or fewer. In one form of hypoplastic kidney, *oligomeganephronia*, the kidney is small but the nephrons are markedly hypertrophied.

**Ectopic Kidneys.**

The development of the definitive metanephros may occur in ectopic foci, usually at abnormally low levels. These kidneys lie either just above the pelvic brim or sometimes within the pelvis. They are usually normal or slightly small in size but otherwise are not remarkable. Because of their abnormal position, kinking or tortuosity of the ureters may cause some obstruction to urinary flow, which predisposes to bacterial infections.

**Horseshoe Kidneys.**

Fusion of the upper or lower poles of the kidneys produces a horseshoe-shaped structure that is continuous across the midline anterior to the great vessels. This anatomic anomaly is common and is found in about 1 in 500 to 1000 autopsies. Ninety per cent of such kidneys are fused at the lower pole, and 10% are fused at the upper pole.

---

## Cystic Diseases of the Kidney

Although not all cysts of the kidney are congenital, all types of cysts are discussed here for convenience.

Cystic diseases of the kidney are a heterogeneous group comprising hereditary, developmental but nonhereditary, and acquired disorders. As a group, they are important for several reasons: (1) they are reasonably common and often represent diagnostic problems for clinicians, radiologists, and pathologists; (2) some forms, such as adult polycystic disease, are major causes of chronic renal failure; and (3) they can occasionally be confused with malignant tumors. A useful classification of renal cysts is as follows:[9]

1. Cystic renal dysplasia
2. Polycystic kidney disease
   a. Autosomal-dominant (adult) polycystic disease
   b. Autosomal-recessive (childhood) polycystic disease
3. Medullary cystic disease
   a. Medullary sponge kidney
   b. Nephronophthisis
4. Acquired (dialysis-associated) cystic disease
5. Localized (simple) renal cysts
6. Renal cysts in hereditary malformation syndromes (e.g., tuberous sclerosis)
7. Glomerulocystic disease
8. Extraparenchymal renal cysts (pyelocalyceal cysts, hilar lymphangitic cysts)

Only the more important of the cystic diseases are discussed below. Table 20-2 summarizes the characteristic features of the principal renal cystic diseases.

**CYSTIC RENAL DYSPLASIA**

This sporadic disorder is due to an abnormality in metanephric differentiation *characterized histologically by the*

**TABLE 20-2** -- Summary of Renal Cystic Diseases

| | Inheritance | Pathologic Features | Clinical Features or Complications | Typical Outcome | Diagrammatic Representation |
|---|---|---|---|---|---|
| Adult polycystic kidney disease | Autosomal dominant | Large multicystic kidneys, liver cysts, berry aneurysms | Hematuria, flank pain, urinary tract infection, renal stones, hypertension | Chronic renal failure beginning at age 40–60 yr | |
| Childhood polycystic kidney disease | Autosomal recessive | Enlarged, cystic kidneys at birth | Hepatic fibrosis | Variable, death in infancy or childhood | |
| Medullary sponge kidney | None | Medullary cysts on excretory urography | Hematuria, urinary tract infection, recurrent renal stones | Benign | |
| Familial juvenile nephronophthisis | Autosomal recessive | Corticomedullary cysts, shrunken kidneys | Salt wasting, polyuria, growth retardation, anemia | Progressive renal failure beginning in childhood | |
| Adult-onset medullary cystic disease | Autosomal dominant | Corticomedullary cysts, shrunken kidneys | Salt wasting, polyuria | Chronic renal failure beginning in adulthood | |
| Simple cysts | None | Single or multiple cysts in normal-sized kidneys | Microscopic hematuria | Benign | |
| Acquired renal cystic disease | None | Cystic degeneration in end-stage kidney disease | Hemorrhage, erythrocytosis, neoplasia | Dependence on dialysis | |

*persistence in the kidney of abnormal structures—cartilage, undifferentiated mesenchyme, and immature collecting ductules—and by abnormal lobar organization*. Most cases are associated with ureteropelvic obstruction, ureteral agenesis or atresia, and other anomalies of the lower urinary tract.

Dysplasia can be unilateral or bilateral and is almost always cystic. In gross appearance, the kidney is usually enlarged, extremely irregular, and multicystic ( Fig. 20-6*A* ). The cysts vary in size from microscopic structures to some that are several centimeters in diameter. On histologic examination, they are lined by flattened epithelium. Although normal nephrons are present, many have immature ducts. The characteristic histologic feature is the *presence of islands of undifferentiated mesenchyme, often with cartilage, and immature collecting ducts* ( Fig. 20-6*B* ).

When unilateral, the dysplasia is discovered by the appearance of a flank mass that leads to surgical exploration and nephrectomy. The function of the opposite kidney is normal, and such patients have an excellent prognosis after surgical removal of the affected kidney. In bilateral renal dysplasia, renal failure may ultimately result.

**AUTOSOMAL-DOMINANT (ADULT) POLYCYSTIC KIDNEY DISEASE**

Autosomal-dominant (adult) polycystic kidney disease (ADPKD) is a hereditary disorder characterized by multiple expanding cysts of both kidneys that ultimately destroy the renal parenchyma and cause renal failure.[10] It is a common condition affecting roughly 1 of every 400 to 1000 live births and accounting for about 5% to 10% of cases of chronic renal failure requiring transplantation or dialysis. The pattern of inheritance is *autosomal dominant*, with high penetrance. The disease is universally bilateral; reported unilateral cases probably represent multicystic dysplasia. The cysts initially involve only portions of the nephrons, so renal function is retained until about the fourth or fifth decade of life. ADPKD is genetically

**Figure 20-6** Renal dysplasia. *A*, Gross appearance. *B*, Histologic section showing disorganized architecture, dilated tubules with cuffs of primitive stroma, and an island of cartilage (H&E stain). *(A, courtesy of Dr. D. Schofield, Children's Hospital, Los Angeles, CA; B, courtesy of Dr. Laura Finn, Children's Hospital, Seattle, WA.)*
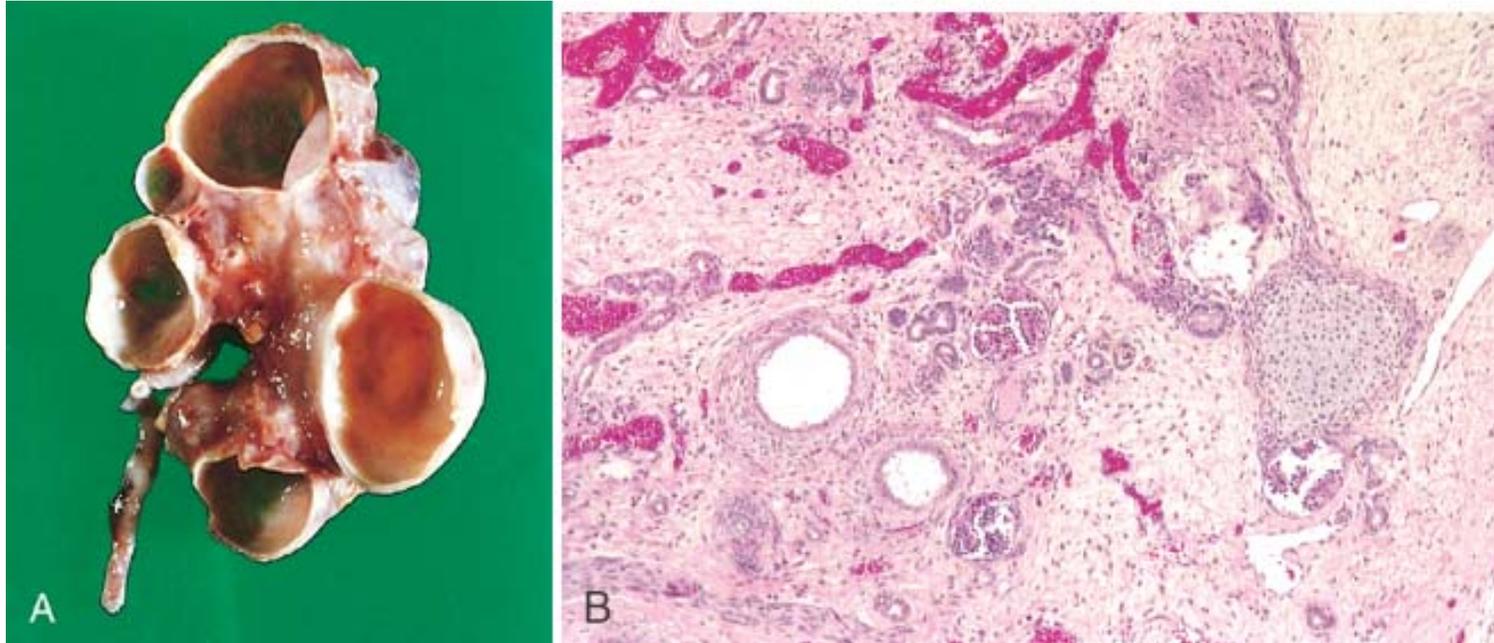


**Figure 20-7** Possible mechanisms of cyst formation in polycystic kidney disease (see text).
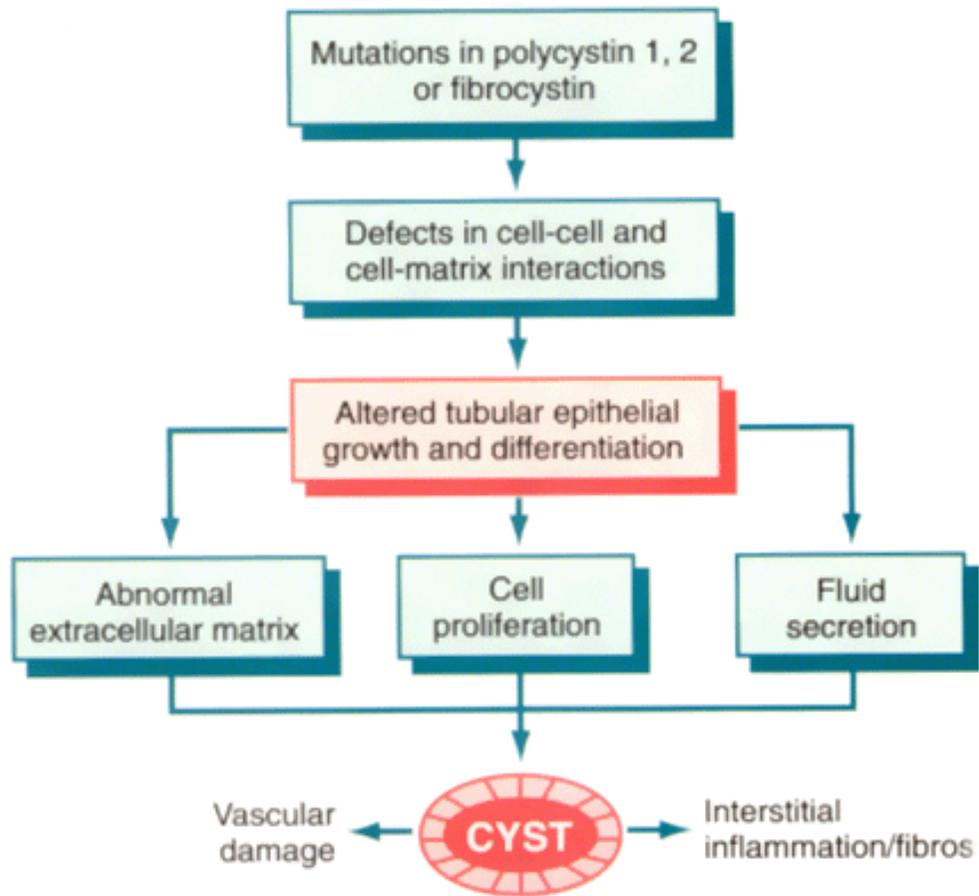
**Figure 20-8** *A* and *B*, Autosomal-dominant adult polycystic kidney disease (ADPKD) viewed from the external surface and bisected. The kidney is markedly enlarged with numerous dilated cysts. *C*, Autosomal-recessive childhood polycystic kidney disease, showing smaller cysts and dilated channels at right angles to the cortical surface. *D*, Liver with cysts in adult PKD.
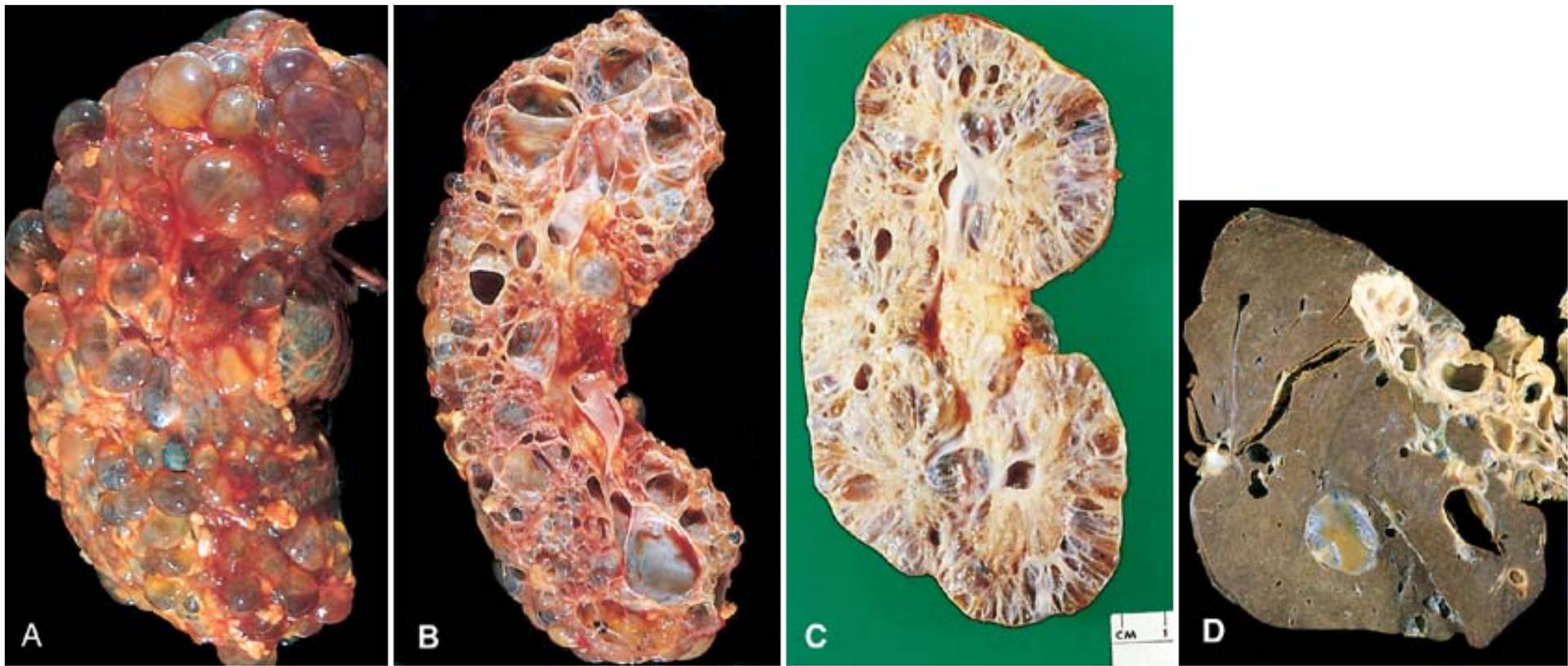
**Figure 20-9** Uremic medullary cystic disease. Cut section of kidney showing cysts at the corticomedullary junction and in the medulla.

**TABLE 20-3** -- Glomerular Diseases

| |
|---|
| *Primary Glomerulopathies* |
| Acute diffuse proliferative glomerulonephritis |
| ••Poststreptococcal |
| ••Non-poststreptococcal |
| Rapidly progressive (crescentic) glomerulonephritis |
| Membranous glomerulopathy |
| Minimal change disease |
| Focal segmental glomerulosclerosis |
| Membranoproliferative glomerulonephritis |
| IgA nephropathy |
| Chronic glomerulonephritis |
| *Systemic Diseases with Glomerular Involvement* |
| Systemic lupus erythematosus |
| Diabetes mellitus |
| Amyloidosis |
| Goodpasture syndrome |
| Microscopic polyarteritis/polyangiitis |
| Wegener granulomatosis |
| Henoch-Schönlein purpura |
| Bacterial endocarditis |
| *Hereditary Disorders* |
| Alport syndrome |
| Thin basement membrane disease |
| Fabry disease |

**TABLE 20-4** -- The Glomerular Syndromes

| | |
|---|---|
| Acute nephritic syndrome | • Hematuria, azotemia, variable proteinuria, oliguria, edema, and hypertension |
| Rapidly progressive glomerulonephritis | • Acute nephritis, proteinuria, and acute renal failure |
| Nephrotic syndrome | • >3.5 gm proteinuria, hypoalbuminemia, hyperlipidemia, lipiduria |

| Chronic renal failure | • Azotemia → uremia progressing for years |
| Asymptomatic hematuria or proteinuria | • Glomerular hematuria; subnephrotic proteinuria |

**Basement Membrane Thickening.**

By light microscopy, this change appears as thickening of the capillary walls, best seen in sections stained with periodic acid-Schiff (PAS). By electron microscopy, such thickening can be resolved as one of two alterations: (1) deposition of amorphous electrondense material, most often immune complexes, on the endothelial or epithelial side of the basement membrane or within the GBM itself. Fibrin, amyloid, cryoglobulins, and abnormal fibrillary proteins may also deposit in the GBM; or (2) thickening of the basement membrane proper, as occurs in diabetic glomerulosclerosis.

**Hyalinization and Sclerosis.**

Hyalinization, or hyalinosis, as applied to the glomerulus, denotes the accumulation of material that is homogeneous and eosinophilic by light microscopy. By electron microscopy, the hyalin is extracellular and consists of amorphous substance, made up of plasma proteins that have exuded from circulating plasma into glomerular structures. This change contributes to obliteration of capillary lumina of the glomerular tuft (a feature of sclerosis). Hyalinosis is usually a consequence of endothelial or capillary wall injury and typically is the end result of various forms of glomerular damage. Additional alterations include *intraglomerular thrombosis* or *accumulation of lipid* or other metabolic materials.

Because many of the primary glomerulonephritides are of unknown cause, they are often classified by their histology, as

can be seen in Table 20-3 . The histologic changes can be further subdivided into *diffuse*, involving all glomeruli; *global*, involving the entire glomerulus; *focal*, involving only a proportion of the glomeruli; *segmental*, affecting a part of each glomerulus; and *mesangial*, affecting predominantly the mesangial region. These terms are sometimes appended to the histologic classifications.

**PATHOGENESIS OF GLOMERULAR INJURY**

Although we know little of etiologic agents and triggering events, it is clear that immune mechanisms underlie most forms of primary glomerulonephritis and many of the secondary glomerular disorders[25] [26] ( Table 20-5 ). Glomerulonephritis can be readily induced experimentally by antigen-antibody reactions. Furthermore, glomerular deposits of immunoglobulins, often with various components of complement, are found in the majority of patients with glomerulonephritis. Cell-mediated immune reactions also clearly play a role, usually in concert with antibody-mediated events. We therefore begin this discussion with a review of antibody-instigated injury.

Two forms of antibody-associated injury have been established: (1) injury by *antibodies reacting in situ within the glomerulus, either with insoluble fixed (intrinsic) glomerular antigens or with molecules planted within the glomerulus*, and (2) injury resulting from *deposition of circulating antigen-antibody complexes* in the glomerulus. In addition, there is experimental evidence that *cytotoxic antibodies* directed against glomerular cell components may cause glomerular injury. These pathways are not mutually exclusive, and in humans, all may contribute to injury.

**In Situ Immune Complex Deposition**

In this form of injury, antibodies react directly with intrinsic tissue antigen, or antigens "planted" in the glomerulus from the circulation. There are two well-established experimental

**TABLE 20-5** -- Immune Mechanisms of Glomerular Injury

| |
|---|
| ***Antibody-Mediated Injury*** |
| ***In Situ Immune Complex Deposition*** |
| Fixed intrinsic tissue antigens |
| ••NC1 domain of collagen type IV antigen (anti-GBM nephritis) |
| ••Heymann antigen (membranous glomerulopathy) |
| ••Mesangial antigens |
| ••Others |
| Planted antigens |
| ••Exogenous (infectious agents, drugs) |
| ••Endogenous (DNA, nuclear proteins, immunoglobulins, immune complexes, IgA) |
| ***Circulating Immune Complex Deposition*** |
| Endogenous antigens (e.g., DNA, tumor antigens) |
| Exogenous antigens (e.g., infectious products) |
| ***Cytotoxic Antibodies*** |
| ***Cell-Mediated Immune Injury*** |
| ***Activation of Alternative Complement Pathway*** |

models for anti-tissue antibody-mediated glomerular injury, for which there are counterparts in human disease: antiglomerular basement membrane (anti-GBM) antibody-induced nephritis and Heymann nephritis.

**Anti-GBM Antibody-Induced Nephritis**

In this type of injury, *antibodies are directed against intrinsic fixed antigens that are normal components of the GBM proper*. It has its experimental counterpart in so-called Masugi or nephrotoxic nephritis, produced in rats by injections of anti-rat kidney antibodies prepared in rabbits by immunization with rat kidney tissue. The injected antibodies bind along the entire length of the GBM, *resulting in a diffuse linear pattern of staining for the antibodies by immunofluorescent techniques* ( Figs. 20-10*B* and *E* ). This is contrasted with the granular lumpy pattern of immunofluorescent staining seen in other in situ models, such as the Heymann model of membranous glomerulopathy, or after deposition of circulating immune complexes.

In the Masugi model, the injected anti-GBM antibody is rabbit immunoglobulin, which is foreign to the host and thus acts as an antigen eliciting anti-Ig antibody in the rat. The rat antibodies then react with the rabbit immunoglobulin deposited in the basement membrane, leading to further glomerular injury. Thus, experimental anti-GBM antibody-mediated glomerulonephritis consists of an initial *heterologous phase* caused by the injected anti-GBM antibody, and a subsequent, more injurious, *autologous phase* caused by host antibodies against the injected Ig. Often the anti-GBM antibodies cross-react with other basement membranes, especially those in the lung alveoli, resulting in simultaneous lung and kidney lesions (*Goodpasture syndrome*). *The GBM antigen that is responsible for classic anti-GBM antibody-induced nephritis and Goodpasture syndrome is a component of the non-collagenous domain*

*(NC1) of the $\alpha_3$ -chain of collagen type IV,* which, as was discussed earlier (see Fig. 20-3 ), is critical for maintenance of GBM superstructure.[3] [4] [5] [27] Anti-GBM antibody-induced nephritis accounts for fewer than 5% of cases of human glomerulonephritis. It is solidly established as the cause of injury in Goodpasture syndrome, discussed later. Most instances of anti-GBM antibody-induced nephritis are characterized by severe crescentic glomerular damage and the clinical syndrome of rapidly progressive glomerulonephritis.

**Heymann Nephritis**

The Heymann model of rat glomerulonephritis is induced by immunizing animals with an antigen contained within preparations of proximal tubular brush border ( Fig. 20-10*C* ). The rats develop antibodies to this antigen, and a membranous glomerulopathy, resembling human membranous glomerulopathy, develops (discussed later; see also Fig. 20-19 ). On electron microscopy, the glomerulopathy is characterized by the presence of numerous electron-dense deposits (made up largely of immune reactants) along the *subepithelial aspect* of the basement membrane. The pattern of immune deposition by immunofluorescence microscopy is *granular* rather than linear ( Fig. 20-10*C* ). It is now clear that this type of disease results largely from the reaction of antibody with an antigen complex located on the basal surface of visceral epithelial cells and cross-reacting with the brush

969

**Figure 20-10** Antibody-mediated glomerular injury can result either from the deposition of circulating immune complexes (*A*) or, more commonly, from in situ formation of complexes exemplified by anti-GBM disease (*B*) or Heymann nephritis (*C*). *D* and *E*, Two patterns of deposition of immune complexes as seen by immunofluorescence microscopy: granular, characteristic of circulating and in situ immune complex nephritis (*D*) and linear, characteristic of classic anti-GBM disease (*E*).



CIRCULATING

IN SITU

CIRCULATING
IMMUNE COMPLEX DEPOSITION

IN SITU
ANTI-GBM          HEYMANN

Epithelial cell    Foot processes

Endothelium

Subepithelial deposit (rare)

Basement membrane

Endothelium

Circulating complex

Subendothelial deposit

Antibody          Antigen

Antibody          Antigen

A          B          C
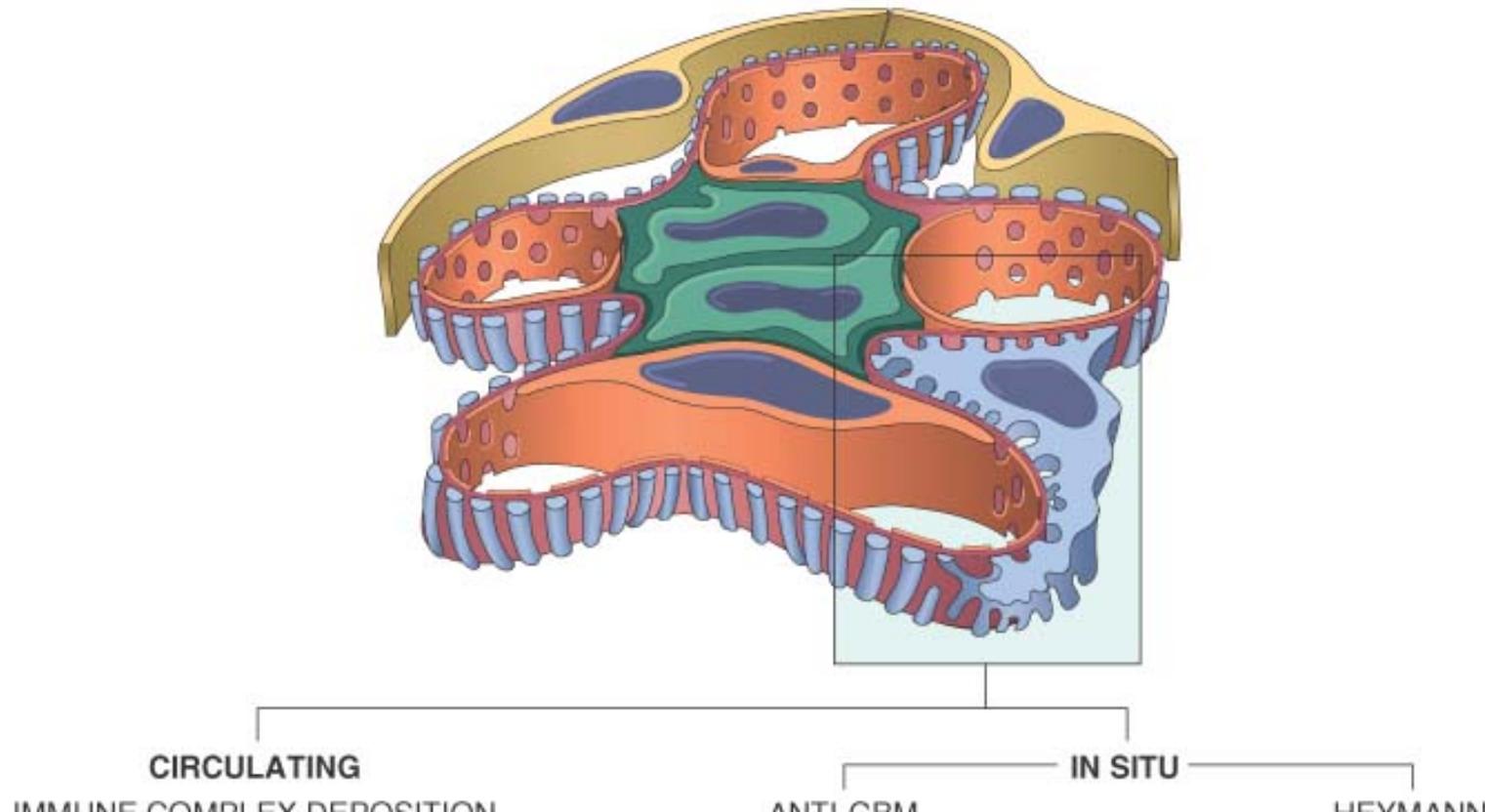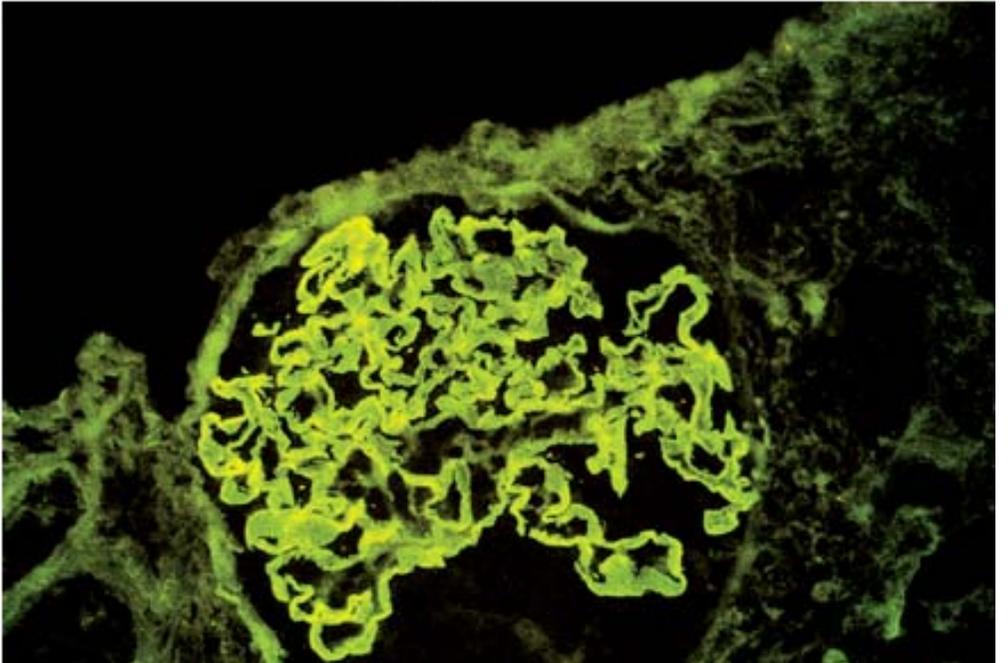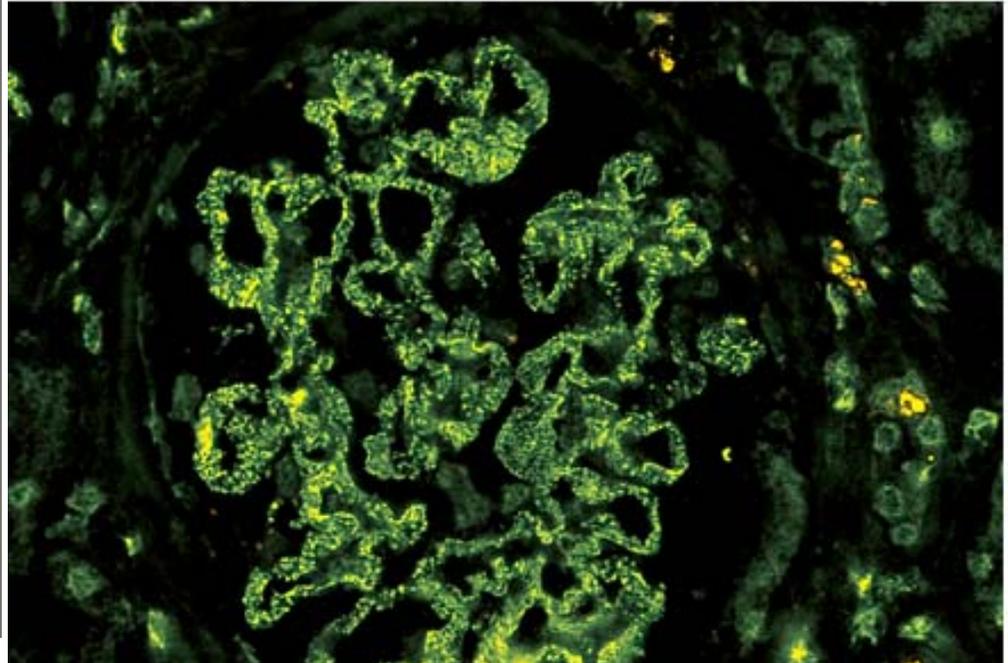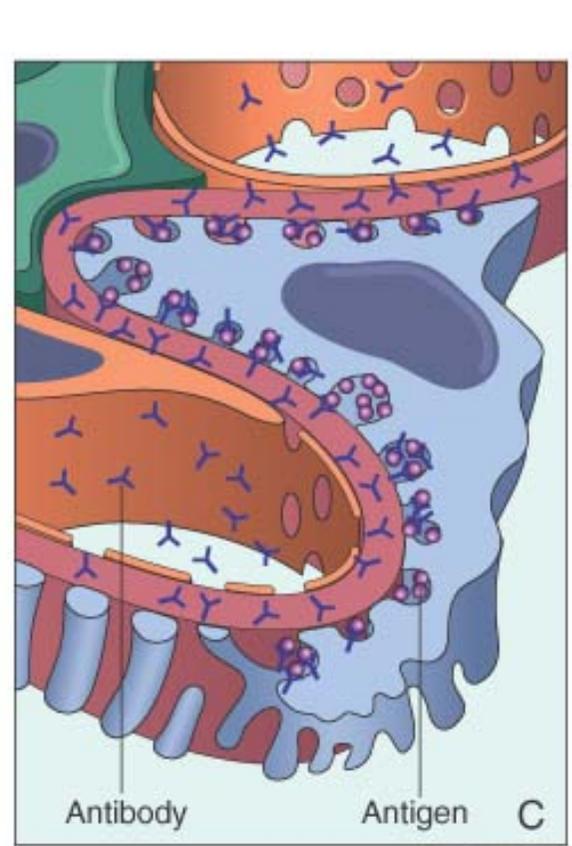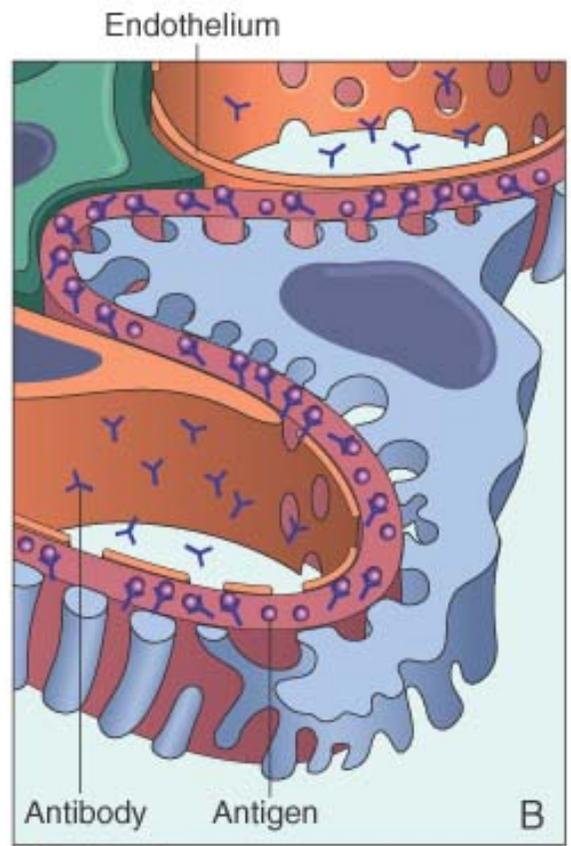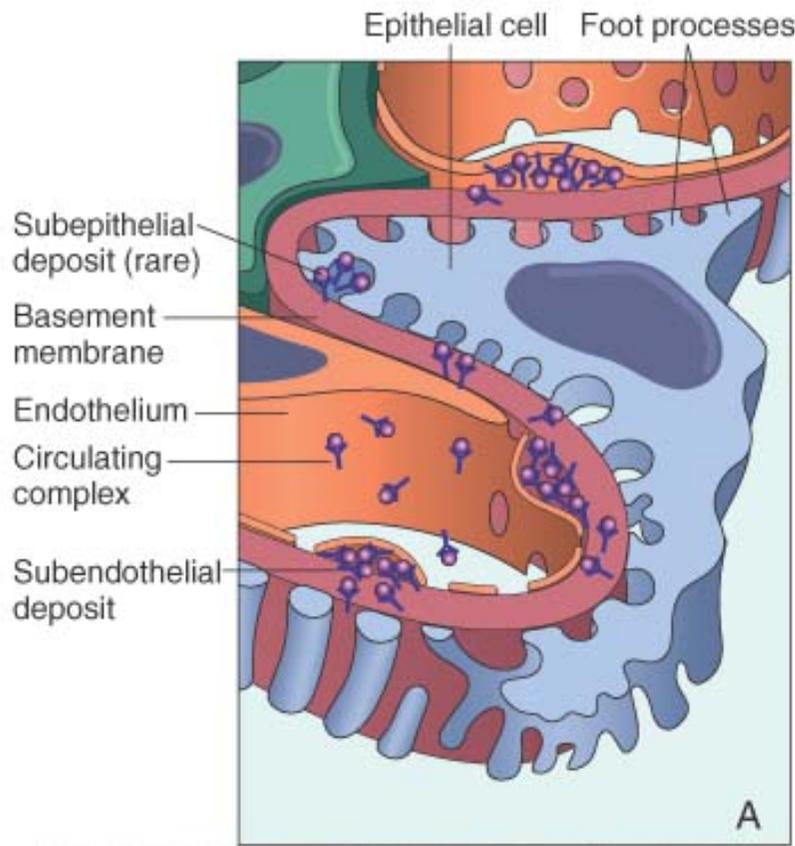
**Figure 20-12** Epithelial cell injury. The postulated sequence is a consequence of antibodies against epithelial cell antigens, toxins, cytokines, or other factors causing injury with foot process effacement and sometimes detachment of epithelial cells and protein leakage through defective GBM and filtration slits.



NORMAL

EPITHELIAL CELL FOOT PROCESS
EFFACEMENT AND DETACHMENT

Filtration slit

Epithelial foot processes

Effacement

Antibody
Cytokine
Toxin

Adhesion molecule

Endothelium

Basement membrane
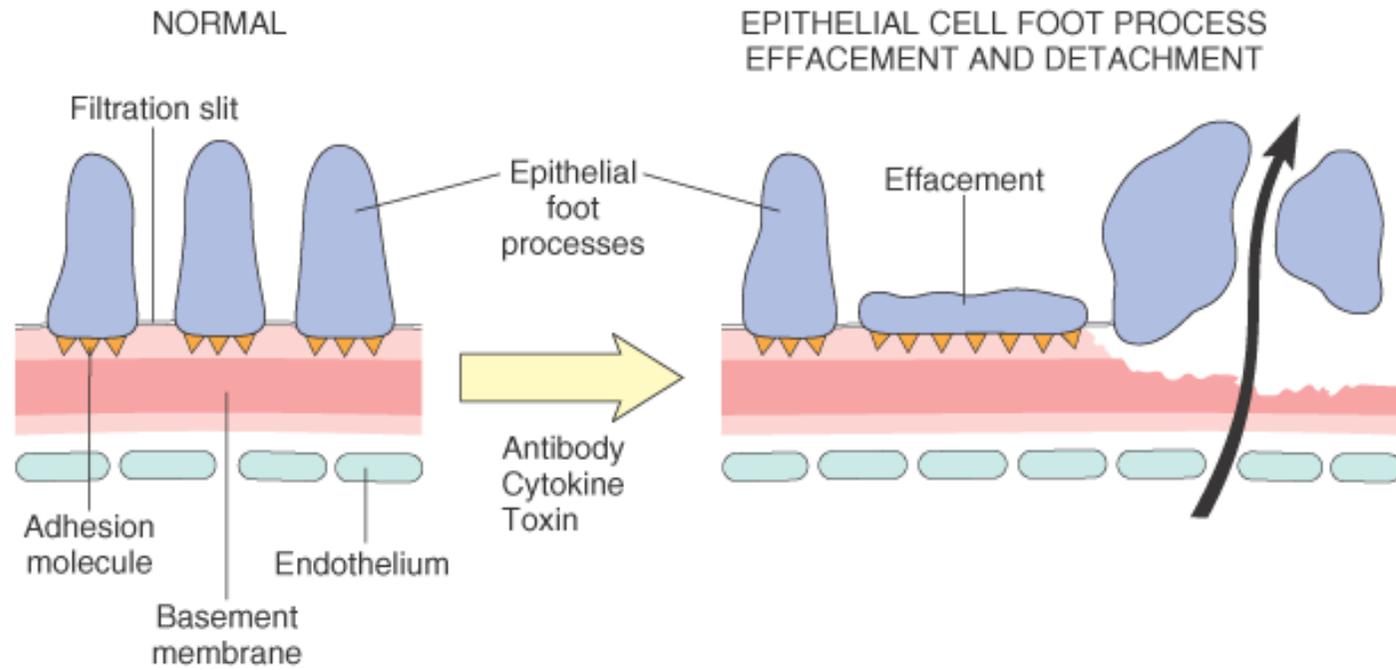
**Figure 20-13** Mediators of immune glomerular injury including cells and soluble mediators (see text). *(Modified from Couser WG: Mediation of immune glomerular injury. J Am Soc Nephrol 1:13, 1990.)*

**Figure 20-14** Renal ablation focal segmental glomerulosclerosis. The adaptive changes in glomeruli (hypertrophy and glomerular capillary hypertension), as well as systemic hypertension, cause epithelial and endothelial injury and resultant proteinuria. The mesangial response, involving mesangial cell proliferation and extracellular matrix (ECM) production together with intraglomerular coagulation, causes the glomerulosclerosis. This results in further loss of functioning nephrons and a vicious circle of progressive glomerulosclerosis.



**Figure 20-15** Mechanisms of chronic tubulointerstitial injury in glomerulonephritis (see text). Various components of the protein-rich filtrate and cytokines derived from leukocytes cause tubular cell activation and secretion of cytokines, growth factors, and other mediators. These, together with products of macrophages, incite interstitial inflammation and fibrosis. ET-1, endothelin-1, PAI-1, plasminogen activator inhibitor-1; TIMP-1, tissue inhibitor of metalloproteinases. *(Adapted and modified from Remuzzi G, Ruggenenti P, Benigni A: Understanding the nature of renal disease progression. Kidney Int 51:2, 1997; Schena FP, et al: Progression of renal damage in human glomerulonephritis. Kidney Int 52:1439, 1997; Fogo AB:*

*Progression and potential regression of glomerulosclerosis. Kidney Int 59:804, 2001.)*

**TABLE 20-6** -- Summary of Major Primary Glomerulonephritides

| Disease | Most Frequent Clinical Presentation | Pathogenesis | Glomerular Pathology | | |
| --- | --- | --- | --- | --- | --- |
| | | | *Light Microscopy* | *Fluorescence Microscopy* | *Electron Microscopy* |
| Poststreptococcal glomerulonephritis | Acute nephritis | Antibody mediated; circulating or planted antigen | Diffuse proliferation; leukocytic infiltration | Granular IgG and C3 in GBM and mesangium | Subepithelial humps |
| Goodpasture syndrome | Rapidly progressive glomerulonephritis | Anti-GBM COL4-A3 antigen | Proliferation; crescents | Linear IgG and C3; fibrin in crescents | No deposits; GBM disruptions; fibrin |
| Idiopathic RPGN | Rapidly progressive glomerulonephritis | Anti-GBM antibody | Proliferation; focal necrosis; crescents | Linear IgG and C3 | No deposits |
| | | Immune complex | | Granular IgG or IgA or IgM | Deposits may be present |
| | | ANCA-associated | | Negative or equivocal | No deposits |
| Membranous glomerulopathy | Nephrotic syndrome | In situ antibody-mediated; antigen unknown | Diffuse capillary wall thickening | Granular IgG and C3; diffuse | Subepithelial deposits |

| Minimal change disease | Nephrotic syndrome | Unknown, loss of glomerular polyanion; podocyte injury | Normal; lipid in tubules | Negative | Loss of foot processes; no deposits |
|---|---|---|---|---|---|
| Focal segmental glomerulosclerosis | Nephrotic syndrome; non-nephrotic proteinuria | Unknown, Ablation nephropathy Plasma factor (?); podocyte injury | Focal and segmental sclerosis and hyalinosis | Focal; IgM and C3 | Loss of foot processes; epithelial denudation |
| Membranoproliferative glomerulonephritis (MPGN) Type I | Nephrotic syndrome | (I) Immune complex | | (I) IgG + C3; C1q + C4 | (I) Subendothelial deposits |
| | | | Mesangial proliferation; basement membrane thickening; splitting | | |
| Dense deposit disease (MPGN Type II) | Hematuria | (II) Autoantibody: alternative complement pathway | | (II) C3 ± IgG; no C1q or C4 | (II) Dense deposits |
| | Chronic renal failure | | | | |
| IgA nephropathy | Recurrent hematuria or proteinuria | Unknown; see text | Focal proliferative glomerulonephritis; mesangial widening | IgA +/- IgG, IgM, and C3 in mesangium | Mesangial and paramesangial dense deposits |
| Chronic glomerulonephritis | Chronic renal failure | Variable | Hyalinized glomeruli | Granular or negative | |

ANCA, antineutrophil cytoplasmic antibody; GBM, glomerular basement membrane; RPGN, rapidly progressive glomerulonephritis.

all lobules of all glomeruli. There is also swelling of endothelial cells, and the combination of proliferation, swelling, and leukocyte infiltration obliterates the capillary lumens. There may be interstitial edema and inflammation, and the tubules often contain red cell casts.

By **immunofluorescence microscopy,** there are granular deposits of IgG, IgM, and C3 in the mesangium and along the basement membrane. Although almost universally present, they are often focal and sparse. The characteristic **electron microscopic findings** are discrete, amorphous, electrondense deposits on the epithelial side of the membrane, often having the appearance of "humps" ( Fig. 20-16*C)* , presumably representing the antigen-antibody complexes at the epithelial cell surface. Subendothelial and intramembranous deposits are also commonly seen, and mesangial deposits may be present. There is often swelling of endothelial and mesangial cells.

**Clinical Course.**

In the classic case, a young child abruptly develops malaise, fever, nausea, oliguria, and hematuria (smoky or cocoa-colored urine) 1 to 2 weeks after recovery from a sore throat. The patients exhibit red cell casts in the urine, mild proteinuria (usually less than 1 mg/day), periorbital edema, and mild to moderate hypertension. In adults, the onset is more likely to be atypical, with the sudden appearance of hypertension or edema, frequently with elevation of BUN. During epidemics caused by nephritogenic streptococcal infections, glomerulonephritis may be asymptomatic, discovered only on screening for microscopic hematuria. Important laboratory findings include elevations of antistreptococcal antibody (ASO) titers and a decline in the serum concentration of C3 and other components of the complement cascade and the presence of cryoglobulins in the serum.

More than 95% of affected children eventually recover totally with conservative therapy aimed at maintaining sodium and water balance. A small minority of children (perhaps less than 1%) do not improve, become severely oliguric, and develop a rapidly progressive form of glomerulonephritis

**Figure 20-16** Acute proliferative glomerulonephritis. *A*, Normal glomerulus. *B*, Glomerular hypercellularity is due to intracapillary leukocytes and proliferation of intrinsic glomerular cells. *C*, Typical electron-dense subepithelial "hump" and a neutrophil in the lumen. *(Courtesy of Dr. H. Rennke, Brigham and Women's Hospital, Boston, MA.)*
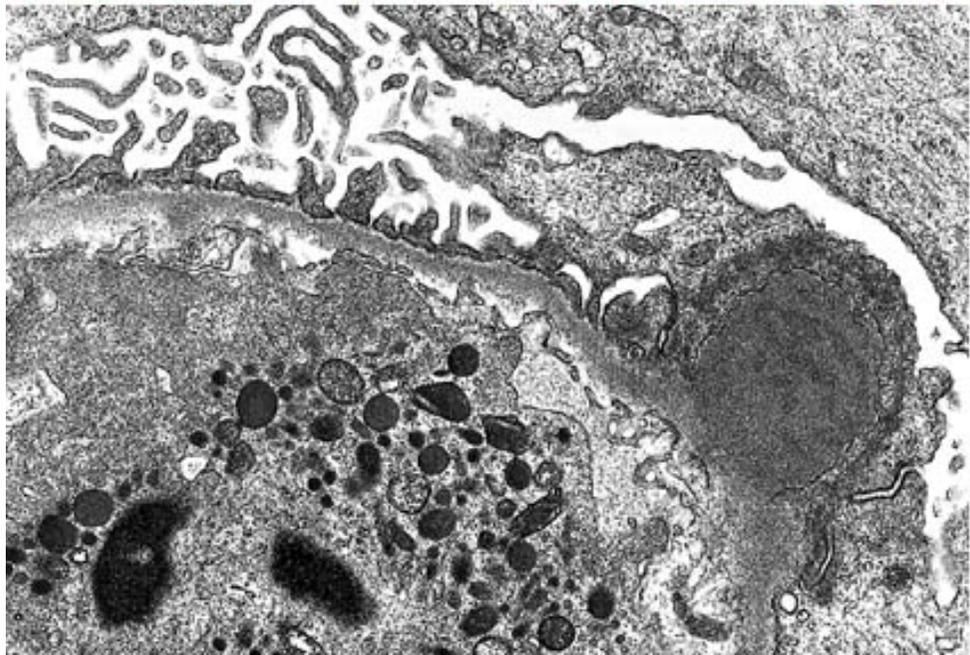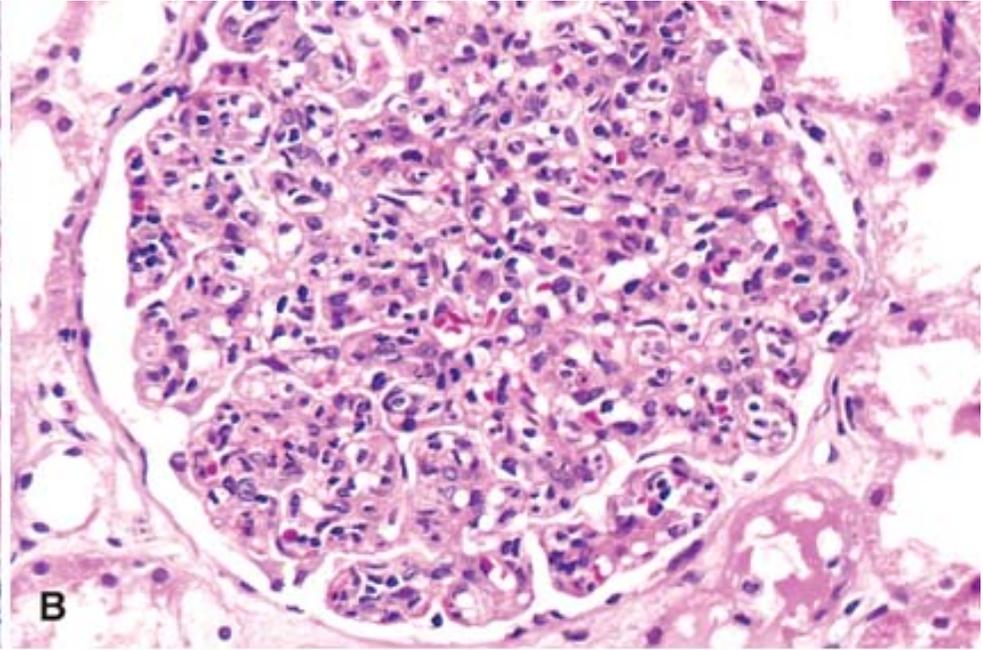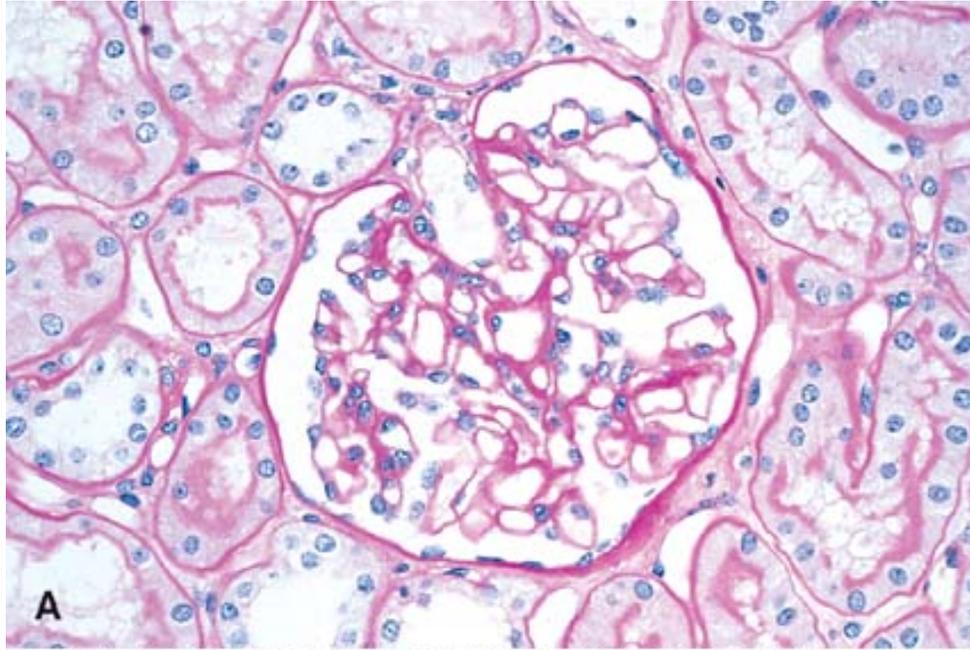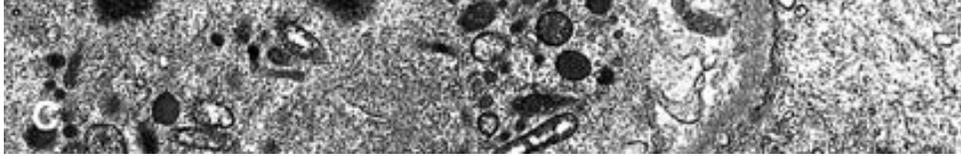
**TABLE 20-7** -- Rapidly Progressive Glomerulonephritis (RPGN)

| *Type I RPGN (Anti-GBM Antibody)* |
| --- |
| Idiopathic |
| Goodpasture syndrome |
| *Type II RPGN (Immune Complex)* |
| Idiopathic |
| Postinfectious |
| Systemic lupus erythematosus |
| Henoch-Schönlein purpura (IgA) |
| Others |
| *Type III RPGN (Pauci-Immune)* |
| ANCA associated |
| Idiopathic |
| Wegener granulomatosis |
| Microscopic polyarteritis nodosa/microscopic polyangiitis |

previously described.[48] In some of these patients, the anti-GBM antibodies cross-react with pulmonary alveolar basement membranes to produce the clinical picture of pulmonary hemorrhage associated with renal failure (*Goodpasture syndrome*). Plasmapheresis to remove the pathogenic circulating antibodies is usually part of the treatment, which also includes therapy to suppress the underlying immune response.

The Goodpasture antigen, as was noted earlier, is a peptide within the noncollagenous portion of the $\alpha_3$ -chain of collagen type IV. [27] What triggers the formation of these antibodies is unclear in most patients. Exposure to viruses or hydrocarbon solvents (found in paints and dyes) has been implicated in some patients, as have various drugs and cancers. There is a high prevalence of certain HLA subtypes and haplotypes (e.g., HLA-DRB1) in affected patients, a finding consistent with the genetic predisposition to autoimmunity.[49]

The second type of *RPGN* is the result of *immune complex-mediated disease*. It can be a complication of any of the immune complex nephritides, including postinfectious glomerulonephritis, SLE, IgA nephropathy, and Henoch-Schönlein purpura. In all of these cases, immunofluorescence studies reveal the granular pattern of staining characteristic of immune complex deposition. These patients cannot usually be helped by plasmapheresis, and they require treatment for the underlying disease.

The third type of *RPGN*, also called *pauci-immune type*, is defined by the lack of anti-GBM antibodies or immune complexes by immunofluorescence and electron microscopy. Most patients with this type of RPGN have *antineutrophil cytoplasmic antibodies* (ANCA), of cytoplasmic (C) or perinuclear (P) patterns, in the serum, which, as we have seen ( Chapter 11 ), play a role in some vasculitides. Hence, in some cases, this type of RPGN is a component of a systemic vasculitis such as Wegener granulomatosis or microscopic polyarteritis. In many

cases, however, pauci-immune crescentic glomerulonephritis is isolated and hence *idiopathic*. More than 90% of such idiopathic cases have c-ANCA or p-ANCA in the sera.[50] The presence of circulating ANCAs in both idiopathic RPGN and cases of RPGN that occur as a component of systemic vasculitis, and the similar pathologic features in either setting, have led to the idea that these disorders are pathogenetically related. According to this concept, all cases of RPGN of the pauci-immune type are manifestations of small vessel vasculitis or polyangiitis, which is limited to glomerular and perhaps peritubular capillaries in cases of idiopathic crescentic glomerulonephritis. [51] The clinical distinction between systemic vasculitis with pauci-immune renal involvement and idiopathic crescentic glomerulonephritis accordingly has become deemphasized, as these entities are viewed as part of a spectrum of vasculitic disease. ANCAs have proved to be invaluable as a highly sensitive diagnostic marker for pauci-immune RPGN, but proof of their role as a direct cause of RPGN has been elusive. Recent strong evidence of their pathogenic potential has been obtained by studies in which antibodies against myeloperoxidase (the target antigen of most p-ANCAs) are transferred into mice.[52]

To summarize, all three types of RPGN may be associated with a well-defined renal or extrarenal disease, but in many cases (approximately 50%), the disorder is idiopathic. Of the patients with this syndrome, about one fifth have anti-GBM antibody-induced disease without lung involvement; another one fourth have immune complex-mediated disease RPGN; and the remainder are of the pauci-immune type. *The common denominator in all types of RPGN is severe glomerular injury.*

**Morphology.**

The kidneys are enlarged and pale, often with petechial hemorrhages on the cortical surfaces. Depending on the underlying cause, the glomeruli may show focal necrosis, diffuse or focal endothelial proliferation, and mesangial proliferation. The histologic picture, however, is dominated by the formation of distinctive **crescents** ( Fig. 20-17 ). Crescents are formed by proliferation of parietal cells and by migration of monocytes and macrophages into the urinary space. Neutrophils and lymphocytes may be present. The crescents eventually obliterate Bowman space and compress the glomerular tuft. **Fibrin strands are prominent between the cellular layers in the crescents;** indeed, as discussed earlier, the escape of fibrin into Bowman space is an important

**Figure 20-17** Crescentic glomerulonephritis (PAS stain). Note the collapsed glomerular tufts and the crescent-shaped mass of proliferating cells and leukocytes internal to Bowman capsule. *(Courtesy of Dr. M.A. Venkatachalam, University of Texas Health Sciences Center, San Antonio, TX.)*
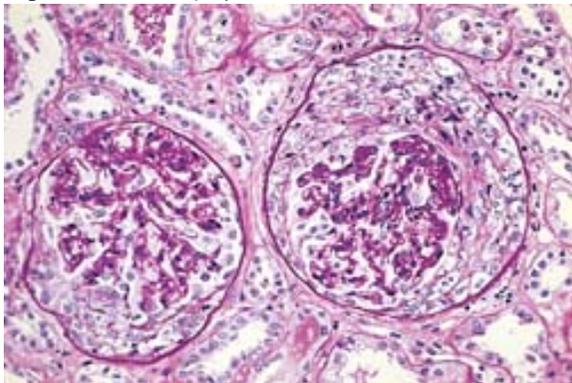


**Figure 20-18** Rapidly progressive glomerulonephritis. Electron micrograph showing characteristic wrinkling of GBM with focal disruptions in its continuity (*arrows*).
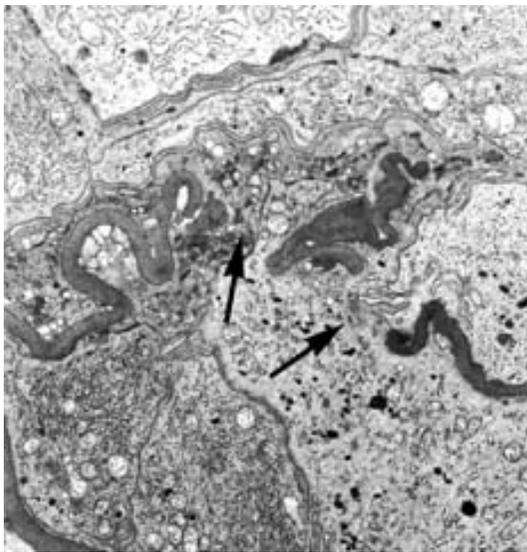
**TABLE 20-8** -- Causes of Nephrotic Syndrome

| | Prevalence (%) [*] | |
| --- | --- | --- |
| | *Children* | *Adults* |
| *Primary Glomerular Disease* | | |
| Membranous glomerulopathy | 5 | 30 |
| Minimal change disease | 65 | 10 |
| Focal segmental glomerulosclerosis | 10 | 35 |
| Membranoproliferative glomerulonephritides | 10 | 10 |
| Other proliferative glomerulonephritis (focal, "pure mesangial," IgA nephropathy) | 10 | 15 |
| *Systemic Diseases* | | |
| Diabetes mellitus | | |
| Amyloidosis | | |
| Systemic lupus erythematosus | | |
| Drugs (nonsteroidal anti-inflammatory, penicillamine, "street heroin") | | |
| Infections (malaria, syphilis, hepatitis B and C, acquired immunodeficiency syndrome) | | |
| Malignant disease (carcinoma, lymphoma) | | |
| Miscellaneous (bee-sting allergy, hereditary nephritis) | | |

*Approximate prevalence of primary disease = 95% in children, 60% in adults. Approximate prevalence of systemic disease = 5% in children, 40% in adults.

**MEMBRANOUS GLOMERULOPATHY (MEMBRANOUS NEPHROPATHY)**

*Membranous glomerulopathy is the most common cause of the nephrotic syndrome in adults. It is characterized by diffuse thickening of the glomerular capillary wall and the accumulation of electron-dense, immunoglobulin-containing deposits along the subepithelial side of the basement membrane.*[54]

Membranous glomerulopathy occurring in association with other systemic diseases and a variety of identifiable etiologic agents is referred to as secondary membranous glomerulopathy. The most notable such associations are as follows:

- *Drugs* (penicillamine, captopril, gold, nonsteroidal anti-inflammatory drugs [NSAIDs]): 1% to 7% of patients with rheumatoid arthritis treated with penicillamine or gold (drugs now used infrequently for this purpose) develop membranous glomerulopathy. NSAIDs, as we shall see, also cause minimal change disease.
- *Underlying malignant tumors*, particularly carcinoma of the lung and colon and melanoma. According to some investigators, these are present in up to 5% to 10% of adults with membranous glomerulopathy.[55]
- *SLE.* About 15% of glomerulonephritis in SLE is of the membranous type.
- *Infections* (chronic hepatitis B, hepatitis C, syphilis, schistosomiasis, malaria)
- *Other autoimmune disorders*, such as thyroiditis

In about 85% of patients, no associated condition can be uncovered, and the disease is considered idiopathic.

**Etiology and Pathogenesis.**

Membranous glomerulopathy is a form of chronic immune complex-mediated disease. In secondary membranous glomerulopathy, particular antigens can sometimes be identified in the immune complexes. For example, membranous glomerulopathy in SLE is associated with deposition of autoantigen-antibody complexes. Exogenous (hepatitis B, *Treponema* antigens) or endogenous (thyroglobulin) antigens have been identified within deposits in some patients.

The lesions bear a striking resemblance to those of experimental Heymann nephritis, which, as you might recall, is induced by antibodies to a *megalin* antigenic complex. A similar but still unidentified antigen is presumed to be present in most cases of idiopathic membranous glomerulopathy in humans. Susceptibility to Heymann nephritis in rats and membranous glomerulopathy in humans is linked to the MHC locus, which influences the ability to produce antibodies to the nephritogenic antigen. Thus, idiopathic membranous glomerulopathy, like Heymann nephritis, is considered *an autoimmune disease linked to susceptibility genes and caused by antibodies to a renal autoantigen*.

How does the glomerular capillary wall become leaky in membranous glomerulopathy? There is a paucity of neutrophils, monocytes, or platelets in glomeruli and the virtually uniform presence of complement, and experimental work suggests a direct action of C5b-C9, the pathway leading to the formation of the membrane attack complex. C5b-C9 causes activation of glomerular epithelial and mesangial cells, inducing them to liberate proteases and oxidants, which cause capillary wall injury and increased protein leakage.

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**Morphology.**

By light microscopy, the glomeruli either appear normal in the early stages of the disease or exhibit **uniform, diffuse thickening of the glomerular capillary wall** ( Fig. 20-19*A* ). By

electron microscopy, the thickening is seen to be caused by irregular dense deposits between the basement membrane and the overlying epithelial cells, the latter

**Figure 20-19** Membranous glomerulonephritis. *A*, PAS stain. Note the marked diffuse thickening of the capillary wall without an increase in the number of cells. *B*, Electron micrograph showing electron-dense deposits (*arrow*) along the epithelial side of the basement membrane (*B*). Note the obliteration of foot process overlying deposits. CL, capillary lumen; End, endothelium; Ep, epithelium. *C*, Characteristic granular immunofluorescent deposits of IgG along GBM. *D*, Diagrammatic representation of membranous glomerulonephritis.



Epithelium with
effaced foot processes

Thickened
basement
membrane

Subepithelial
deposits

D
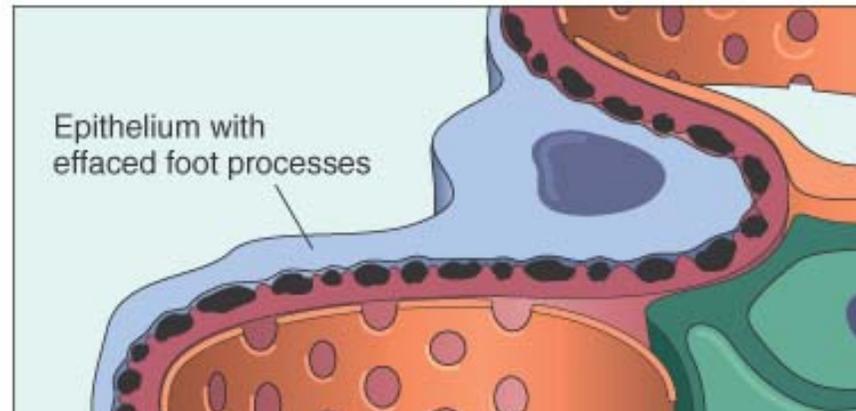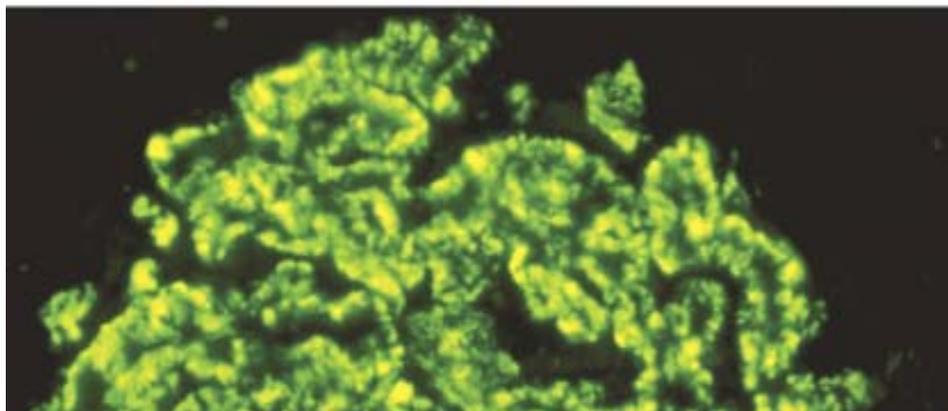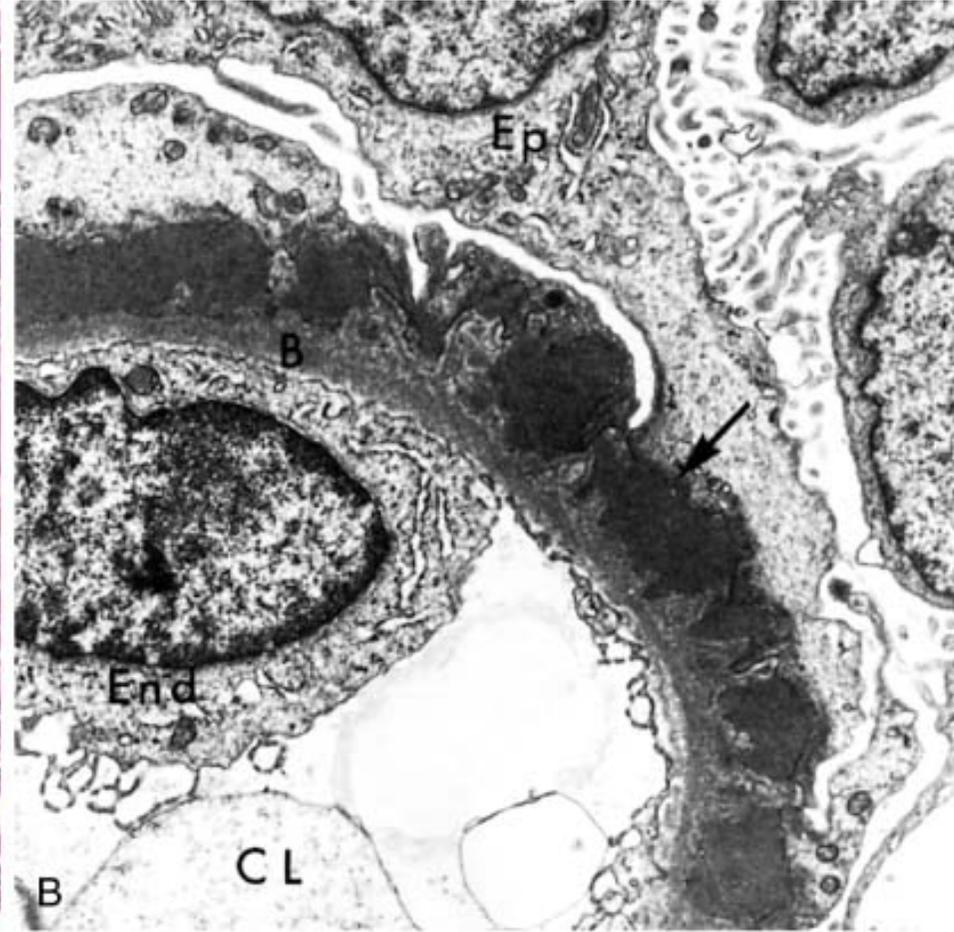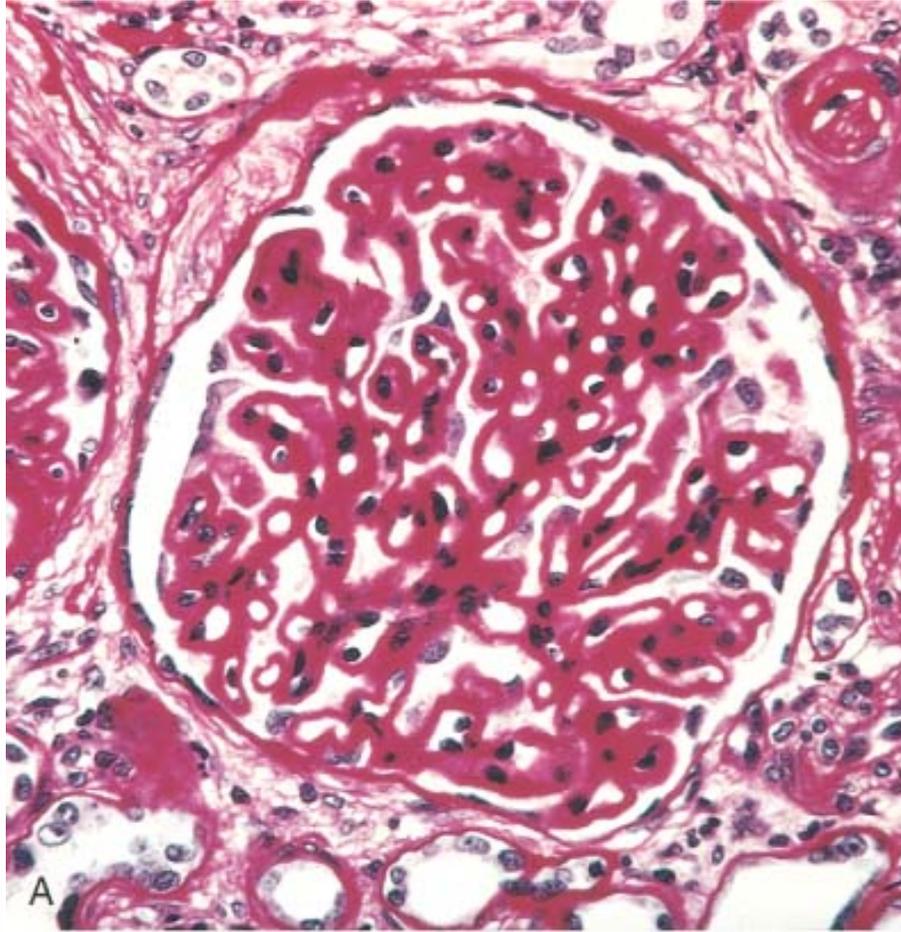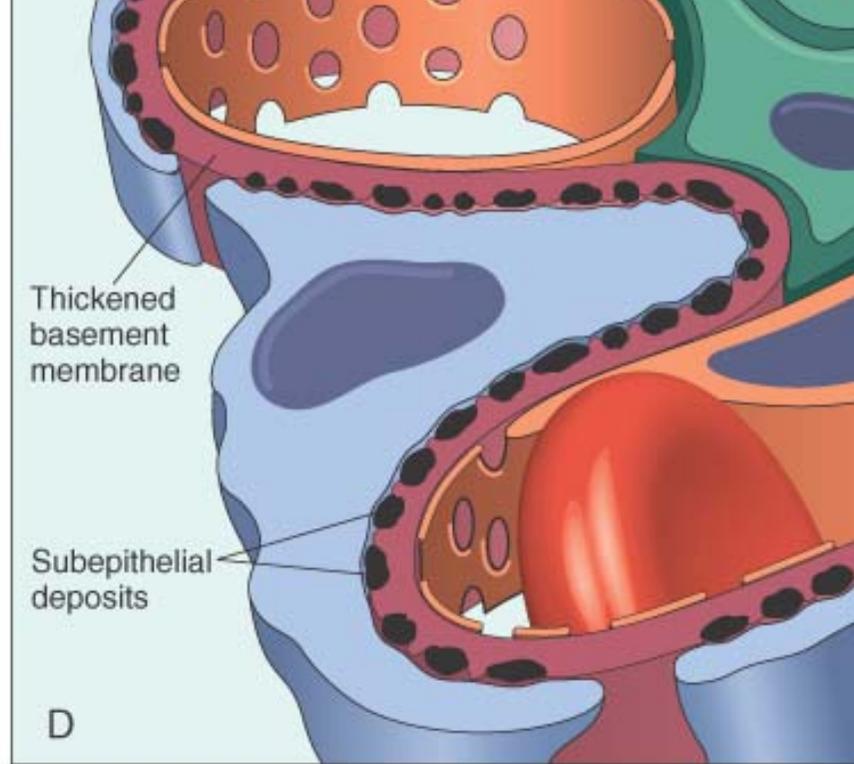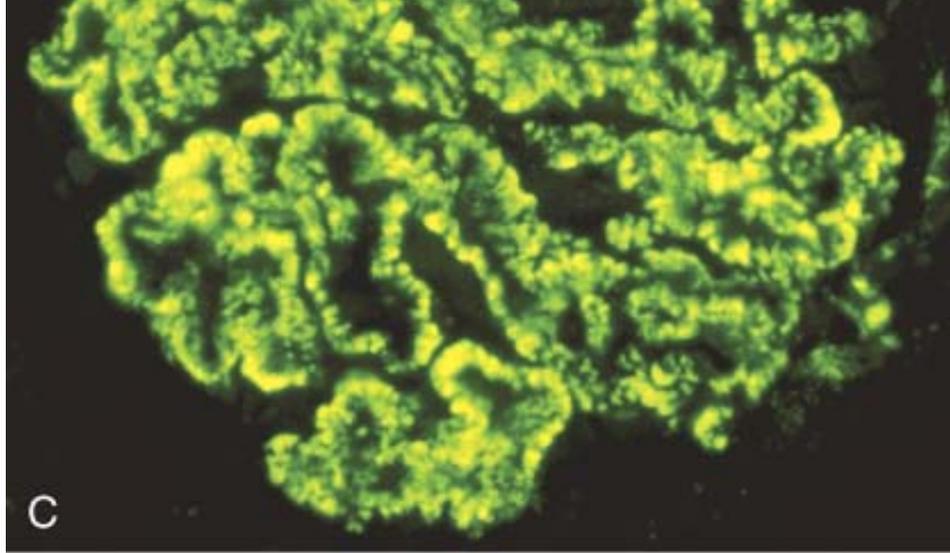
**Figure 20-20** Minimal change disease. Glomerulus stained with PAS. Note normal basement membrane and absence of proliferation. Compare with membranous glomerulopathy in Figure 20-19*A* .
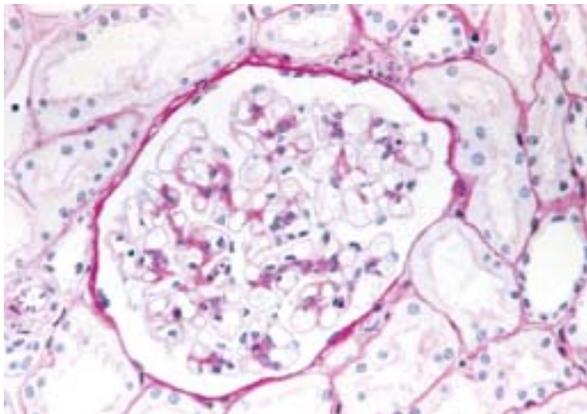


**Figure 20-21** *A*, Ultrastructural characteristics of minimal change disease: effacement of foot processes (*double arrows*), absence of deposits, vacuoles (V), and microvilli in visceral epithelial cells (*single arrow*). *B*, Schematic representation of minimal change disease, showing diffuse effacement of foot processes.
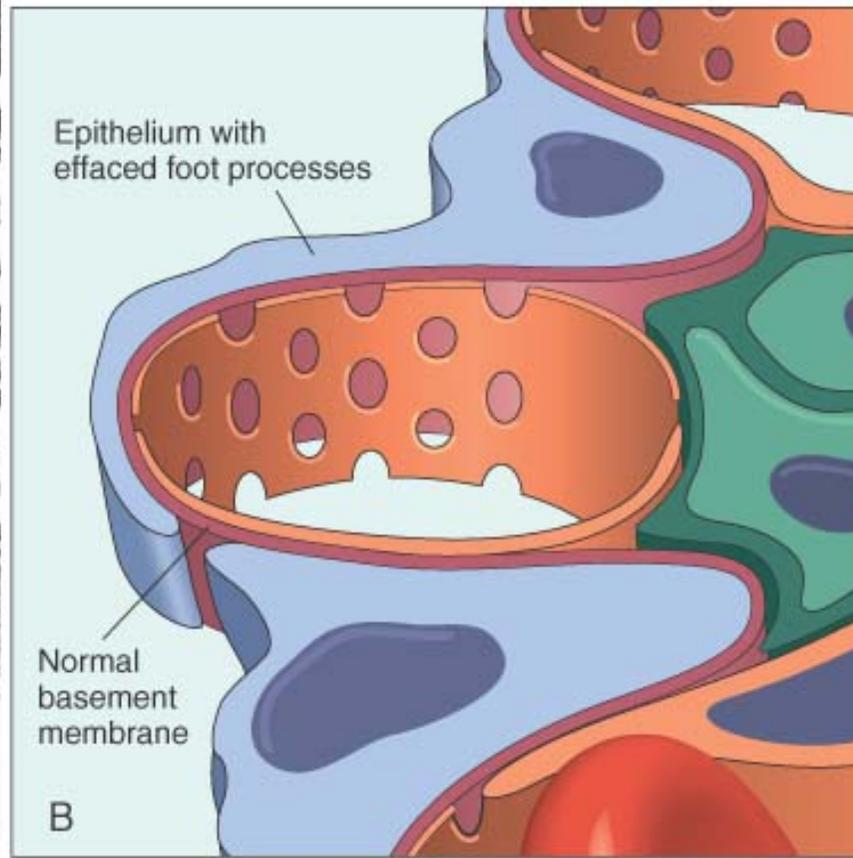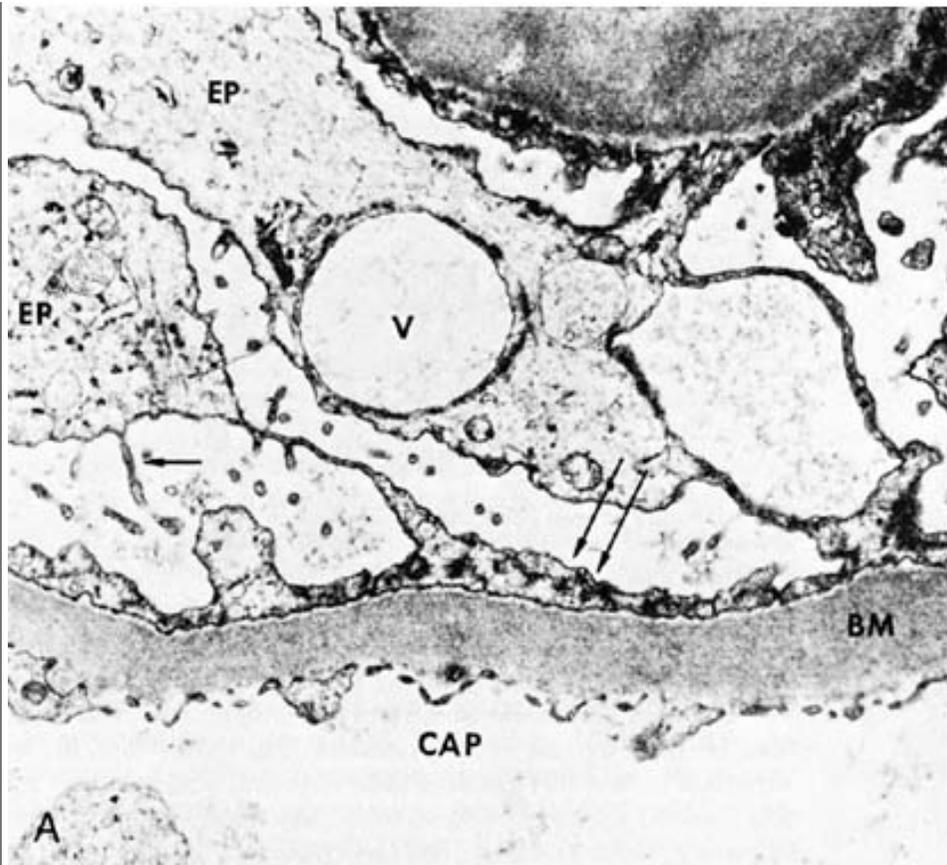
**Figure 20-22** Focal segmental glomerulosclerosis, PAS stain. *A*, Low-power view showing segmental sclerosis in one of three glomeruli (at 3 o'clock). *B*, High-power view showing hyaline insudation and lipid (small vacuoles) in sclerotic area.
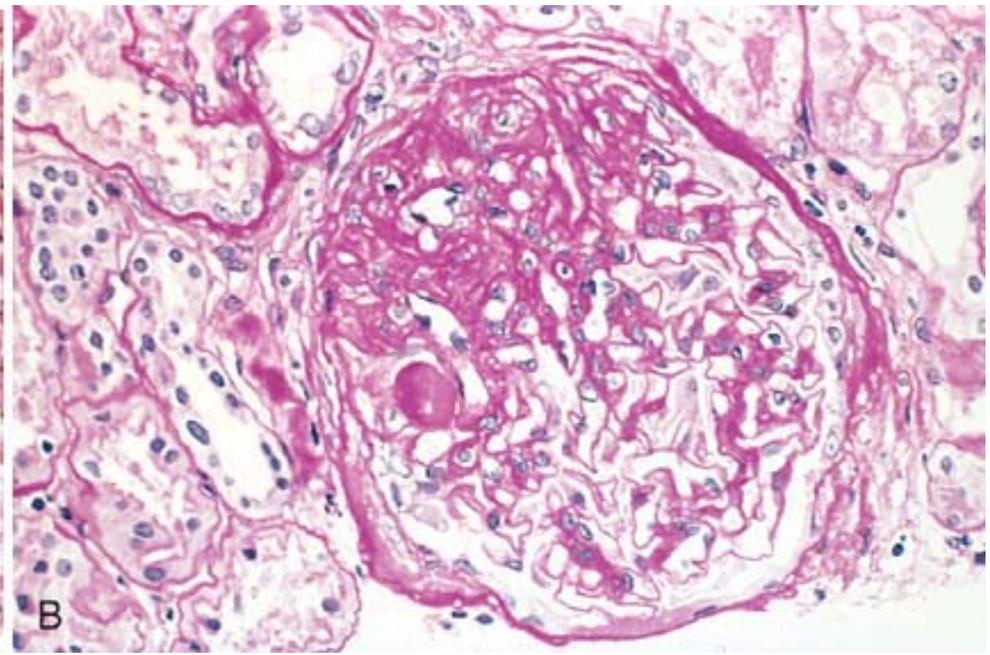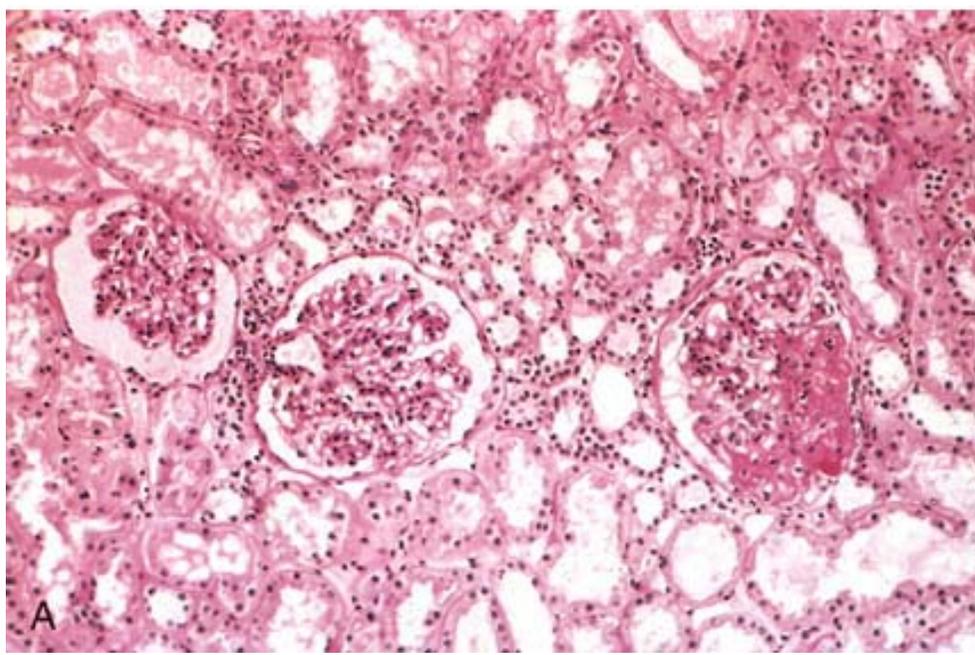
**Figure 20-23** Membranoproliferative glomerulonephritis, showing mesangial cell proliferation, increased mesangial matrix (staining black with silver stain), basement membrane thickening and focal splitting, accentuation of lobular architecture, swelling of cells lining peripheral capillaries, and influx of leukocytes.
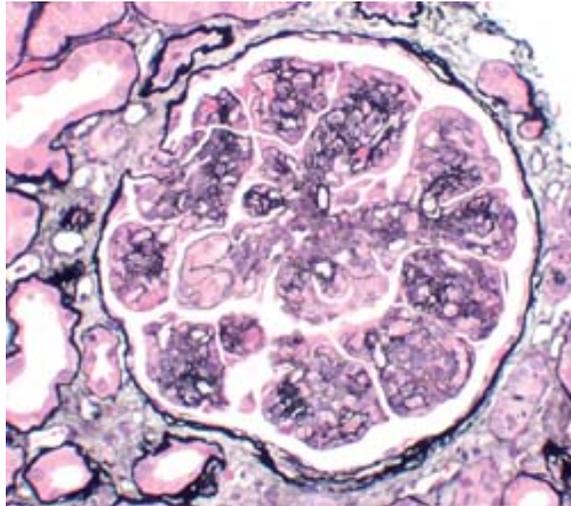


**Figure 20-24** *A*, Membranoproliferative glomerulonephritis, type I. Note the large subendothelial deposit (*arrow*) incorporated into mesangial matrix (M). E, endothelium; EP, epithelium; CL, capillary lumen. *B*, Type II membranoproliferative glomerulonephritis, dense-deposit disease. There are markedly dense homogeneous deposits within the basement membrane proper. CL, capillary lumen. *C*, Schematic representation of patterns in the two types of membranoproliferative GN. In type I there are subendothelial deposits; type II is characterized by intramembranous dense deposits (dense-deposit disease). In both, mesangial interposition gives the appearance of split basement membranes when viewed in the light microscope.

TYPE I

Subendothelial deposit

Interposed mesangial cell process

Intramembranous deposit

TYPE II
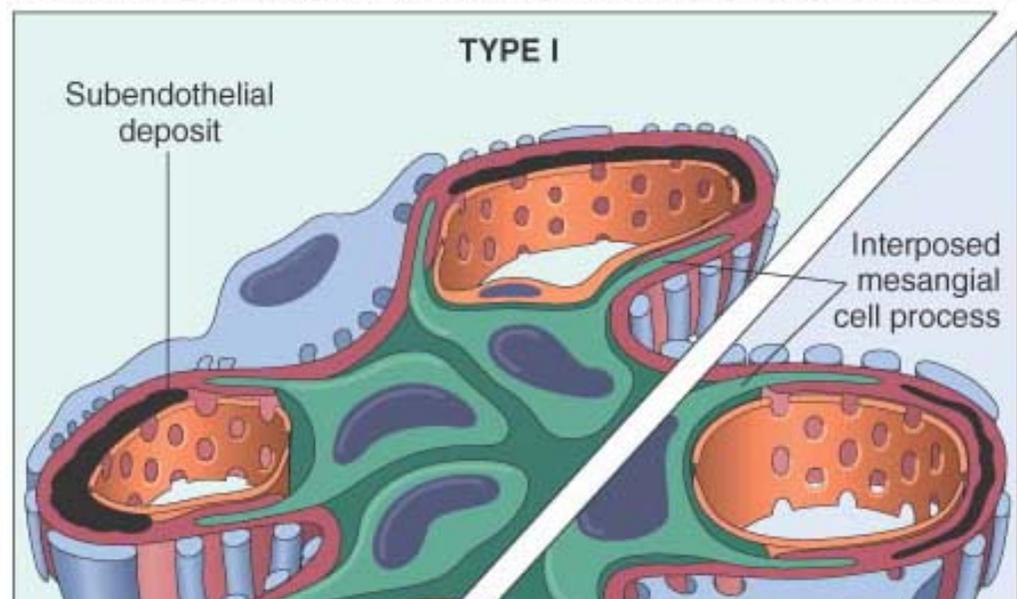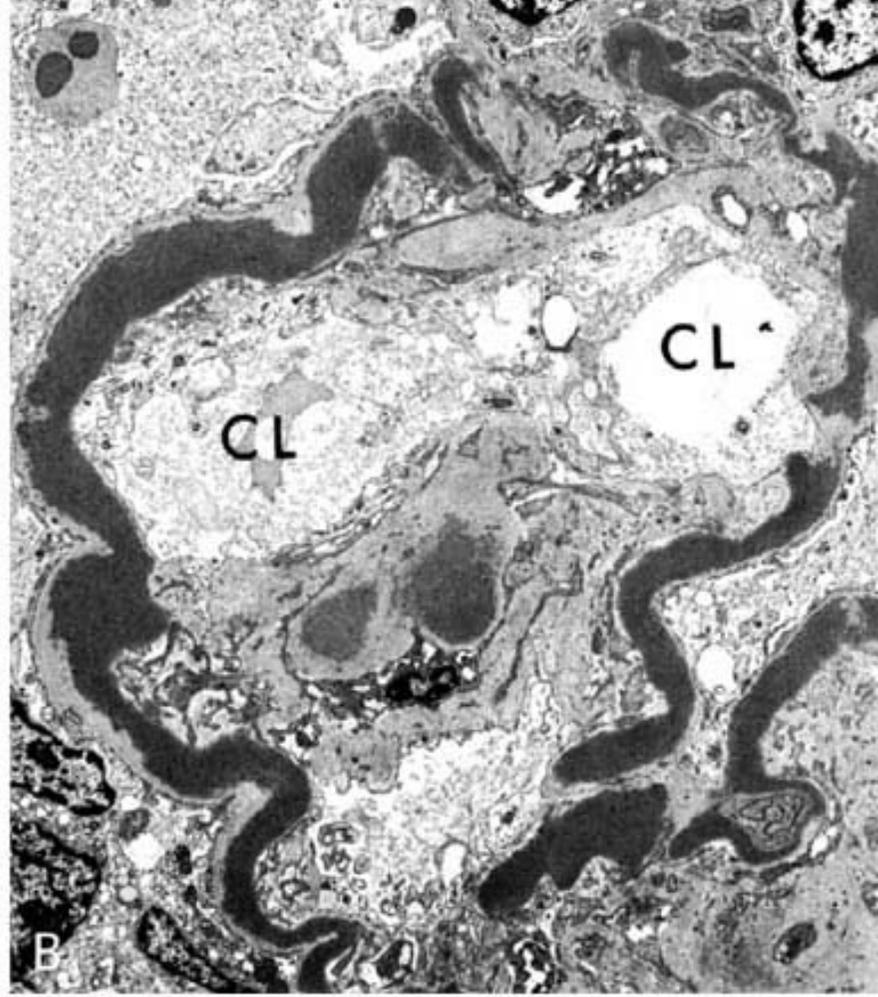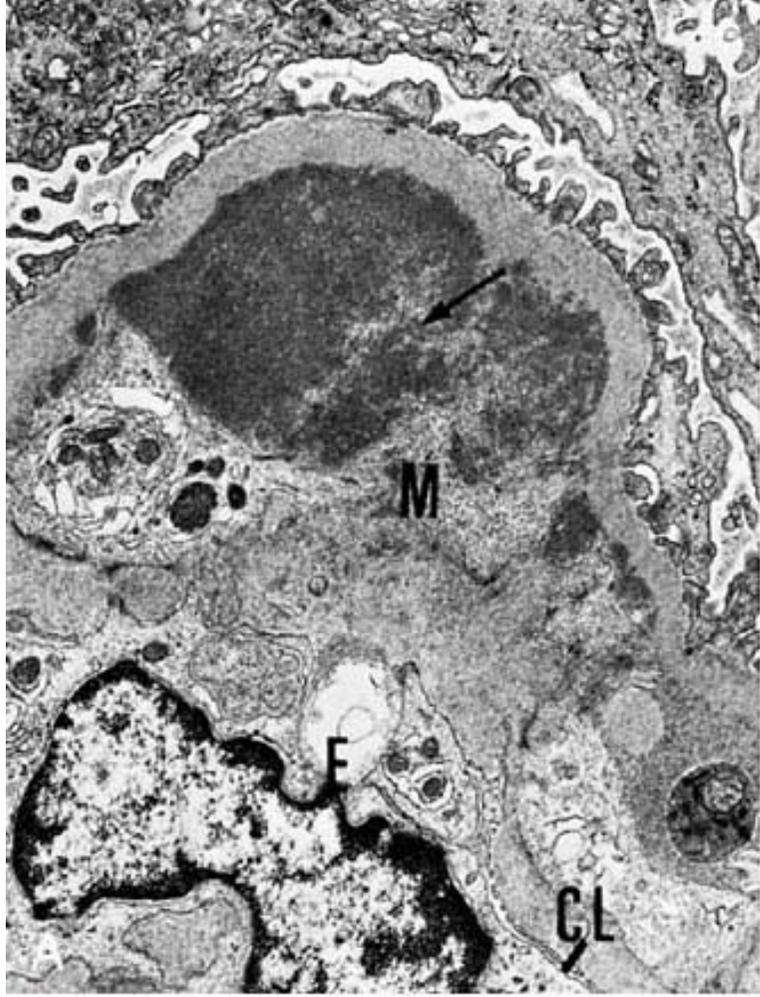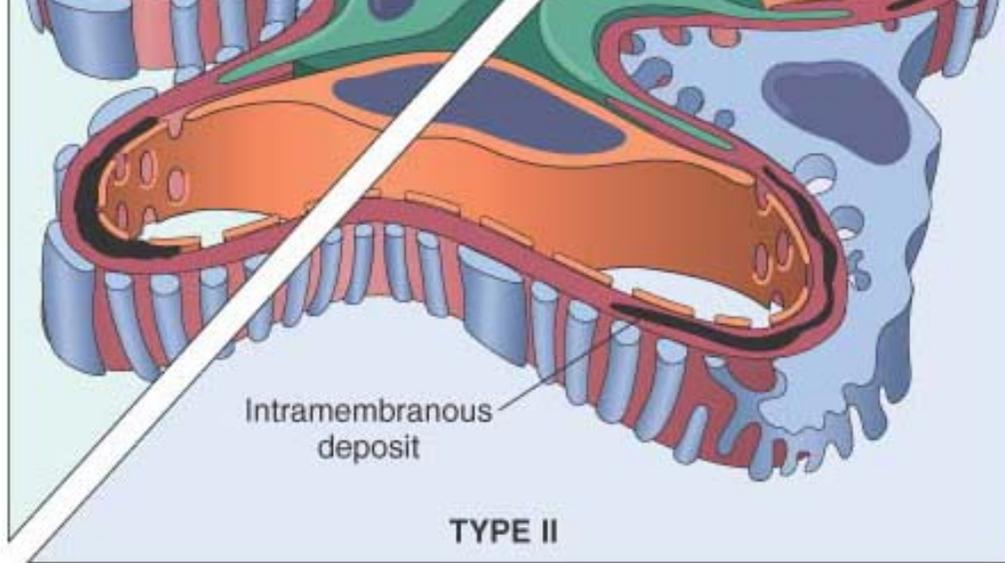
C

**Figure 20-25** The alternative complement pathway. Note that C3NeF, present in the serum of patients with membranoproliferative glomerulonephritis, acts at the same step as properdin, serving to stabilize the alternative pathway C3 convertase, thus enhancing C3 breakdown and causing hypocomplementemia.



Polysaccharide, endotoxin, IgA aggregates

C3

$B, \bar{D}, Mg^{2+}$

$\overline{C3bBb}$
(alternative pathway C3 convertase)

Properdin    stabilize
**C3NeF**
                degrade    I,H    C3b feedback

C3 ——————————→ C3b
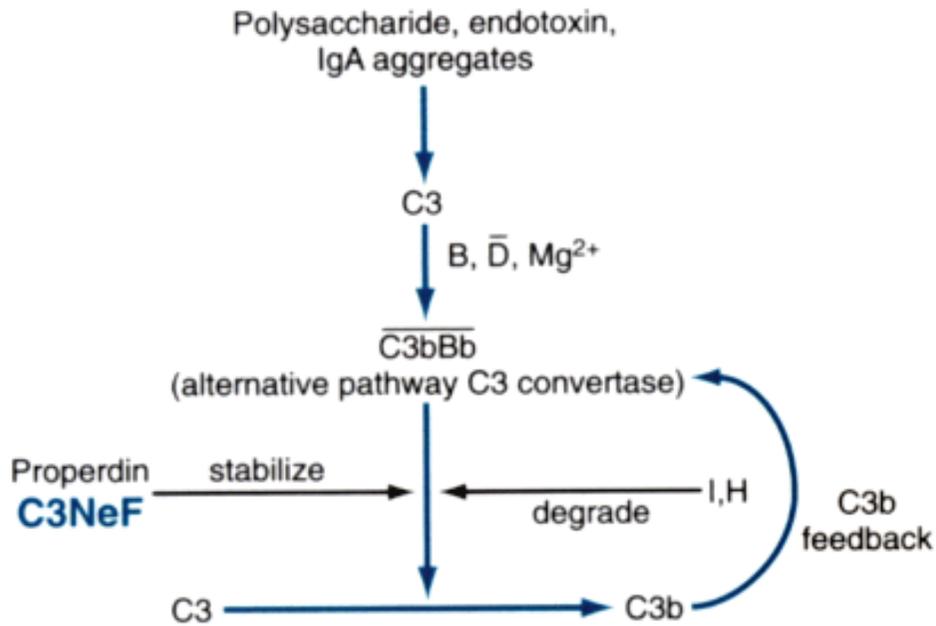
**Figure 20-26** IgA nephropathy. *A*, Light microscopy showing mesangial proliferation and matrix increase. *B*, Characteristic deposition of IgA, principally in mesangial regions, detected by immunofluorescence.
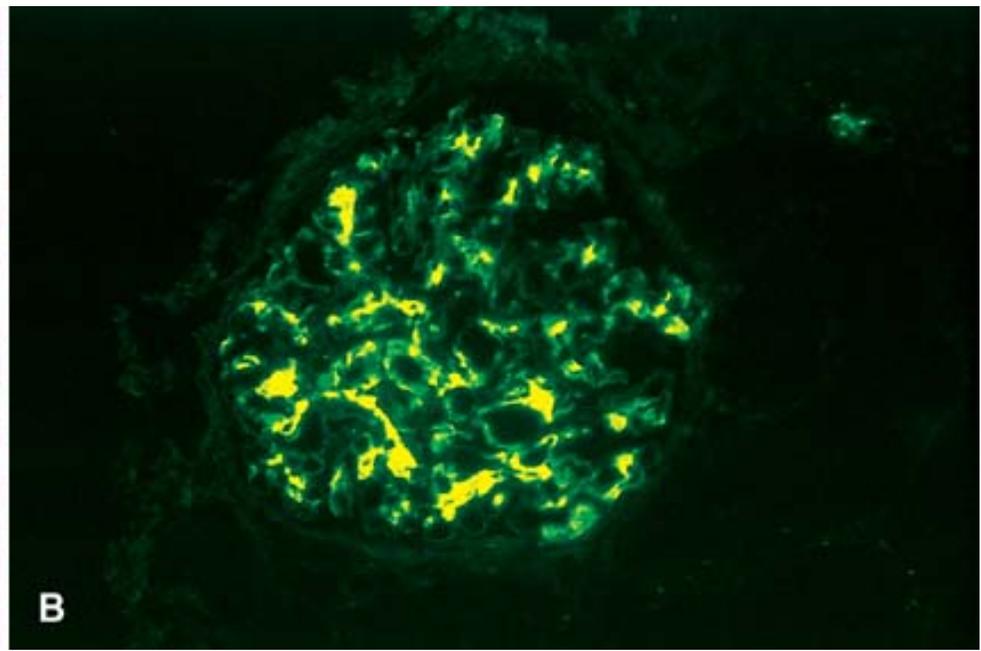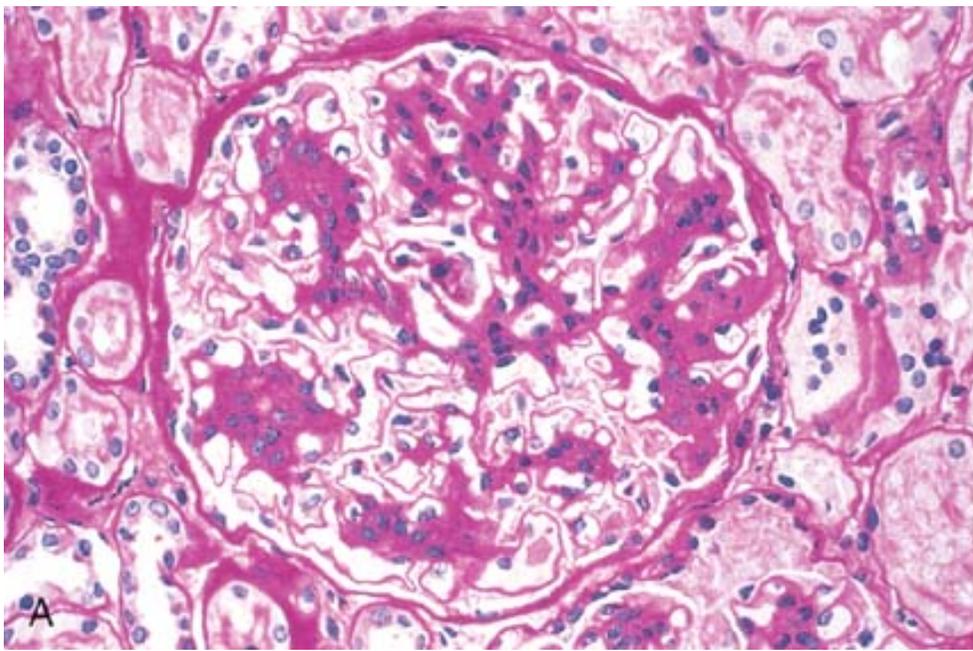
**Figure 20-27** Hereditary nephritis. Electron micrograph of glomerulus with irregular thickening of the basement membrane, lamination of the lamina densa, and foci of rarefaction. Such changes may be present in other diseases but are most pronounced and widespread in hereditary nephritis. CL, capillary lumen; Ep, epithelium.
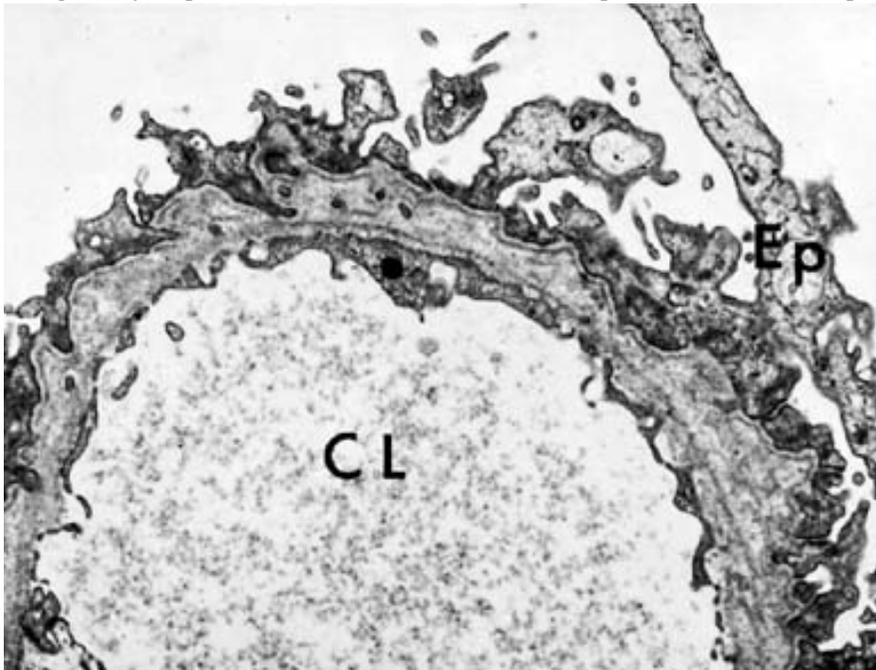


**Figure 20-28** Primary glomerular diseases leading to chronic glomerulonephritis (GN). The thickness of the arrows reflects the approximate proportion of patients in each group who progress to chronic glomerulonephritis: poststreptococcal (1% to 2%); rapidly progressive (crescentic) (90%), membranous (30% to 50%), focal glomerulosclerosis (50% to 80%),

membranoproliferative glomerulonephritis (50%), IgA nephropathy (30% to 50%).



Poststreptococcal

Rapidly progressive GN

Membranous GN → Chronic GN ← Others

Focal glomerulosclerosis

Membranoproliferative GN

IgA
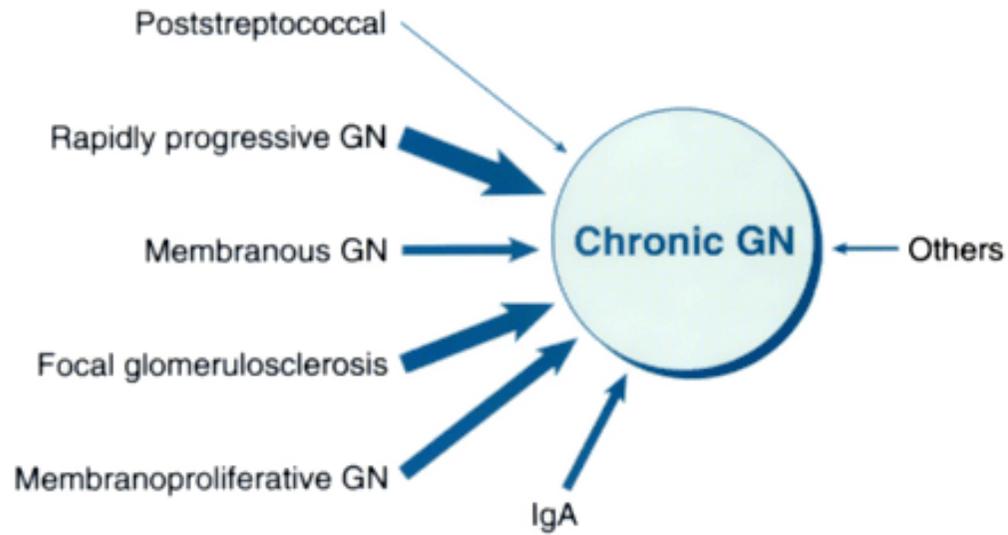
**Figure 20-29** Chronic glomerulonephritis. A Masson trichrome preparation shows complete replacement of virtually all glomeruli by blue-staining collagen. *(Courtesy of Dr. M.A. Venkatachalam, Department of Pathology, University of Texas Health Sciences Center, San Antonio, TX.)*
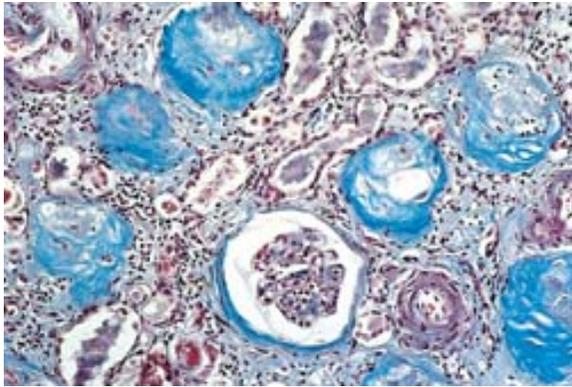


**Figure 20-30** Electron micrograph of advanced diabetic glomerulosclerosis. Note the massive increase in mesangial matrix (Mes) encroaching on the glomerular capillary lumina (CL). The GBM and Bowman capsule (C) are markedly thickened. Ep, epithelium; E, endothelium.
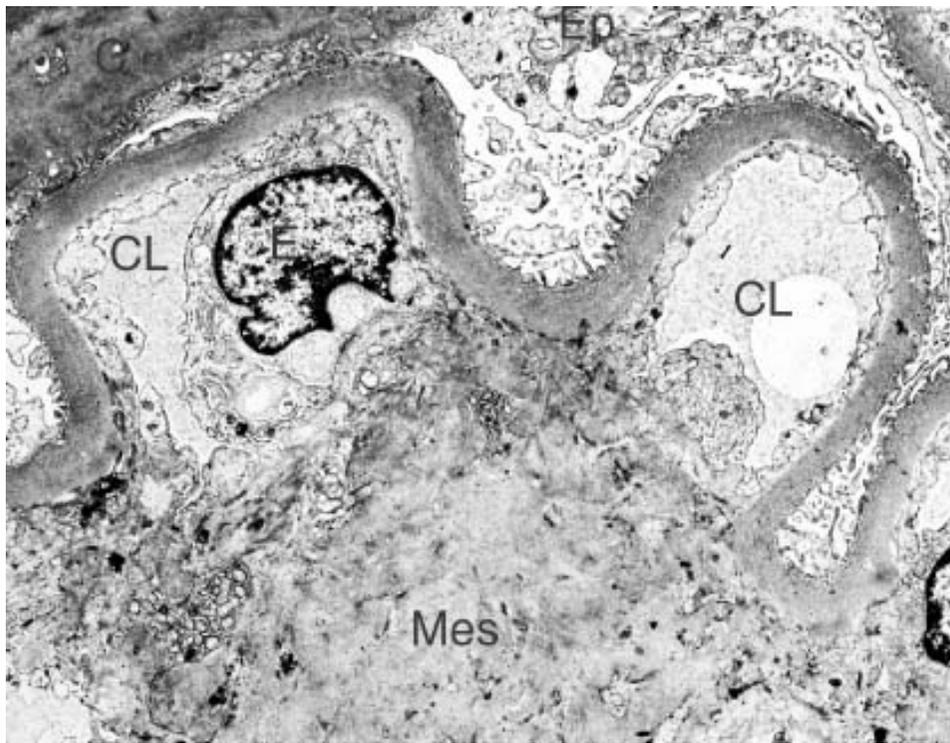
**Figure 20-31** Diffuse and nodular diabetic glomerulosclerosis (PAS stain). Note the diffuse increase in mesangial matrix and characteristic acellular PAS-positive nodules.
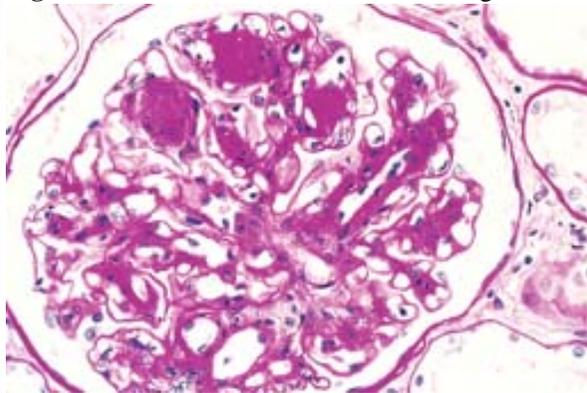


Ischemia causes numerous structural and functional alterations in epithelial cells, as discussed in Chapter 1 . The structural changes include those of reversible injury (such as cellular swelling, loss of brush border, blebbing, loss of polarity, and cell detachment) and those associated with lethal injury (necrosis and apoptosis). Biochemically, there is depletion of adenosine triphosphate; accumulation of intracellular calcium; activation of proteases (e.g., calpain), which cause cytoskeletal disruption, and phospholipases, which damage membranes; generation of reactive oxygen species; and activation of caspases, which induce apoptotic cell death. One early reversible result of ischemia is *loss of*

*cell polarity* due to redistribution of membrane proteins (e.g., the enzyme Na$^+$ K$^+$ -ATPase) from the basolateral to the luminal surface of the tubular cells, resulting in abnormal ion transport across the cells, and *increased sodium delivery to distal tubules*. The latter incites vasoconstriction via *tubuloglomerular feedback*, which will be discussed below.[82] In addition, ischemic tubular cells express cytokines and adhesion molecules (such as ICAM-1), thus recruiting leukocytes that appear to participate in the subsequent injury.[83] In time, injured cells detach from the basement membranes and cause *luminal tubule obstruction*, increased intratubular pressure, and decreased GFR. In addition, fluid from the damaged tubules can leak into the interstitium, resulting in interstitial edema, increased interstitial pressure, and further damage to the tubule. All these effects, as shown in Figure 20-32 , contribute to the decreased GFR.

   • *Disturbances in blood flow:* Ischemic renal injury is also characterized by *hemodynamic alterations* that cause reduced GFR. The major one is *intrarenal vasoconstriction*, which results in both reduced glomerular plasma flow and reduced oxygen delivery to the functionally important tubules in the outer medulla (thick ascending limb and straight segment of the proximal tubule). A number of vasoconstrictor pathways have been implicated, including the renin-angiotensin mechanism, stimulated by increased distal sodium delivery (via *tubuloglomerular feedback*), and *sublethal endothelial injury*, leading to increased release of the vasoconstrictor *endothelin* and decreased production of the vasodilators *nitric oxide* and *PGI$_2$* . Finally, there is also some evidence of a direct effect of ischemia or toxins on the glomerulus, causing a reduced glomerular ultrafiltration coefficient, possibly due to mesangial contraction.

The patchiness of tubular necrosis and maintenance of the integrity of the basement membrane along many segments allow ready repair of the necrotic foci and recovery of function if the precipitating cause is removed. This repair is dependent on the capacity of reversibly injured epithelial cells to proliferate and differentiate. Re-epithelialization is mediated by a variety of growth factors and cytokines produced locally by the tubular cells themselves (autocrine stimulation) or by inflammatory cells in the vicinity of necrotic foci (paracrine stimulation).[84] Of these, epidermal growth factor (EGF), TGF-α, insulin-like growth factor type I, and hepatocyte growth factor have been shown to be particularly important in renal tubular repair. Growth factors, indeed, are being explored as possible therapeutic agents to enhance re-epithelialization in ATN.[84]


**Figure 20-32** Possible pathogenetic mechanisms in ischemic acute renal failure (see text).
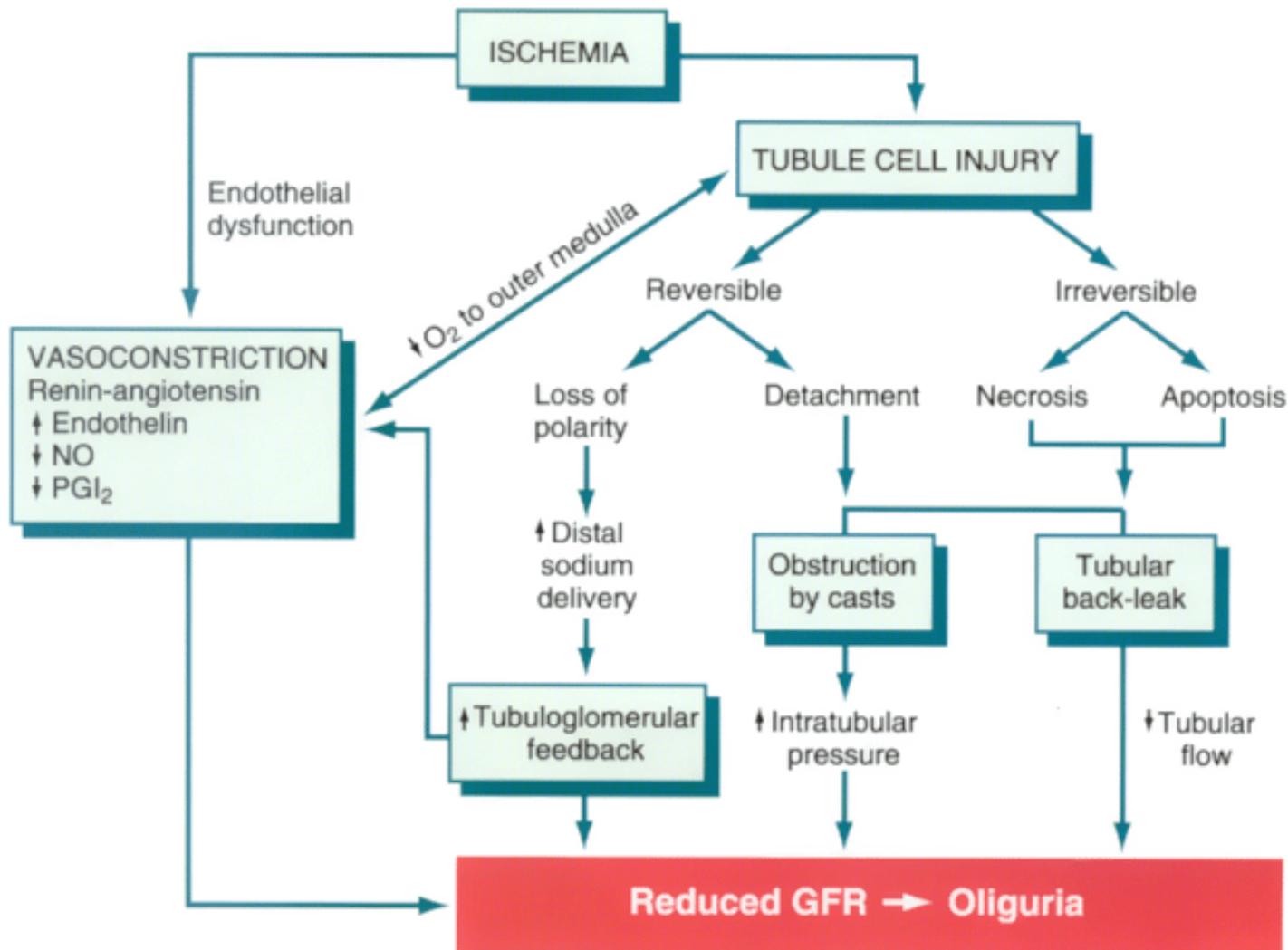
**Figure 20-33** Patterns of tubular damage in ischemic and toxic acute tubular necrosis. In the ischemic type, tubular necrosis is patchy, relatively short lengths of tubules are affected, and straight segments of proximal tubules (PST) and ascending limbs of Henle's loop (HL) are most vulnerable. In toxic acute tubular necrosis, extensive necrosis is present along the proximal tubule segments (PCT) with many toxins (e.g., mercury), but necrosis of the distal tubule, particularly ascending Henle's loop, also occurs. In both types, lumens of the distal convoluted tubules (DCT) and collecting ducts (CD) contain casts.
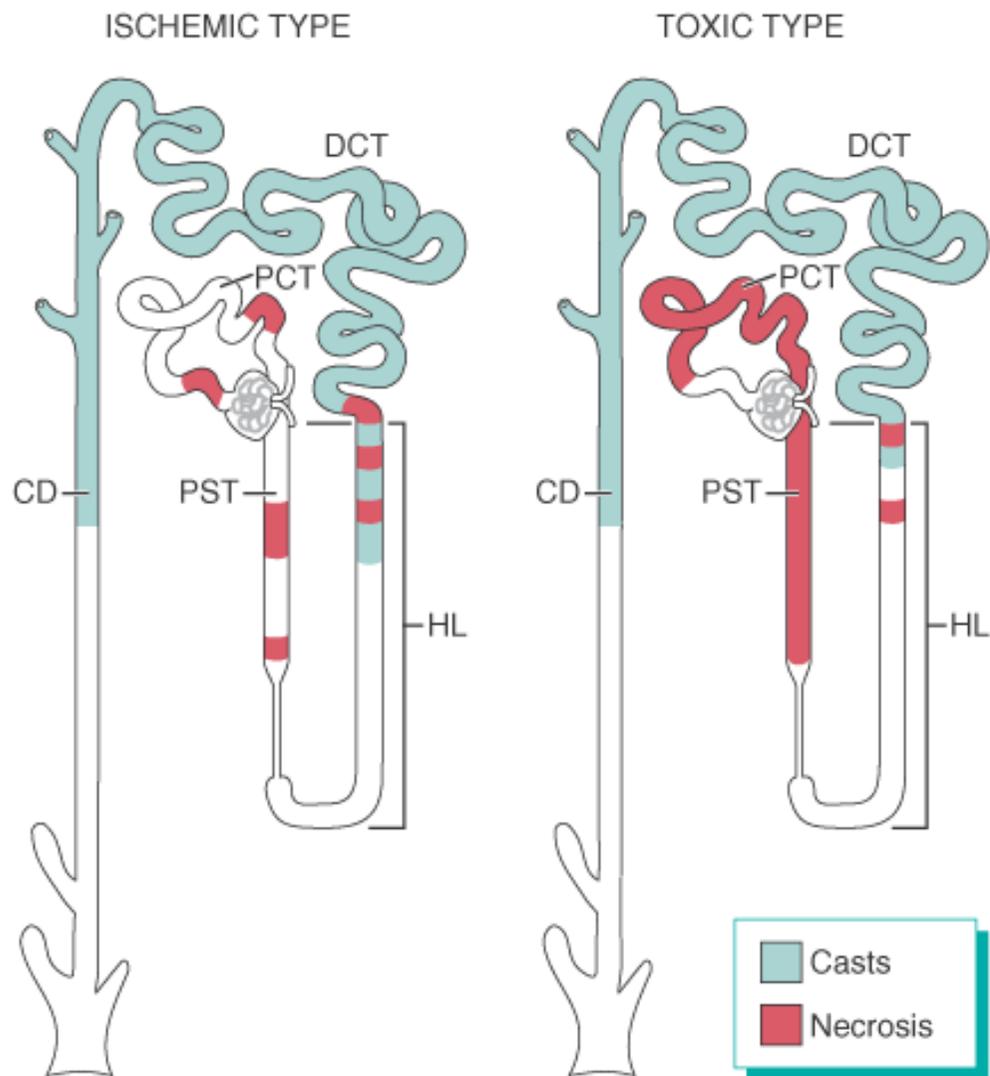
**Figure 20-34** Acute tubular necrosis. Some of the tubular epithelial cells in the tubules are necrotic, and many have become detached (from their basement membranes) and been sloughed into the tubular lumina, whereas others are swollen, vacuolated, and regenerating. *(Courtesy of Dr. Agnes Fogo, Vanderbilt University, Nashville, TN.)*
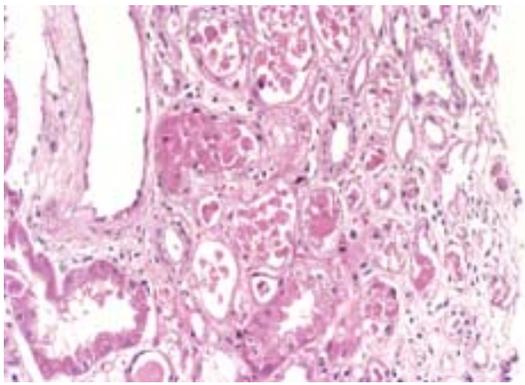
**TABLE 20-9** -- Causes of Tubulointerstitial Nephritis

| *Infections* |
| Acute bacterial pyelonephritis |
| Chronic pyelonephritis (including reflux nephropathy) |
| Other infections (e.g., viruses, parasites) |
| *Toxins* |
| Drugs |
| Acute hypersensitivity interstitial nephritis |
| Analgesic nephropathy |
| Heavy metals |
| Lead, cadmium |
| *Metabolic Diseases* |
| Urate nephropathy |
| Nephrocalcinosis (hypercalcemic nephropathy) |
| Hypokalemic nephropathy |
| Oxalate nephropathy |
| *Physical Factors* |
| Chronic urinary tract obstruction |
| Radiation nephropathy |
| *Neoplasms* |
| Multiple myeloma (cast nephropathy) |

| |
|---|
| *Immunologic Reactions* |
| Transplant rejection |
| Sjögren syndrome |
| Sarcoidosis |
| *Vascular Diseases* |
| *Miscellaneous* |
| Balkan nephropathy |
| Nephronophthisis-medullary cystic disease complex |
| "Idiopathic" interstitial nephritis |

are identified by cause or by associated disease (e.g., analgesic nephropathy, radiation nephropathy). Glomerular and vascular abnormalities may also be present but either are mild or occur only in advanced stages of these diseases.

Tubulointerstitial nephritis can be acute or chronic. Acute tubulointerstitial nephritis has a rapid clinical onset and is characterized histologically by interstitial edema, often accompanied by leukocytic infiltration of the interstitium and tubules, and focal tubular necrosis. In *chronic interstitial nephritis*, there is infiltration with predominantly mononuclear leukocytes, prominent interstitial fibrosis, and widespread tubular atrophy. Morphologic features that are helpful in separating acute from chronic tubulointerstitial nephritis include edema and, when present, eosinophils and neutrophils in the acute form, contrasted with fibrosis and tubular atrophy in the chronic form.

These conditions are distinguished clinically from the glomerular diseases by the absence, in early stages, of such hallmarks of glomerular injury as nephritic or nephrotic syndromes and by the presence of defects in tubular function. The latter may be subtle and include impaired ability to concentrate urine, evidenced clinically by polyuria or nocturia; salt wasting; diminished ability to excrete acids (metabolic acidosis); and isolated defects in tubular reabsorption or secretion. The advanced forms, however, may be difficult to distinguish clinically from other causes of renal insufficiency.

Some of the specific conditions listed in Table 20-9 are discussed elsewhere in this book. In this section, we deal principally with pyelonephritis and interstitial diseases induced by drugs.

**Pyelonephritis and Urinary Tract Infection**

Pyelonephritis is a renal disorder affecting the tubules, interstitium, and renal pelvis and is one of the most common diseases of the kidney. It occurs in two forms. *Acute pyelonephritis* is caused by bacterial infection and is the renal lesion associated with urinary tract infection. *Chronic pyelonephritis* is a more complex disorder: bacterial infection plays a dominant role, but other factors (vesicoureteral reflux, obstruction) are involved in its pathogenesis. Pyelonephritis is a serious complication of an extremely common clinical spectrum of *urinary tract infections* that affect the urinary bladder (cystitis), the kidneys and their collecting systems (pyelonephritis), or both. Bacterial infection of the lower urinary tract may be completely asymptomatic (asymptomatic bacteriuria) and most often remains localized to the bladder without the development of renal infection. However, lower urinary tract infection always carries the potential of spread to the kidney.

**Etiology and Pathogenesis.**

The dominant etiologic agents, accounting for more than 85% of cases of urinary tract infection, are the Gram-negative bacilli that are normal inhabitants of the intestinal tract.[86] By far the most common is *Escherichia coli*, followed by *Proteus*, *Klebsiella*, and *Enterobacter*. *Streptococcus faecalis*, also of enteric origin, staphylococci, and virtually every other bacterial and fungal agent can also cause lower urinary tract and renal infection. In immunocompromised patients, particularly those with transplanted organs, viruses such as polyoma virus,

cytomegalovirus, and adenovirus can also be a cause of renal infection.

*In most patients with urinary tract infection, the infecting organisms are derived from the patient's own fecal flora.* This is thus a form of *endogenous infection.* There are two routes by which bacteria can reach the kidneys: (1) through the blood-stream (hematogenous infection) and (2) from the lower urinary tract (ascending infection) ( Fig. 20-35 ). Although the hematogenous route is the less common of the two, acute pyelonephritis does result from seeding of the kidneys by bacteria from distant foci in the course of septicemia or infective endocarditis. Hematogenous infection is more likely to occur in the presence of ureteral obstruction, in debilitated patients, in patients receiving immunosuppressive therapy, and with nonenteric organisms, such as staphylococci and certain fungi and viruses.

*Ascending infection* is the most common cause of clinical pyelonephritis. Normal human bladder and bladder urine are sterile; therefore, a number of steps must occur for renal infection to occur:

• The first step in the pathogenesis of ascending infection appears to be the *colonization of the distal urethra and introitus* (in the female) by coliform bacteria. This colonization is influenced by the ability of bacteria to adhere to urethral mucosal cells. Such bacterial adherence, as discussed in Chapter 8 , involves adhesive molecules (adhesins) on the P-fimbriae (pili) of bacteria that interact with receptors on the surface of uroepithelial cells. Specific adhesins (e.g., the *pap* variant) are associated with infection. In addition, certain types of fimbriae promote renal tropism, or persistence of infection, or an enhanced inflammatory response to bacteria.[87]

• *From the urethra to the bladder*, organisms gain entrance during urethral catheterization or other instrumentation. Long-term catheterization, in particular, carries a risk of infection. In the absence of instrumentation, *urinary infections are much more common in females*, and this has been variously ascribed to the shorter urethra in females, the absence of antibacterial properties such as are found in prostatic fluid, hormonal changes affecting adherence of bacteria to the mucosa, and urethral trauma during sexual intercourse or a combination of these factors.

• *Multiplication in the bladder.* Ordinarily, organisms introduced into the bladder are cleared by the continual flushing of voiding and by antibacterial mechanisms. However, outflow obstruction or bladder dysfunction results in incomplete emptying and increased residual volume of urine. In the presence of stasis, bacteria introduced into the bladder can multiply unhindered without being flushed out or destroyed in the bladder wall. Accordingly, urinary tract infection is particularly frequent among patients with lower urinary tract obstruction, such as may occur with benign prostatic hypertrophy, tumors, or calculi or with neurogenic bladder dysfunction caused by diabetes or spinal cord injury.

• *Vesicoureteral reflux.* Although obstruction is an important predisposing factor in the pathogenesis of ascending infection, *it is incompetence of the vesicoureteral valve* that allows bacteria to ascend the ureter into the renal pelvis. The normal ureteral insertion into the bladder is a competent one-way valve that prevents retrograde flow of urine, especially during micturition, when the intravesical pressure rises. An incompetent vesicoureteral orifice allows the reflux of bladder urine into the ureters (*vesicoureteral reflux*) ( Fig. 20-36 ). Reflux is most often due to a congenital absence or shortening of the intravesical portion of the ureter ( Fig. 20-37 ), such that the ureter is not compressed during micturition. In addition, bladder infection itself, probably as a result of the action of bacterial or inflammatory products on ureteral contractility, can cause or accentuate vesicoureteral reflux, particularly in children. *Acquired vesicoureteral reflux* in adults can result from persistent bladder atony caused by spinal cord injury. The effect of

vesicoureteral reflux is similar to that of an obstruction in that after voiding, there is residual urine in the urinary tract, which favors bacterial growth.

• *Intrarenal reflux.* Vesicoureteral reflux also affords a ready mechanism by which the infected bladder urine can be propelled up to the renal pelvis and deep into the renal parenchyma through open ducts at the tips of the papillae (intrarenal reflux). Intrarenal reflux is most common in the upper and lower poles of the kidney, where papillae tend to have flattened or concave tips rather than the convex pointed type present in the midzones of the kidney (and depicted in most textbooks). Reflux can be demonstrated radiographically by a voiding cystourethrogram: The bladder is filled with a radio-opaque dye, and films are taken during micturition. Vesicoureteral reflux can be demonstrated in about 30% of infants and children with urinary tract infection (see Fig. 20-36 ).

**Figure 20-35** Schematic representation of pathways of renal infection. Hematogenous infection results from bacteremic spread. More common is ascending infection, which results from a combination of urinary bladder infection, vesicoureteral reflux, and intrarenal reflux.



HEMATOGENOUS INFECTION

Common agents:
 Staphylococcus
 E. coli

Aorta

Bacteremia

Intrarenal reflux

Vesicoureteral reflux

Deranged vesicoureteral junction

Bacteria enter bladder

enter bladder

Bacterial colonization
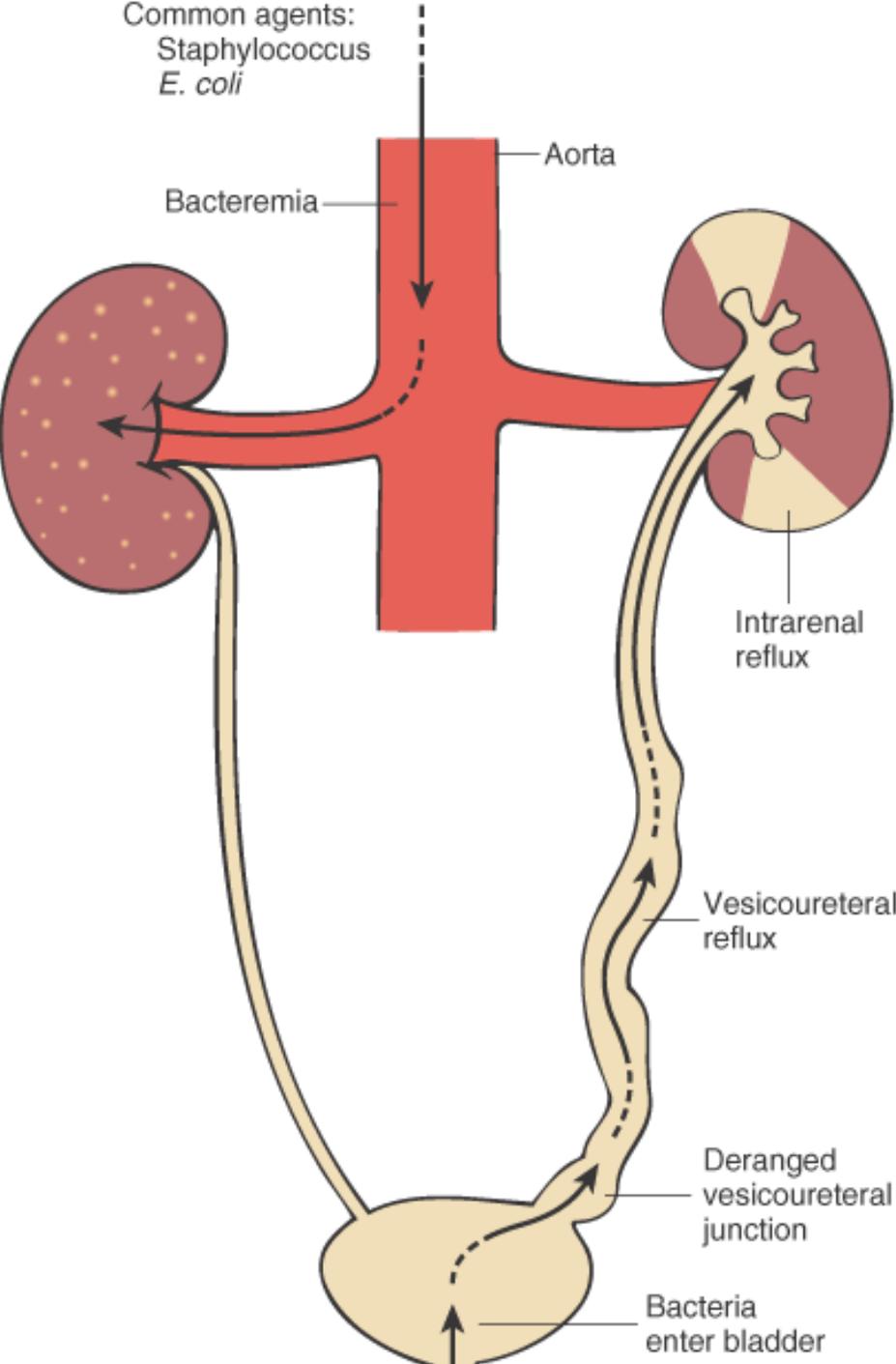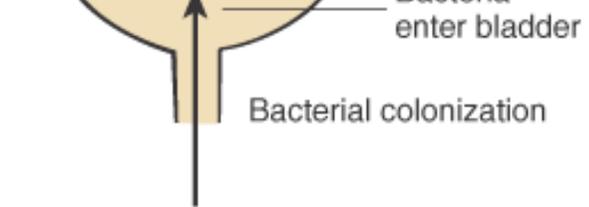
**ASCENDING INFECTION**

Common agents:
  *E. coli*
  *Proteus*
  *Enterobacter*

**Figure 20-36** Vesicoureteral reflux demonstrated by a voiding cystourethrogram. Dye injected into the bladder refluxes into both dilated ureters, filling the pelvis and calyces.

**Figure 20-37** The vesicoureteral junction. In normal individuals (*A*), the intravesical portion of the ureter is oblique, such that the ureter is closed by muscle contraction during micturition. The most common cause of reflux is congenital complete or partial absence of the intravesical ureter (*B*).

A   NORMAL          B   REFLUX
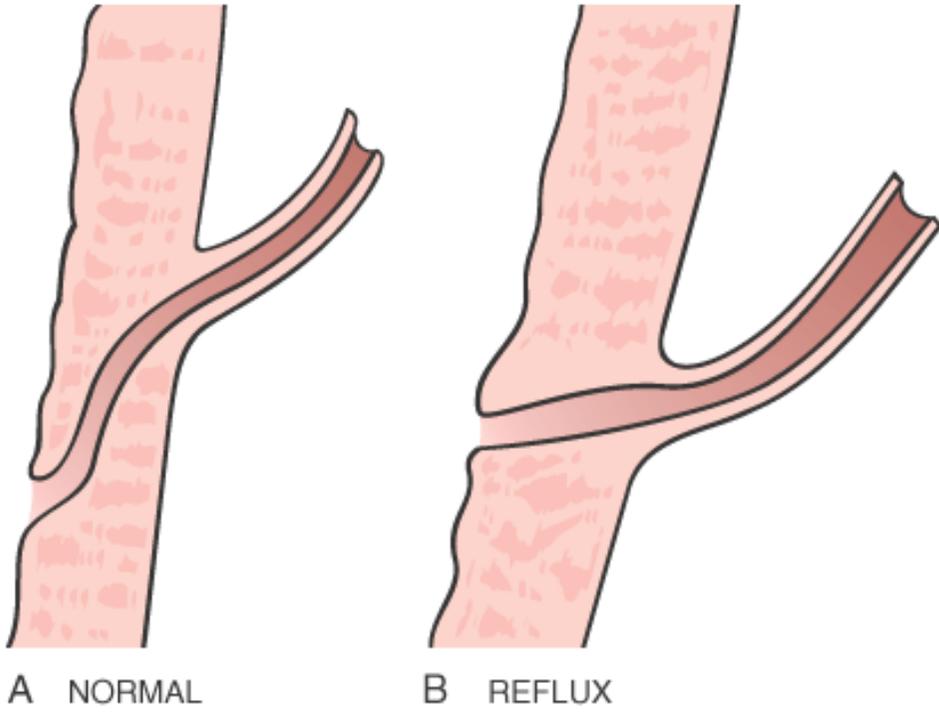
**Figure 20-38** Acute pyelonephritis. Cortical surface exhibits grayish white areas of inflammation and abscess formation.

**Figure 20-39** Acute pyelonephritis marked by an acute neutrophilic exudate within tubules and the renal substance.
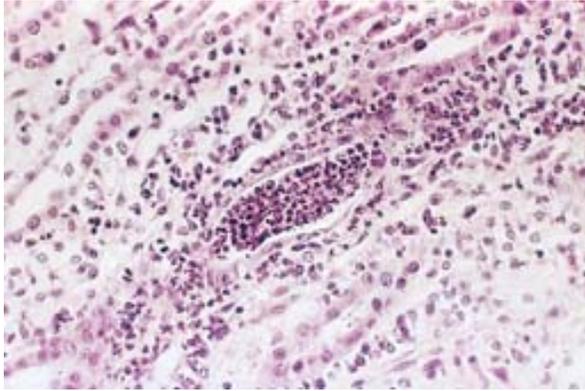


**Figure 20-40** Papillary necrosis. Areas of pale gray necrosis are limited to the papillae.



**Figure 20-41** Polyoma virus nephropathy. *A*, The kidney shows enlarged tubular epithelial cells with nuclear inclusions (*arrow*) and interstitial inflammation (*arrowheads*). *B*, Intranuclear viral inclusions visualized by electron microscopy. *(Courtesy of Dr. Jean Olson, Department of Pathology, University of California San Francisco, San Francisco, CA.)*
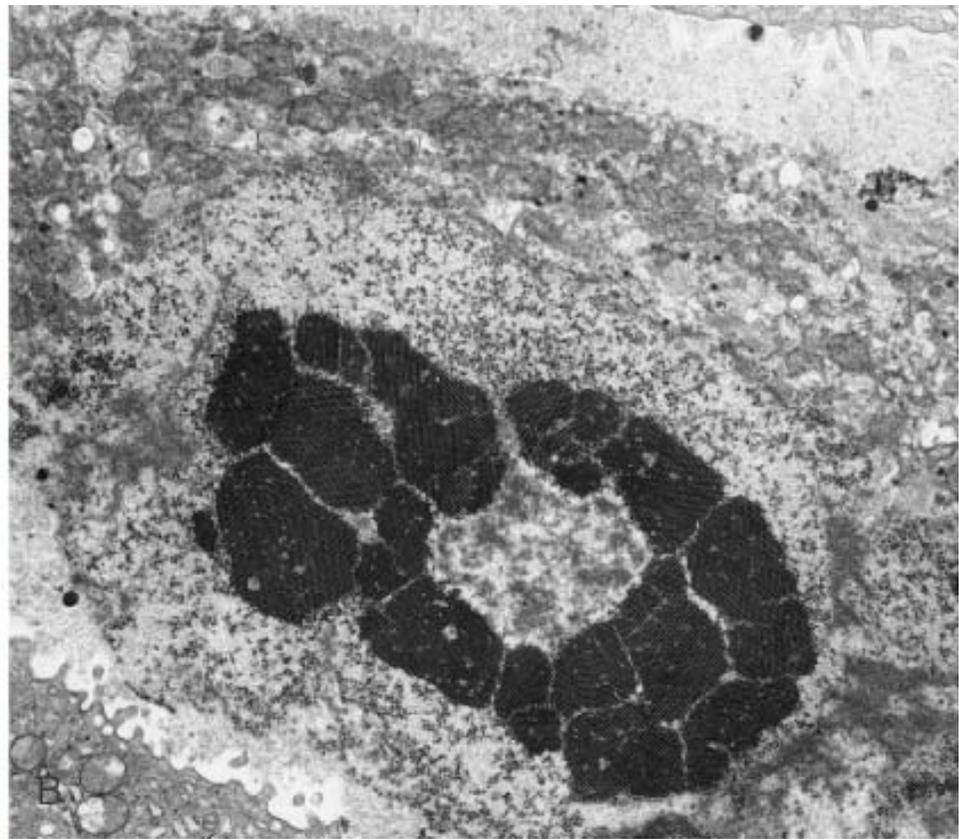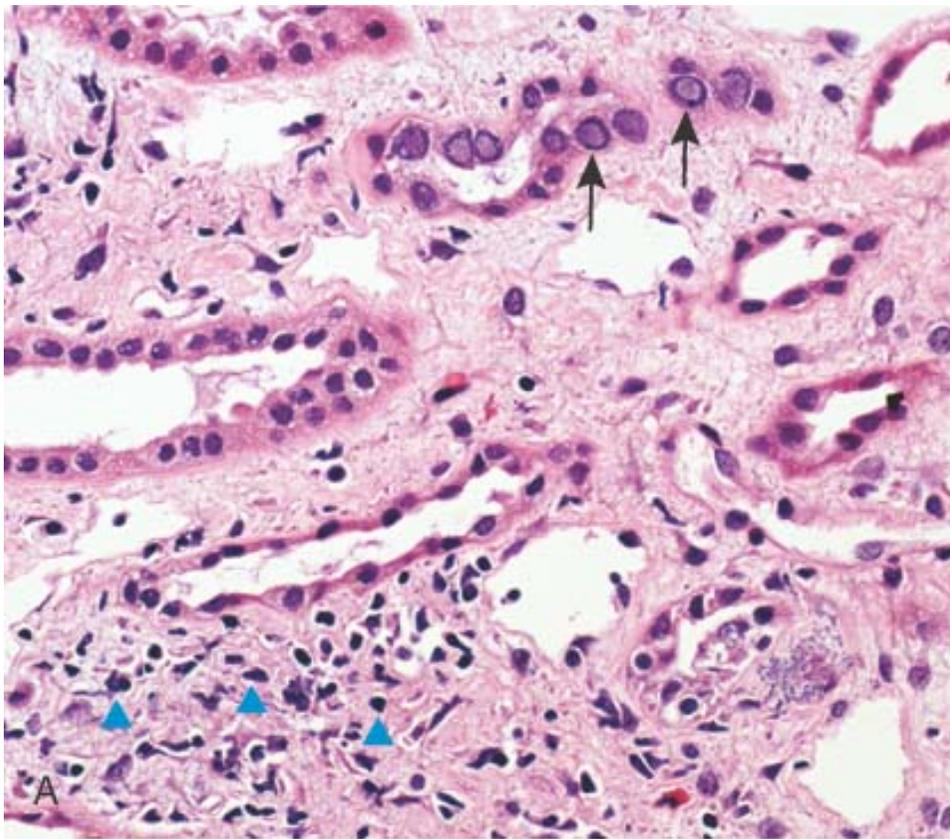
**Figure 20-42** Typical coarse scars of chronic pyelonephritis associated with vesicoureteral reflux. The scars are usually polar and are associated with underlying blunted calyces.
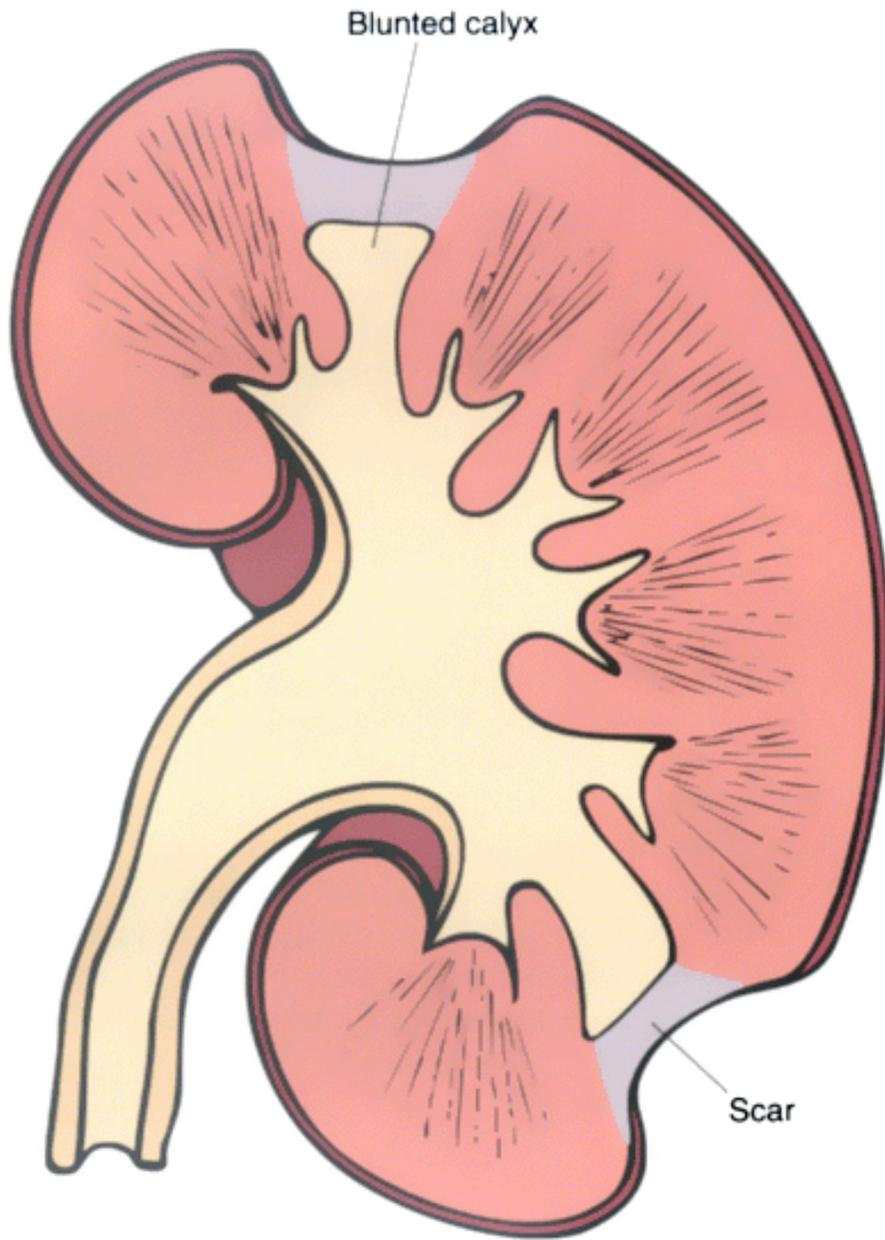
**Figure 20-43** *A*, Chronic pyelonephritis. The surface (*left*) is irregularly scarred. The cut section (*right*) reveals characteristic dilation and blunting of calyces. The ureter is dilated and thickened, a finding that is consistent with chronic vesicoureteral reflux. *B*, Low-power view showing a corticomedullary renal scar with an underlying dilated deformed calyx. Note the thyroidization of tubules in the cortex.
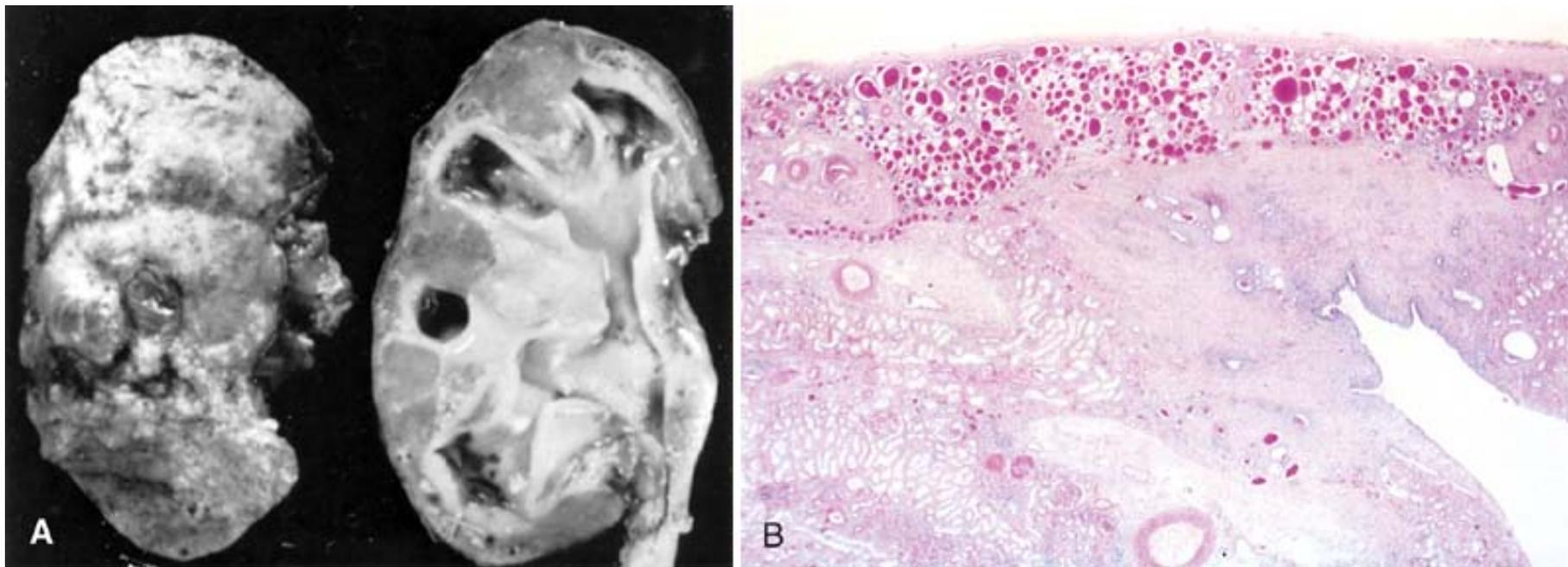
**Figure 20-44** Drug-induced interstitial nephritis, with prominent eosinophilic and mononuclear cell infiltrate. *(Courtesy of Dr. H. Rennke, Brigham and Women's Hospital, Boston, MA.)*
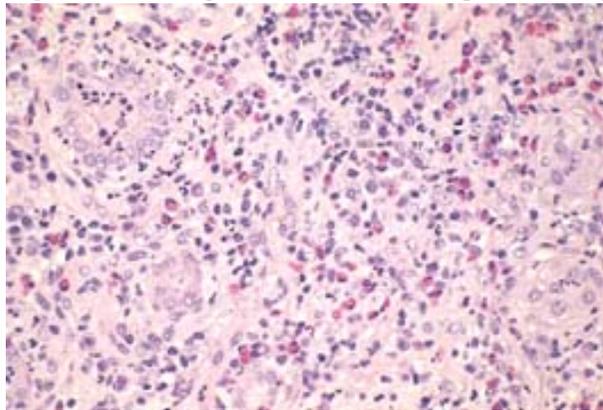


**Figure 20-45** Analgesic nephropathy. *A,* The brownish necrotic papilla, transformed to a necrotic, structureless mass, fills the pelvis. *B,* Microscopic view. Note the fibrosis in the medulla. *(Courtesy of Dr. F.J. Gloor, Institut für Pathologie, Kantonsspital, St. Gallen, Switzerland.)*
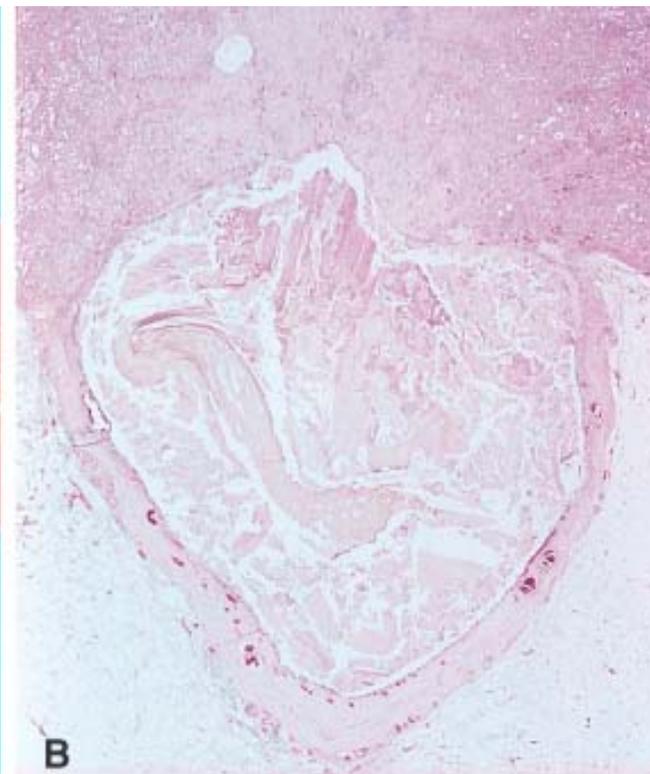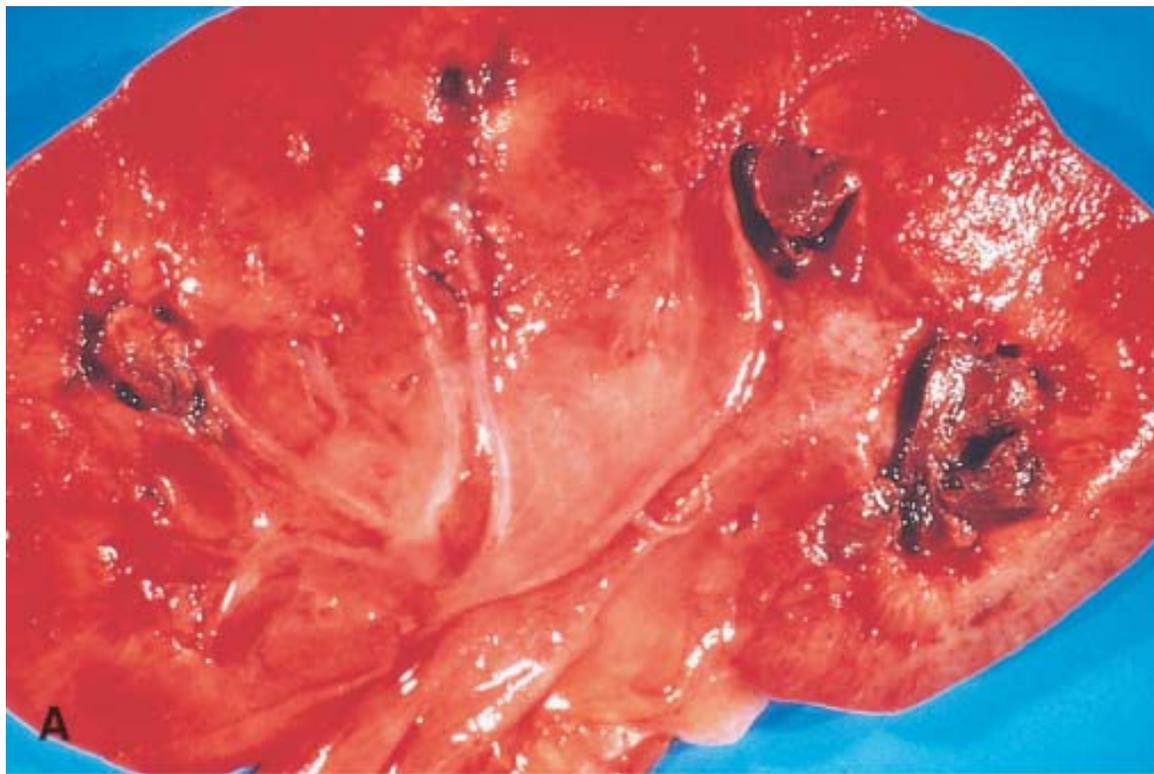
**TABLE 20-10** -- Causes of Papillary Necrosis

|  | **Diabetes Mellitus** | **Analgesic Nephropathy** | **Sickle Cell Disease** | **Obstruction** |
|---|---|---|---|---|
| Male-to-female ratio | 1:3 | 1:5 | 1:1 | 9:1 |
| Time course | 10 years | 7 years of abuse | Variable | Variable |
| Infection | 80% | 25% | ± | 90% |
| Calcification | Rare | Frequent | Rare | Frequent |
| Number of papillae affected | Several; all of same stage | Almost all; different stages of necrosis | Few | Variable |

*Data from Seshan S, et al (eds): Classification and Atlas of Tubulointerstitial and Vascular Diseases. Baltimore, Williams & Wilkins, 1999.*

**Chinese Herbs Nephropathy**

A syndrome of chronic tubulointerstitial nephritis caused by aristolochic acid, a supplement found in some formulations of herbal remedies, has been recognized recently. The drug causes a distinctive picture of renal failure with histopathologic features of interstitial fibrosis with a relative paucity of infiltrating interstitial leukocytes. As with analgesic nephropathy, there is an increased incidence of carcinoma in the kidney and urinary tract.

**Other Tubulointerstitial Diseases**

**Urate Nephropathy**

Three types of nephropathy can occur in patients with hyperuricemic disorders:

> • *Acute uric acid nephropathy* is caused by the precipitation of uric acid crystals in the renal tubules, principally in collecting ducts, leading to obstruction of nephrons and the development of acute renal failure. This type is particularly likely to occur in patients with leukemias and lymphomas who are undergoing chemotherapy; the drugs increase the death of tumor cells, and uric acid is released as the nuclei of these cells disintegrate. Precipitation of uric acid is favored by the acidic pH in collecting tubules.
>
> • *Chronic urate nephropathy*, or gouty nephropathy, occurs in patients with more protracted forms of hyperuricemia. The lesions are ascribed to the deposition of monosodium urate crystals in the acidic milieu of the distal tubules and collecting ducts as well as in the interstitium. *These deposits have a distinct histologic appearance and may form birefringent needle-like crystals either in the tubular lumina or in the interstitium* ( Fig. 20-46 ). The urates induce a *tophus* consisting of foreign body giant cells, other

---

mononuclear cells, and a fibrotic reaction ( Chapter 26). Tubular obstruction by the urates causes cortical atrophy and scarring. Arterial and arteriolar thickening is common in these kidneys, owing to the relatively high frequency of hypertension in patients with gout. Clinically, urate nephropathy is a subtle disease associated with tubular defects that may progress slowly. Patients with gout who actually develop a chronic nephropathy commonly have evidence of increased exposure to lead, sometimes by way of drinking "moonshine"whiskey contaminated with lead.

> • The third renal syndrome in hyperuricemia is *nephrolithiasis*; uric acid stones are present in 22% of patients with gout and 42% of those with secondary hyperuricemia (see later discussion of renal stones).

**Hypercalcemia and Nephrocalcinosis**

Disorders characterized by hypercalcemia, such as hyperparathyroidism, multiple myeloma, vitamin D intoxication, metastatic bone disease, or excess calcium intake (milk-alkali syndrome), may induce the formation of calcium stones and deposition of calcium in the kidney (nephrocalcinosis). Extensive degrees of calcinosis, under certain conditions, may lead to a form of chronic tubulointerstitial disease and renal insufficiency. The first damage induced by the hypercalcemia is at the *intracellular level*, in the tubular epithelial cells, resulting in mitochondrial distortion and evidence of cell injury. Subsequently, calcium deposits can be demonstrated within the mitochondria, cytoplasm, and basement membrane. Calcified cellular debris contributes to obstruction of tubular lumens and causes obstructive atrophy of nephrons with interstitial fibrosis and nonspecific chronic inflammation. Atrophy of entire cortical areas drained by calcified tubules may occur, and this accounts for the alternating areas of normal and scarred parenchyma seen in such kidneys.

**Figure 20-46** Urate crystals in the renal medulla. Note the giant cells and fibrosis around the crystals.
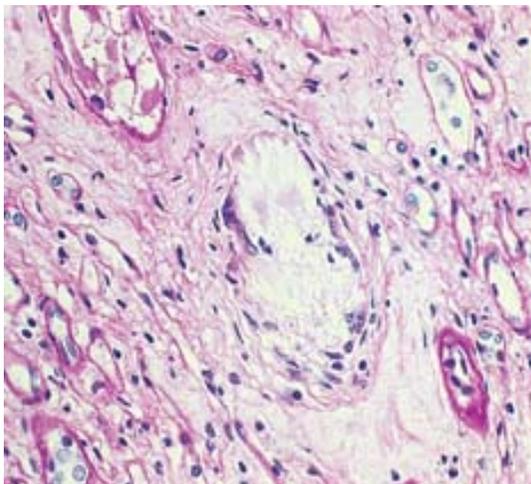
**TABLE 20-11** -- Renal Involvement in Nonrenal Neoplasms

| Direct tumor invasion of renal parenchyma |
| --- |
| ••Ureters (obstruction) |
| ••Artery (renovascular hypertension) |
| Hypercalcemia |
| Hyperuricemia |
| Amyloidosis |
| Excretion of abnormal proteins (multiple myeloma) |
| Glomerulopathy |
| ••Immune complex glomerulonephritis (carcinomas) |
| ••Minimal change disease (Hodgkin disease) |
| ••Membranoproliferative glomerulonephritis (leukemias and lymphomas) |
| Effects of radiotherapy, chemotherapy, secondary infection |

**Morphology.**

The tubulointerstitial changes in multiple myeloma are fairly characteristic. The Bence Jones tubular casts appear as pink to blue amorphous masses, sometimes concentrically laminated, often with a fractured appearance, filling and distending the tubular lumens. Some of the casts are surrounded by multinucleate giant cells that are derived from mononuclear phagocytes ( Fig. 20-47 ). The adjacent interstitial tissue usually shows a nonspecific inflammatory response and fibrosis. On occasion, the casts erode their way from the tubules into the interstitium and here evoke a granulomatous inflammatory reaction. The histologic features of amyloidosis, light-chain deposition disease and nephrocalcinosis and infection, may also be present.

Clinically, the renal manifestations are of several types. In the most common form, *chronic renal failure* develops insidiously and usually progresses slowly during a period of several months to years. Another form occurs suddenly and is manifested by *acute renal failure* with oliguria. Precipitating factors in these patients include dehydration, hypercalcemia, acute

infection, and treatment with nephrotoxic antibiotics. *Bence Jones proteinuria* occurs in 70% of patients with myeloma; the presence of significant non-light-chain proteinuria (e.g., albumin) suggests secondary amyloidosis or light-chain deposition disease.

**Diseases of Blood Vessels**

Nearly all diseases of the kidney involve the renal blood vessels secondarily. Systemic vascular diseases, such as various

**Figure 20-47** Myeloma kidney. Note the angulated and tubular casts with macrophages, including multinucleate cells, engulfing them.
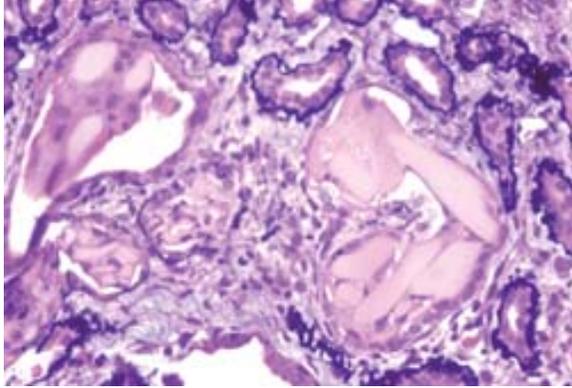


**Figure 20-48** Close-up of the gross appearance of the cortical surface in benign nephrosclerosis illustrating the fine, leathery granularity of the surface.



**Figure 20-49** Hyaline arteriolosclerosis. High-power view of two arterioles with hyaline deposition, marked thickening of the walls, and a narrowed lumen. *(Courtesy of Dr. M.A. Venkatachalam, Department of Pathology, University of Texas Health Sciences Center, San Antonio, TX.)*
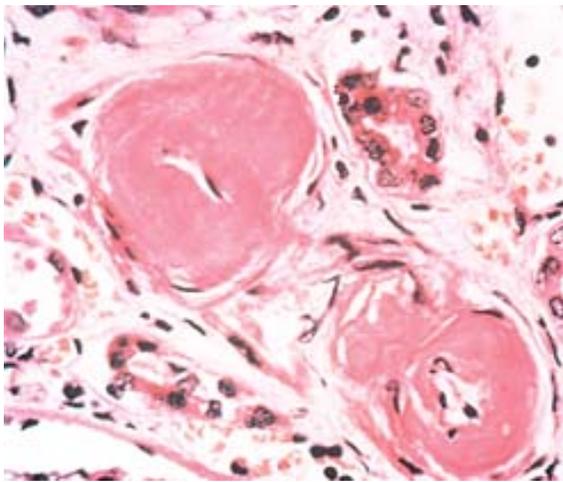
**TABLE 20-12** -- Types of Hypertension

| *Primary or Essential Hypertension* |
| --- |
| *Secondary Hypertension* |
| Renal |
| ••Acute glomerulonephritis |
| ••Chronic renal disease |
| ••Renal artery stenosis |
| ••Renal vasculitis |
| ••Renin-producing tumors |
| Endocrine |
| ••Adrenocortical hyperfunction (Cushing syndrome) |
| ••Oral contraceptives |
| ••Pheochromocytoma |
| ••Acromegaly |
| ••Myxedema |
| ••Thyrotoxicosis (systolic hypertension) |
| Vascular |
| ••Coarctation of aorta |
| ••Polyarteritis nodosa |
| ••Aortic insufficiency (systolic hypertension) |

| Neurogenic |
| •• Psychogenic |
| •• Increased intracranial pressure |
| •• Polyneuritis, bulbar poliomyelitis, others |

hyperplastic arteriolosclerosis that is typical of malignant hypertension and further narrowing of the lumens. The kidneys become markedly ischemic. With severe involvement of the renal afferent arterioles, the renin-angiotensin system receives a powerful stimulus; indeed, *patients with malignant hypertension have markedly elevated levels of plasma renin*. This then sets up a self-perpetuating cycle in which angiotensin II causes intrarenal vasoconstriction, and the attendant renal ischemia perpetuates renin secretion. Other vasoconstrictors (e.g., endothelin) and loss of vasodilators (nitric oxide) may also contribute to vasoconstriction. Aldosterone levels are also elevated, and salt retention undoubtedly contributes to the elevation of blood pressure. The consequences of the markedly elevated blood pressure on the blood vessels throughout the body are known as *malignant arteriosclerosis*, and the renal disorder is malignant nephrosclerosis.

**Morphology.**

On gross inspection, the kidney size depends on the duration and severity of the hypertensive disease. Small, pinpoint petechial hemorrhages may appear on the cortical surface from rupture of arterioles or glomerular capillaries, giving the kidney a peculiar "flea-bitten" appearance.

Two histologic alterations characterize blood vessels in malignant hypertension ( Fig. 20-50 ):

• **Fibrinoid necrosis of arterioles.** This appears as an eosinophilic granular change in the blood vessel wall, which stains positively for fibrin by histochemical or immunofluorescence techniques. This change represents an acute event, and it may be accompanied by limited inflammatory infiltrate within the wall. However, usually this pattern of necrosis is not accompanied by prominent inflammation.
• In the interlobular arteries and arterioles, there is intimal thickening caused by a proliferation of elongated, concentrically arranged smooth muscle cells, together with fine concentric layering of collagen and accumulation of pale staining material that likely represents accumulations of proteoglycans and plasma proteins. This alteration has been referred to as **onion-skinning** because of its concentric appearance. The lesion, also called hyperplastic arteriolitis, correlates well with renal failure in malignant hypertension. Sometimes the glomeruli become necrotic and infiltrated with neutrophils, and the glomerular capillaries may thrombose. The arteriolar and arterial lesions result in considerable narrowing of all vascular lumens, with ischemic atrophy and, at times, infarction distal to the abnormal vessels.

**Figure 20-50** Malignant hypertension. *A*, Fibrinoid necrosis of afferent arteriole (PAS stain). *B*, Hyperplastic arteriolitis (onion-skin lesion). *(Courtesy of Dr. H. Rennke, Brigham and Women's Hospital, Boston, MA.)*
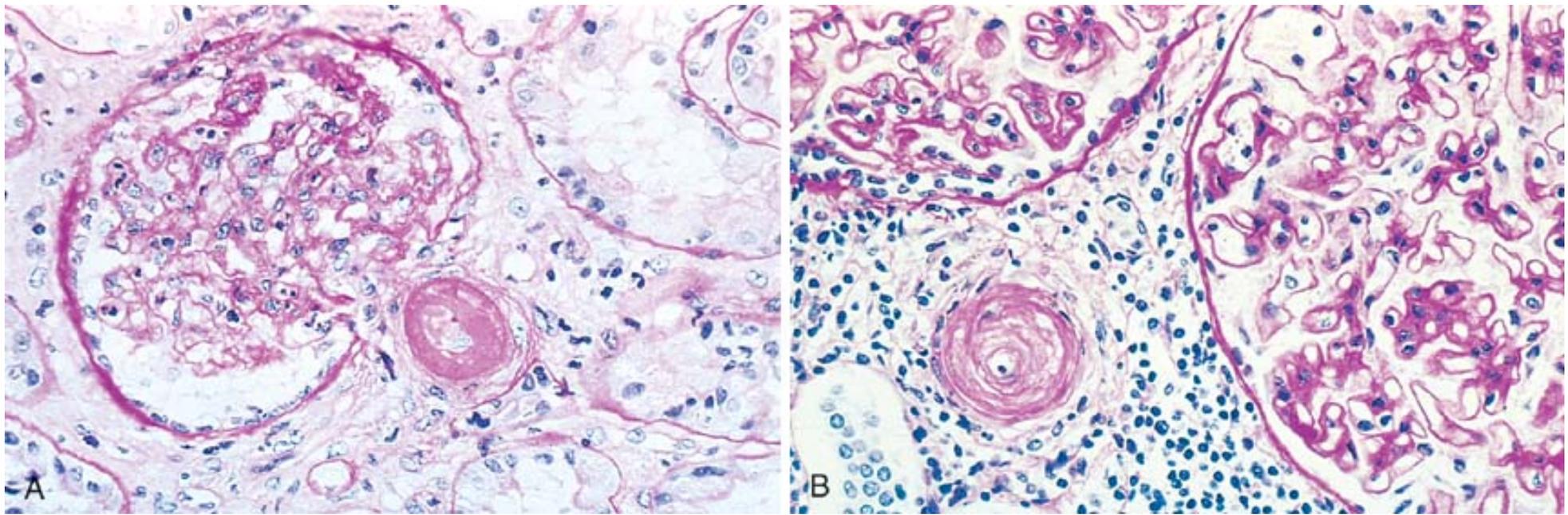
**Figure 20-51** Fibromuscular dysplasia of the renal artery, medial type (elastic tissue stain). The medium shows marked fibrous thickening, and the lumen is stenotic. *(Courtesy of Dr. Seymour Rosen, Beth Israel Hospital, Boston, MA.)*
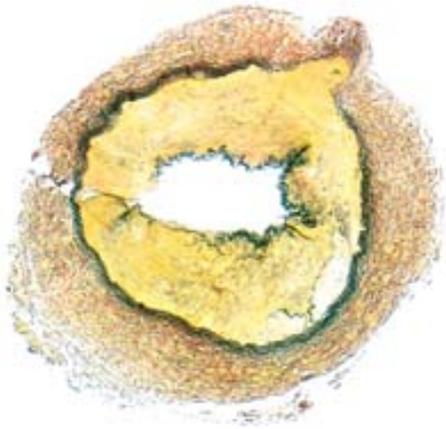


**Figure 20-52** Fibrin stain showing platelet-fibrin thrombi (*red*) in the glomerular capillaries, characteristic of microangiopathic disorders.
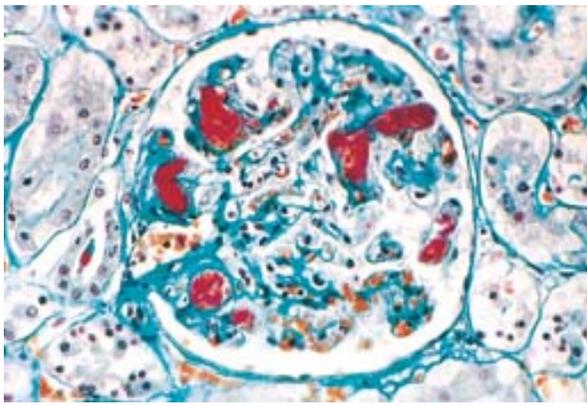
**Figure 20-53** Atheroemboli with typical cholesterol clefts in an interlobar artery.
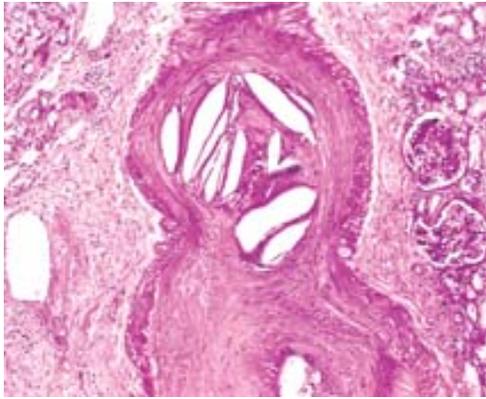


**Figure 20-54** Diffuse cortical necrosis. The pale ischemic necrotic areas are confined to the cortex and columns of Bertin.
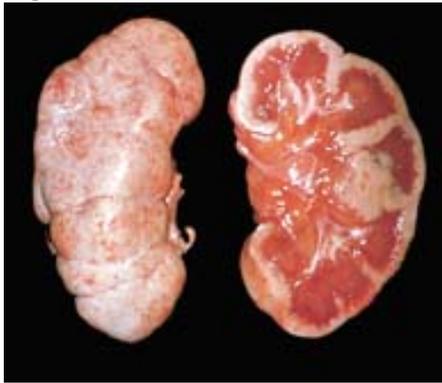


**Figure 20-55** Obstructive lesions of the urinary tract.

PELVIS
- Calculi
- Tumors
- Ureteropelvic stricture

URETER–INTRINSIC
- Calculi
- Tumors
- Clots
- Sloughed papillae
- Inflammation

URETER–EXTRINSIC
- Pregnancy
- Tumors (e.g., cervix)
- Retroperitoneal fibrosis

Vesicoureteral reflux

BLADDER
- Calculi
- Tumors
- Functional (e.g., neurogenic)

URETHRA
- Posterior valve stricture
- Tumors (rare)

PROSTATE
- Hyperplasia
- Carcinoma
- Prostatitis

**Figure 20-56** Hydronephrosis of the kidney, with marked dilation of the pelvis and calyces and thinning of the renal parenchyma.
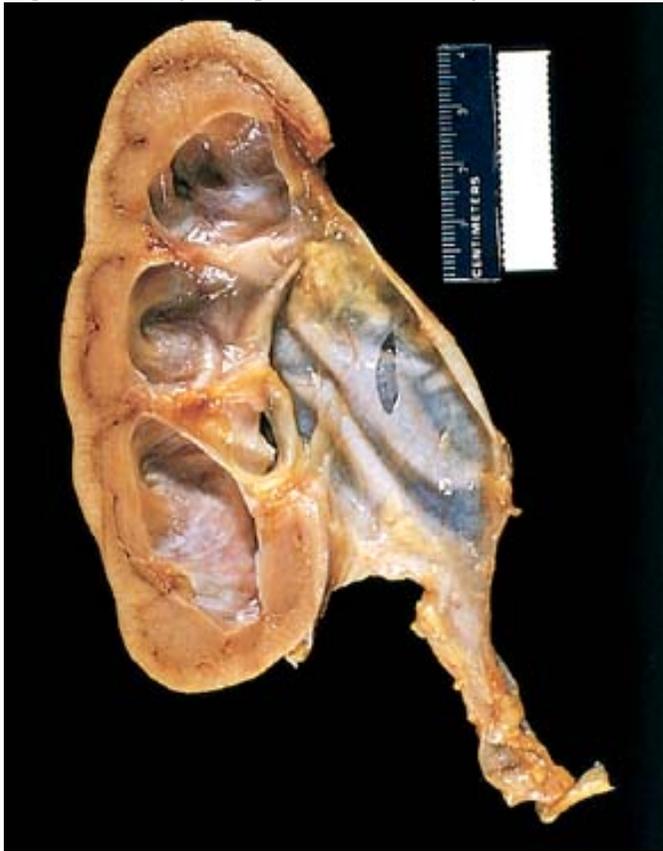


**TABLE 20-13** -- Prevalence of Various Types of Renal Stones

|  | **Percentage of All Stones** |
| --- | --- |
| *Calcium Oxalate and Phosphate* | 70 |
| Idiopathic hypercalciuria (50%) |  |
| Hypercalciuria and hypercalcemia (10%) |  |
| Hyperoxaluria (5%) |  |
| ••Enteric (4.5%) |  |
| ••Primary (0.5%) |  |
| Hyperuricosuria (20%) |  |
| Hypocitraturia |  |
| No known metabolic abnormality (15–20%) |  |
| *Magnesium Ammonium Phosphate (Struvite)* | 15–20 |

| | |
|---|---|
| *Uric Acid* | 5–10 |
| Associated with hyperuricemia | |
| Associated with hyperuricosuria | |
| Idiopathic (50% of uric stones) | |
| *Cystine* | 1–2 |
| *Others or Unknown* | ±5 |

magnesium ammonium phosphate; (3) *5% to 10% are uric acid stones*; and (4) *1% to 2% are made up of cystine*. An organic matrix of mucoprotein, making up 1% to 5% of the stone by weight, is present in all calculi. Although there are many causes for the initiation and propagation of stones, *the most important determinant is an increased urinary concentration of the stones' constituents, such that it exceeds their solubility in urine (supersaturation). A low urine volume* in some metabolically normal patients may also favor supersaturation.

*Calcium oxalate stones* ( Table 20-13 ) are associated in about 5% of patients with both *hypercalcemia* and *hypercalciuria*, caused by hyperparathyroidism, diffuse bone disease, sarcoidosis, and other hypercalcemic states. About 55% have *hypercalciuria without hypercalcemia*. This is caused by several factors, including hyperabsorption of calcium from the intestine (absorptive hypercalciuria), an intrinsic impairment in renal tubular reabsorption of calcium (renal hypercalciuria), or idiopathic fasting hypercalciuria with normal parathyroid function. As many as 20% of calcium oxalate stones are associated with increased uric acid secretion (*hyperuricosuric calcium nephrolithiasis*), with or without hypercalciuria. The mechanism of stone formation in this setting involves "nucleation" of calcium oxalate by uric acid crystals in the collecting ducts. Five per cent are associated with *hyperoxaluria*, either hereditary (primary oxaluria) or, more commonly, acquired by intestinal overabsorption in patients with enteric diseases. The latter, so-called enteric hyperoxaluria, also occurs in vegetarians, because much of their diet is rich in oxalates. *Hypocitraturia* associated with acidosis and chronic diarrhea of unknown cause may produce calcium stones. *In a variable proportion of patients with calcium stones*, no cause can be found (idiopathic calcium stone disease).

*Magnesium ammonium phosphate stones* are formed largely after infections by urea-splitting bacteria (e.g., *Proteus* and some staphylococci), which convert urea to ammonia. The resultant alkaline urine causes the precipitation of magnesium ammonium phosphate salts. These form some of the largest stones, as the amounts of urea excreted normally are huge. Indeed, so-called *staghorn calculi* occupying large portions of the renal pelvis are almost always a consequence of infection.

*Uric acid stones* are common in patients with hyperuricemia, such as gout, and diseases involving rapid cell turnover, such as the leukemias. However, *more than half of all patients with urate calculi have neither hyperuricemia nor increased urinary excretion of uric acid*. In this group, it is thought that an unexplained tendency to excrete urine of pH below 5.5 may predispose to uric acid stones, because uric acid is insoluble in relatively acidic urine. In contrast to the radio-opaque calcium stones, uric acid stones are radiolucent.

*Cystine stones* are caused by genetic defects in the renal reabsorption of amino acids, including cystine, leading to cystinuria. Stones form at low urinary pH.

It can therefore be appreciated that increased concentration of stone constituents, changes in urinary pH, decreased urine volume, and the presence of bacteria influence the formation of calculi. *However, many calculi occur in the absence of these factors; conversely, patients with hypercalciuria, hyperoxaluria, and hyperuricosuria often do not form stones.* It has therefore been postulated that stone formation is enhanced by a *deficiency in inhibitors of crystal formation in urine*. The list of such inhibitors is long, including pyrophosphate, diphosphonate,

citrate, glycosaminoglycans, osteopontin, and a glycoprotein called *nephrocalcin*.

**Morphology.**

Stones are unilateral in about 80% of patients. The favored sites for their formation are within the renal calyces and pelves ( Fig. 20-57 ) and in the bladder. If formed in the renal pelvis, they tend to remain small, having an average diameter of 2 to 3 mm. These may have smooth contours or may take the form of an irregular, jagged mass of spicules. Often, many stones are found within one kidney. On occasion, progressive accretion of salts leads to the development of branching structures known as staghorn stones, which create a cast of the pelvic and calyceal system.

**Clinical Course.**

Stones are of importance when they obstruct urinary flow or produce ulceration and bleeding. They may be present without producing any symptoms or significant renal damage. In general, smaller stones are most hazardous, because they may pass into the ureters, producing pain referred to as colic (one of the most intense forms of pain) as well as ureteral obstruction. Larger stones cannot enter the ureters and are more likely to remain silent within the renal pelvis. Commonly, these larger stones first manifest themselves by hematuria. Stones also predispose to superimposed infection, both by their obstructive nature and by the trauma they produce.

**Tumors of the Kidney**

Both benign and malignant tumors occur in the kidney.[108] [109] With the exception of oncocytoma, the benign tumors rarely cause clinical problems. Malignant tumors, on the other hand, are of great importance clinically and deserve considerable emphasis. By far the most common of these malignant tumors is renal cell carcinoma, followed by Wilms tumor, which is found in children and is described in

**Figure 20-57** Nephrolithiasis. A large stone impacted in the renal pelvis. *(Courtesy of Dr. E. Mosher, Brigham and Women's Hospital, Boston, MA.)*
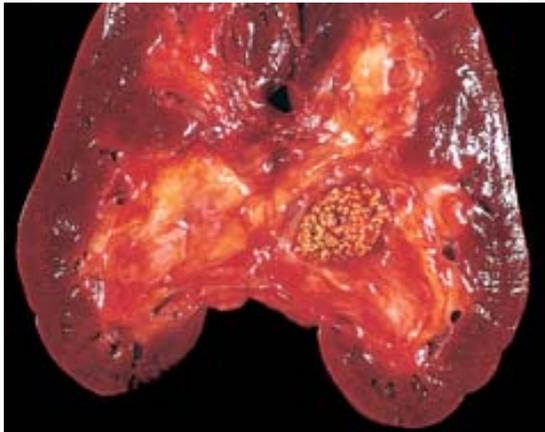


**Figure 20-58** Cytogenetics (*blue*) and genetics (*red*) of clear cell versus papillary renal cell carcinoma. *(Courtesy of Dr. Keith Ligon, Brigham and Women's Hospital, Boston, MA.)*

SPORADIC PAPILLARY
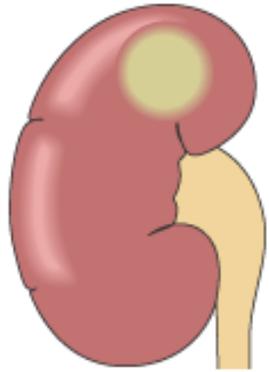
Trisomy 7, 16, 17
Loss of Y
Mutated, activated MET
t(X;1) ⟶ PRCC oncogenes

HEREDITARY PAPILLARY
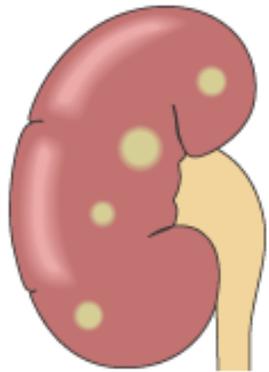
Trisomy 7
Mutated, activated MET

SPORADIC CLEAR CELL
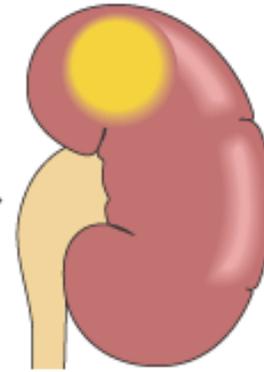
Translocations 3;6, 3;8, 3;11
Deletions on chromosome 3
Loss of VHL
Inactivated, mutated VHL
Hypermethylation of VHL

HEREDITARY CLEAR CELL
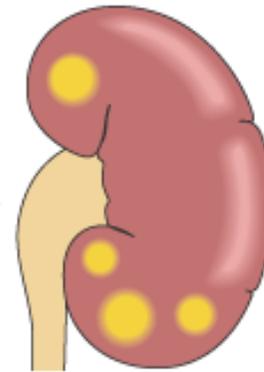
**Figure 20-59** Renal cell carcinoma. Typical cross-section of yellowish, spherical neoplasm in one pole of the kidney. Note the tumor in the dilated thrombosed renal vein.
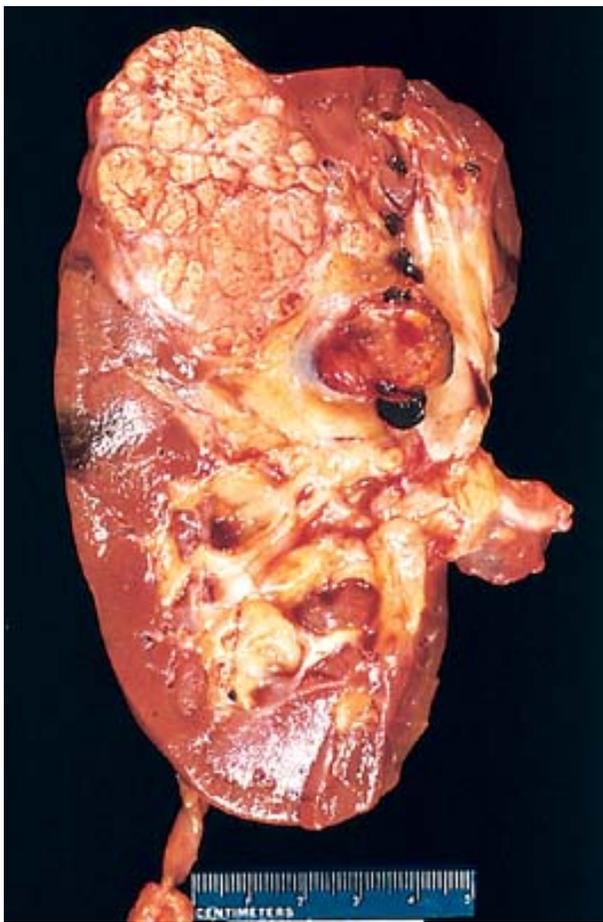
**Figure 20-60** Renal cell carcinoma. *A*, Clear cell type, *B*, Papillary type. Note the papillae and foamy macrophages in the stalk. *C*, Chromophobe type. *(Courtesy of Dr. A. Renshaw, Brigham and Women's Hospital, Boston, MA.)*
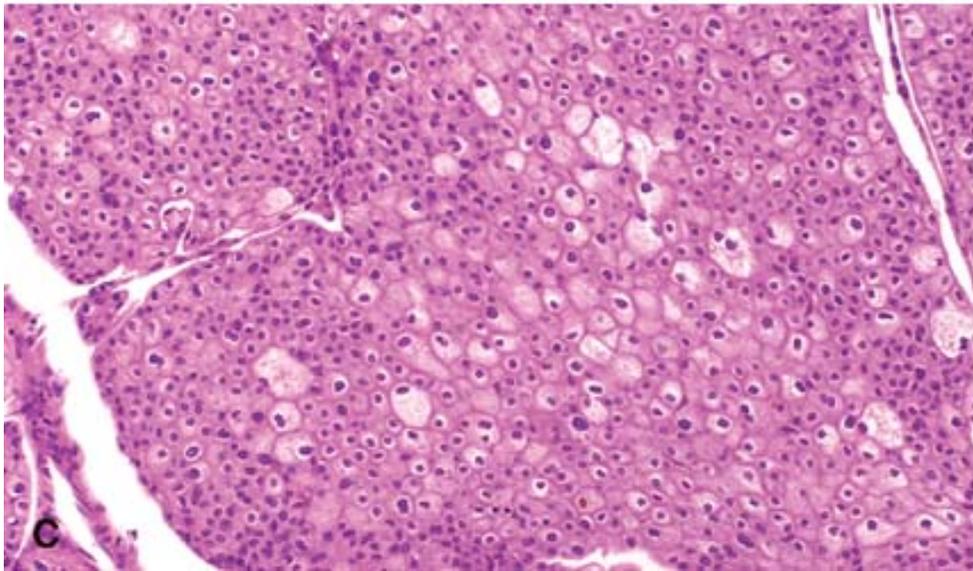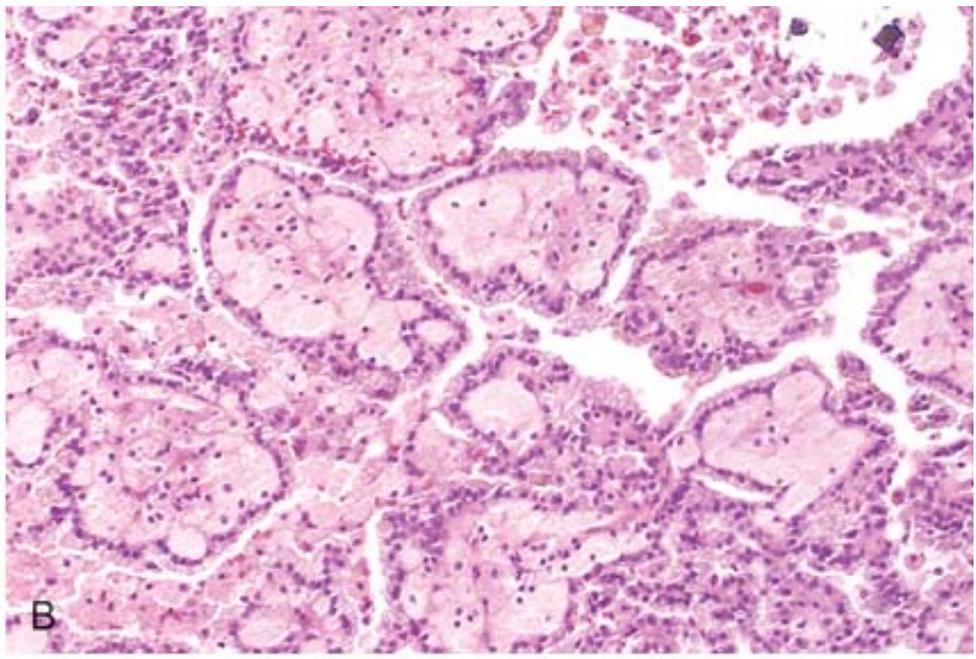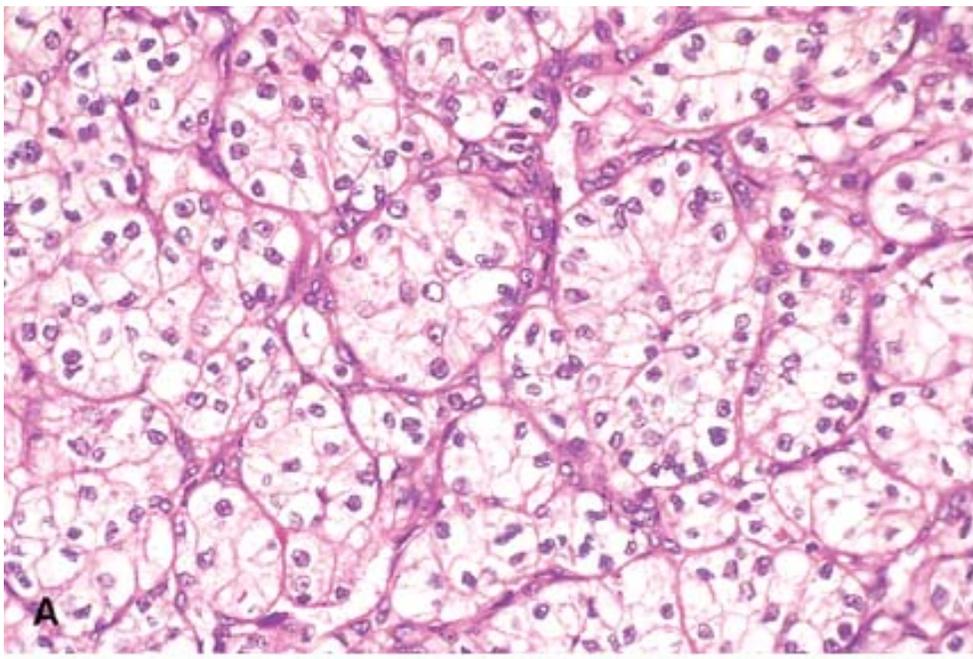
**Figure 20-61** Urothelial carcinoma of the renal pelvis. The pelvis has been opened to expose the nodular irregular neoplasm, just proximal to the ureter.

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**1022**

**1023**

# Chapter 21 - The Lower Urinary Tract and Male Genital System

**Jonathan I. Epstein MD**

**1024**

## The Lower Urinary Tract

### NORMAL

Despite differing embryonic origins, the various components of the lower urinary tract come to have many morphologic similarities. The renal pelves, ureters, bladder, and urethra (except for its terminal portion) are lined by a special form of transitional epithelium (urothelium) that is two to three cells thick in the pelvis, three to five cells thick in the ureters, and three to seven cells thick in the bladder. The surface layer consists of large, flattened "umbrella cells" that cover several underlying cells. The umbrella cells have a trilaminar asymmetric unit membrane and possess apical plaques composed of specific proteins called *uroplakins*. Toward the basal layer, the cells become smaller or more cylindrical (particularly in contracted bladders), but they are capable of some flattening when the underlying wall is stretched. This epithelium rests on a well-developed basement membrane, beneath which there is a lamina

propria. The lamina propria in the urinary bladder contains wisps of smooth muscle that form a discontinuous muscularis mucosae. It is important to differentiate the muscularis mucosae from the deeper well-defined larger muscle bundles of the detrusor muscle (muscularis propria), since bladder cancers are staged on the basis of invasion of the latter. The bladder musculature is capable of great thickening if there is obstruction to the flow of urine.

Several variants of the normal epithelial patterns may be encountered. Nests of urothelium or inbudding of the surface epithelium may be found occasionally in the mucosa lamina propria; these are referred to as *Brunn nests*.

The ureters lie throughout their course in a retroperitoneal position. Retroperitoneal tumors or fibrosis may trap the ureters in neoplastic or dense, fibrous tissue, sometimes obstructing them. As ureters enter the pelvis, they pass anterior to either the common iliac or the external iliac artery. In the female pelvis, they lie close to the uterine arteries and are therefore vulnerable to injury in operations on the female genital tract. There are three points of slight narrowing: at the ureteropelvic junction, where they enter the bladder, and where they cross the iliac vessels, all providing loci where renal calculi may become impacted when they pass from the kidney to the bladder. As the ureters enter the bladder, they pursue an oblique course, terminating in a slitlike orifice. The obliquity of this intramural segment of the ureteral orifice permits the enclosing bladder musculature to act like a sphincteric valve, blocking the upward reflux of urine even in the presence of marked distention of the urinary bladder. As discussed in Chapter 20 , a defect in the intravesical portion of the ureter leads to vesicoureteral reflux. The orifices of the ureters demarcate an area at the base of the bladder known as the trigone. In women, the trigone is frequently covered by glycogenated squamous epithelium, a normal finding, not metaplasia resulting from injury.

The close relationship of the female genital tract to the bladder makes possible the spread of disease from one tract to the other. In middle-aged and elderly women, relaxation of pelvic support leads to prolapse (descent) of the uterus, pulling with it the floor of the bladder. In this fashion, the bladder protrudes into the vagina, creating a pouch (*cystocele*) that fails to empty readily with micturition. In men, the seminal vesicles and prostate have similar close relationships, being situated just posterior and inferior to the neck of the bladder. Thus, enlargement of the prostate, so common in middle to later life, constitutes an important cause of urinary tract obstruction. In the subsequent sections, we discuss the major pathologic lesions in the ureters, urinary bladder, and urethra separately.[1] [2]

**Ureters**

**CONGENITAL ANOMALIES**

Congenital anomalies of the ureters occur in about 2% or 3% of all autopsies. Although most have little clinical significance, certain anomalies may contribute to obstruction to the flow of urine and thus cause clinical disease. Anomalies of the ureterovesical junction, potentiating reflux, are discussed with pyelonephritis in Chapter 20 .

*Double ureters* (derived from a double or split ureteral bud) are almost invariably associated either with totally distinct double renal pelves or with the anomalous development of a large kidney having a partially bifid pelvis terminating in separate ureters. Double ureters may pursue separate courses to the bladder but commonly are joined within the bladder wall and drain through a single ureteral orifice. The majority of double ureters are unilateral and of no clinical significance.

*Ureteropelvic junction obstruction*, a congenital disorder, results in hydronephrosis. It usually presents in infants or children, much more commonly in boys, usually in the left ureter. However, it is bilateral in 20% of cases and may be associated with other congenital anomalies. *It is the most common cause of hydronephrosis in infants and children.* In adults, ureteropelvic junction obstruction is more common in women and is most often unilateral. There is agenesis of the kidney on the opposite side in a significant number of cases, probably resulting from obstructive lesions in utero.

*Diverticula*, saccular outpouchings of the ureteral wall, are uncommon lesions that are usually asymptomatic and found incidentally on imaging studies. They appear as congenital or acquired defects and are of importance as pockets of stasis and secondary infections. Dilation (*hydroureter*), elongation, and tortuosity of the ureters may occur as congenital anomalies or as acquired defects. Congenital hydroureter is thought to reflect some neurogenic defect in the innervation of the ureteral musculature. Massive enlargement of the ureter is known as *megaloureter* and is probably due to a functional defect of ureteral muscle. Hydronephrosis and decreased renal

function results if the lesion goes untreated. These anomalies are sometimes associated with some congenital defect of the kidney.

### INFLAMMATIONS

*Ureteritis* may develop as one component of urinary tract infections. The morphologic changes are entirely nonspecific. Only infrequently does such ureteritis make a significant contribution to the clinical problem. Persistence of infection or repeated acute exacerbations may give rise to chronic inflammatory changes within the ureters.

### Morphology.

In certain cases of long-standing chronic ureteritis, specialized reaction patterns are sometimes observed. The accumulation or aggregation of lymphocytes in the subepithelial region may cause slight elevations of the mucosa and produce a fine granular mucosal surface (**ureteritis follicularis**). At other times, the mucosa may become sprinkled with fine cysts varying in diameter from 1 to 5 mm (**ureteritis cystica**). These changes are also found in the bladder (described in greater detail later, in the section on the urinary bladder). The cysts may aggregate to form small, grapelike clusters ( Fig. 21-1 ). Histologic sections through such cysts demonstrate a lining of modified transitional epithelium with some flattening of the superficial layer of cells.

### TUMORS AND TUMOR-LIKE LESIONS

Primary neoplasia of the ureter is rare. Small *benign tumors* of the ureter are generally of mesenchymal origin. The two most common are fibroepithelial polyps and leiomyomas. The *fibroepithelial polyp* is a tumor-like lesion that grossly presents as a small mass projecting into the lumen. The lesion occurs more commonly in the ureters (left more often than right) but may also appear in the bladder, renal pelves, and urethra. The polyp presents as a loose, vascularized connective tissue mass lying beneath the mucosa.

Primary *malignant tumors* of the ureter follow patterns similar to those arising in the renal pelvis, calyces, and bladder, and the majority are transitional cell carcinomas ( Fig. 21-2 ). They

**Figure 21-1** Opened ureters showing ureteritis cystica. Note the smooth cysts projecting from the mucosa.
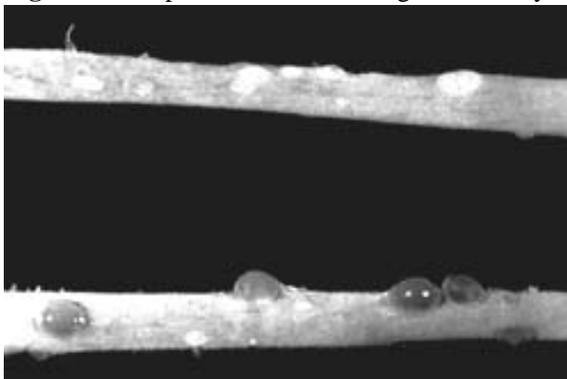


**Figure 21-2** Papillary transitional cell carcinoma extensively involving the ureter. *(Courtesy of Dr. Cristina Magi-Galluzzi, The Johns Hopkins Hospital, Baltimore, MD.)*

**TABLE 21-1** -- Major Causes of Ureteral Obstruction

| *Intrinsic* | |
| --- | --- |
| Calculi | Of renal origin, rarely more than 5 mm in diameter |
| | Larger renal stones cannot enter ureters |
| | Impact at loci of ureteral narrowing—ureteropelvic junction, where ureters cross iliac vessels, and where they enter bladder—and cause excruciating "renal colic" |
| Strictures | Congenital or acquired (inflammations) |
| Tumors | Transitional cell carcinomas arising in ureters |
| | Rarely, benign tumors or fibroepithelial polyps |
| Blood clots | Massive hematuria from renal calculi, tumors, or papillary necrosis |
| Neurogenic | Interruption of the neural pathways to the bladder |
| *Extrinsic* | |
| Pregnancy | Physiologic relaxation of smooth muscle or pressure on ureters at pelvic brim from enlarging fundus |
| Periureteral inflammation | Salpingitis, diverticulitis, peritonitis, sclerosing retroperitoneal fibrosis |
| Endometriosis | With pelvic lesions, followed by scarring |
| Tumors | Cancers of the rectum, bladder, prostate, ovaries, uterus, cervix, lymphomas, sarcomas |

**1026**

typically results from proximal causes, whereas bilateral obstruction arises from distal causes, such as nodular hyperplasia of the prostate. Only sclerosing retroperitoneal fibrosis is discussed further.

**Sclerosing Retroperitoneal Fibrosis.**

This refers to an uncommon cause of ureteral narrowing or obstruction characterized by a *fibrous proliferative inflammatory process encasing the retroperitoneal structures and causing hydronephrosis.*[3] The disorder occurs in middle to late age. In some cases, specific causes can be identified, such as drugs (ergot derivatives, β-adrenergic blockers), adjacent inflammatory conditions (vasculitis, diverticulitis, Crohn disease), or malignant disease (lymphomas, urinary tract carcinomas). However, 70% of cases have no obvious cause and are considered primary or idiopathic (Ormond disease). Several cases have been reported with similar fibrotic changes in other sites (referred to as mediastinal fibrosis, sclerosing cholangitis, and Riedel fibrosing thyroiditis), suggesting that the disorder is systemic in distribution but preferentially involves the retroperitoneum. Thus, an autoimmune reaction, sometimes triggered by drugs, has been proposed.

On microscopic examination, the inflammatory fibrosis is marked by a prominent inflammatory infiltrate of lymphocytes, often with germinal centers, plasma cells, and eosinophils. Sometimes, foci of fat necrosis and granulomatous inflammation are seen in and about the fibrosis.

## Urinary Bladder

Diseases of the bladder, particularly inflammation (cystitis), constitute an important source of clinical signs and symptoms. Usually, however, these disorders are more disabling than lethal. Cystitis is particularly common in young women of reproductive age and in older age groups of both sexes. Tumors of the bladder are an important source of both morbidity and mortality.

### CONGENITAL ANOMALIES

#### Diverticula.

A bladder or vesical diverticulum consists of a pouchlike eversion or evagination of the bladder wall. Diverticula may arise as congenital defects but more commonly are acquired lesions from persistent urethral obstruction.

*Congenital diverticula* may be due to a focal failure of development of the normal musculature or to some urinary tract obstruction during fetal development. *Acquired diverticula* are most often seen with prostatic enlargement (hyperplasia or neoplasia), producing obstruction to urine outflow and marked muscle thickening of the bladder wall. The increased intravesical pressure causes outpouching of the bladder wall and the formation of diverticula. They are frequently multiple and have narrow necks located between the interweaving hypertrophied muscle bundles. In both the congenital and acquired forms, the diverticulum usually consists of a round to ovoid, saclike pouch that varies from less than 1 cm to 5 to 10 cm in diameter.

Although most diverticula are small and asymptomatic, they may be clinically significant, as they constitute sites of urinary stasis and predispose to infection and the formation of bladder calculi. They may also predispose to vesicoureteral reflux as a result of impingement on the ureter. Rarely, carcinomas may arise in bladder diverticuli. When invasive cancers arise in diverticula, they tend to be more advanced in stage as a result of diverticula's thin or absent muscle wall.

#### Exstrophy.

Exstrophy of the bladder implies the presence of a developmental failure in the anterior wall of the abdomen and in the bladder, so that the bladder either communicates directly through a large defect with the surface of the body or lies as an opened sac ( Fig. 21-3 ). These lesions are amenable to surgical correction, and long-term survival is possible. The exposed bladder mucosa may undergo colonic glandular metaplasia and is subject to the development of infections that often spread to upper levels of the urinary system. In the course of persistent chronic infections, the mucosa often becomes converted into an ulcerated surface of granulation tissue, and the preserved marginal epithelium becomes transformed into a stratified squamous type.

There is an increased tendency toward the development of carcinoma later in life, mostly adenocarcinoma of the colon.[4] Patients also have an increased risk of adenocarcinoma arising from the bladder remnant.

#### Miscellaneous Anomalies.

*Vesicoureteral reflux* is the most common and serious anomaly. As a major contributor to renal infection and scarring, it was discussed earlier in Chapter 20 in the consideration of pyelonephritis. Abnormal connections between the bladder and the vagina, rectum, or uterus may create *congenital fistulas*.

Rarely, the *urachus* may remain patent in part or in whole (persistent urachus). When it is totally patent, a fistulous urinary tract is created that connects the bladder with the umbilicus. At times, the umbilical end or the bladder end remains patent, while the central region is obliterated. A sequestered umbilical epithelial rest or bladder diverticulum is formed that may provide a site for the development of infection. At other times, only the central region of the urachus persists, giving rise to *urachal cysts*, lined by either transitional or metaplastic epithelium. *Carcinomas*, mostly glandular tumors resembling colonic adenocarcinomas, may arise in such cysts. These account for only a minority of all bladder cancers (0.1% to 0.3%) but 20% to 40% of bladder adenocarcinomas.[2]

**Figure 21-3** Exstrophy of the bladder in a newborn boy. The tied umbilical cord is seen above the hyperemic mucosa of the everted bladder. Below is an incompletely formed penis with marked epispadias. *(Courtesy of Dr. John Gearhart, The Johns Hopkins Hospital, Baltimore, MD.)*
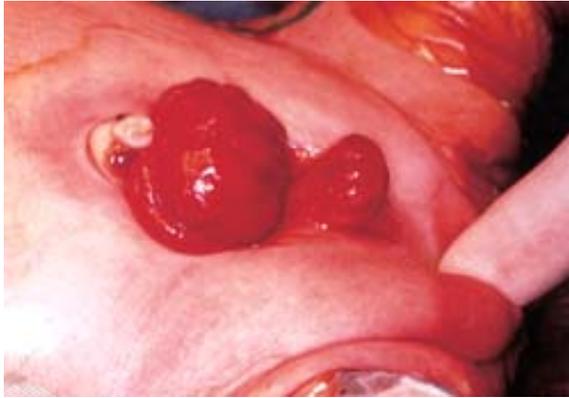


**Figure 21-4** Cystitis with malacoplakia of bladder showing inflammatory exudate and broad, flat plaques.
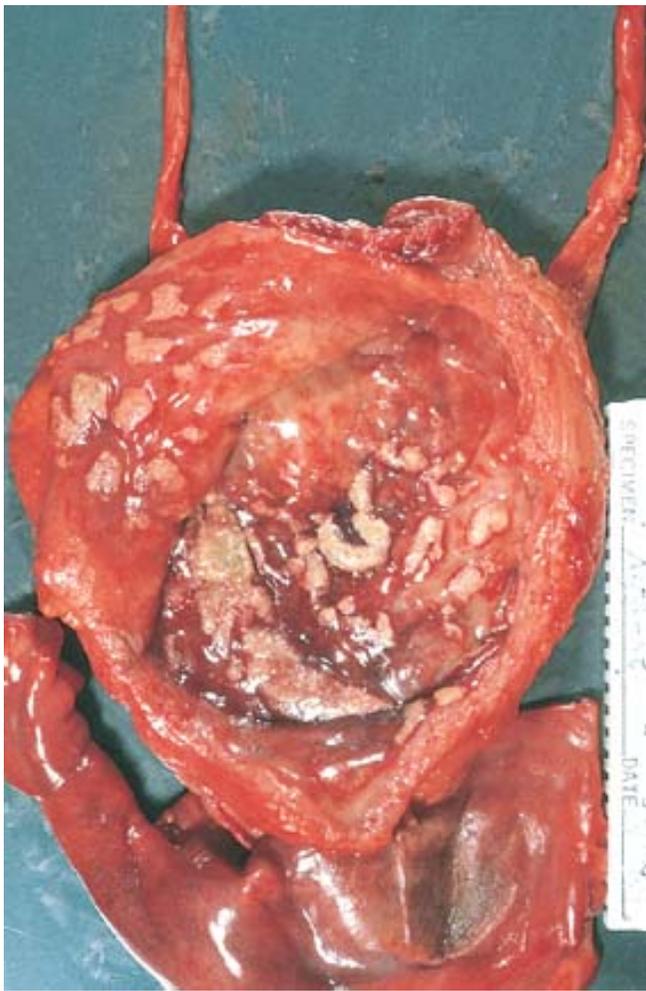
**Figure 21-5** Malacoplakia, PAS stain. Note the large macrophages with granular PAS-positive cytoplasm and several dense, round Michaelis-Gutmann bodies surrounded by artifactual cleared holes in the upper middle field.
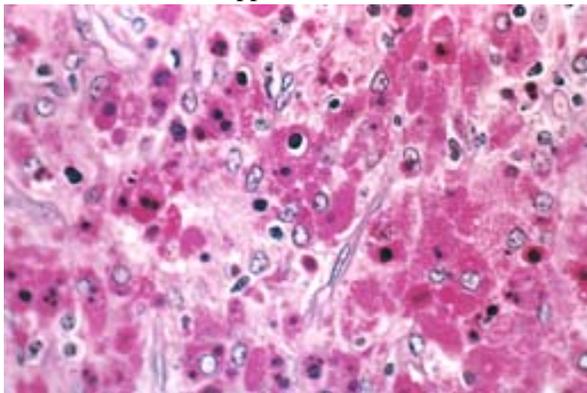
**TABLE 21-2** -- Tumors of the Urinary Bladder

| |
|---|
| Urothelial (transitional cell) tumors |
| ••Inverted papilloma |
| ••Papilloma (exophytic) |
| ••Urothelial tumors of low malignant potential |
| ••Papillary urothelial carcinoma |
| ••Carcinoma in situ |
| Squamous cell carcinoma |
| Mixed carcinoma |
| Adenocarcinoma |
| Small cell carcinoma |
| Sarcomas |

described below may be seen at any site where there is urothelium, from the renal pelvis to the distal urethra.

*There are two distinct precursor lesions to invasive urothelial carcinoma.* The more common are noninvasive papillary tumors, which appear to arise from papillary urothelial hyperplasia.[14] These lesions demonstrate a range of atypia, and several grading systems exist to reflect their biologic behavior. The other precursor lesion is flat urothelial carcinoma, which is simply referred to as carcinoma in situ (CIS). This lesion is by definition high grade and hence not assigned a grade. In about half the patients with invasive bladder cancer, at the time of presentation the tumor has already invaded the bladder wall, and there is no associated precursor lesion. In these cases, it is presumed that the precursor lesion has been destroyed by the high-grade invasive component, which typically appears as a large mass that is often ulcerated. Although invasion into the lamina propria worsens the prognosis, the major decrease in survival is associated with tumor invading the muscularis propria (detrusor muscle). Once muscularis propria invasion occurs, there is a 50% 5-year mortality rate.

Table 21-3 lists two of many systems of grading these tumors.[15] [16] [17] [18] The World Health Organization (WHO) 1973 classification grades tumors into a rare totally benign papilloma and three grades of transitional cell carcinoma (grades I, II, and III). A more recent classification, based on a consensus

**TABLE 21-3** -- Grading of Urothelial (Transitional Cell) Tumors

| |
|---|
| *WHO/ISUP Grades* [*] |
| Urothelial papilloma |
| Urothelial neoplasm of low malignant potential |
| Papillary urothelial carcinoma, low grade |
| Papillary urothelial carcinoma, high grade |
| *WHO Grades* [†] |
| Urothelial papilloma |

| Urothelial neoplasm of low malignant potential |
| Papillary urothelial carcinoma, Grade 1 |
| Papillary urothelial carcinoma, Grade 2 |
| Papillary urothelial carcinoma, Grade 3 |
| WHO, World Health Organization; ISUP, International Society of Urological Pathology. |

*Adopted as the WHO System in 2004.
†The 1973 WHO grades.

**Figure 21-6** Four morphologic patterns of bladder tumors.



Papilloma–
papillary carcinoma

Invasive
papillary carcinoma

Flat noninvasive
carcinoma (CIS)

Flat invasive
carcinoma
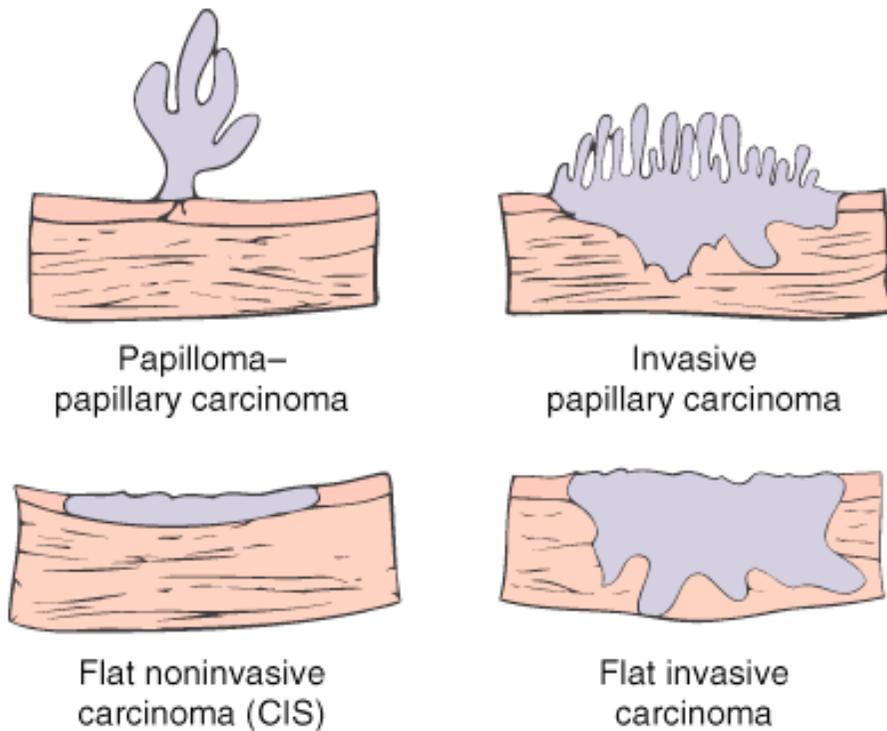
**Figure 21-7** Cross-section of bladder with upper section showing a large papillary tumor. The lower section demonstrates multifocal smaller papillary neoplasms. *(Courtesy of Dr. Fred Gilkey, Sinai Hospital, Baltimore, MD.)*

**Figure 21-8** Papilloma consisting of small papillary fronds lined by normal-appearing urothelium.



**Figure 21-9** Low-grade papillary urothelial carcinoma with an overall orderly appearance, a thicker lining than papilloma, and scattered hyperchromatic nuclei and mitotic figures (*arrows*).
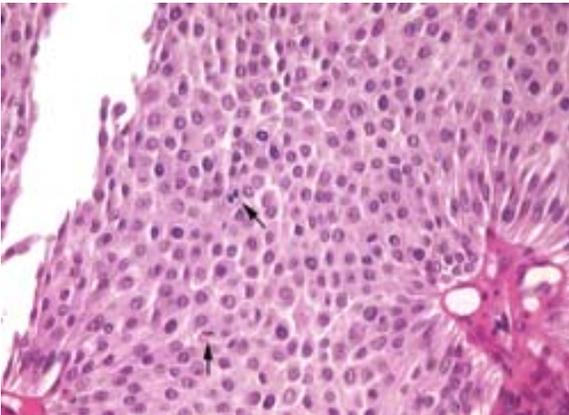


**Figure 21-10** High-grade papillary urothelial carcinoma with marked cytologic atypia.
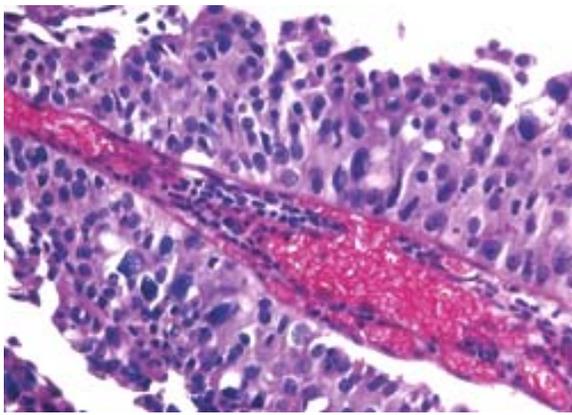
**Figure 21-11** *A*, Normal urothelium with uniform nuclei and well-developed umbrella cell layer. *B*, Flat carcinoma in situ with numerous cells having enlarged and pleomorphic nuclei.
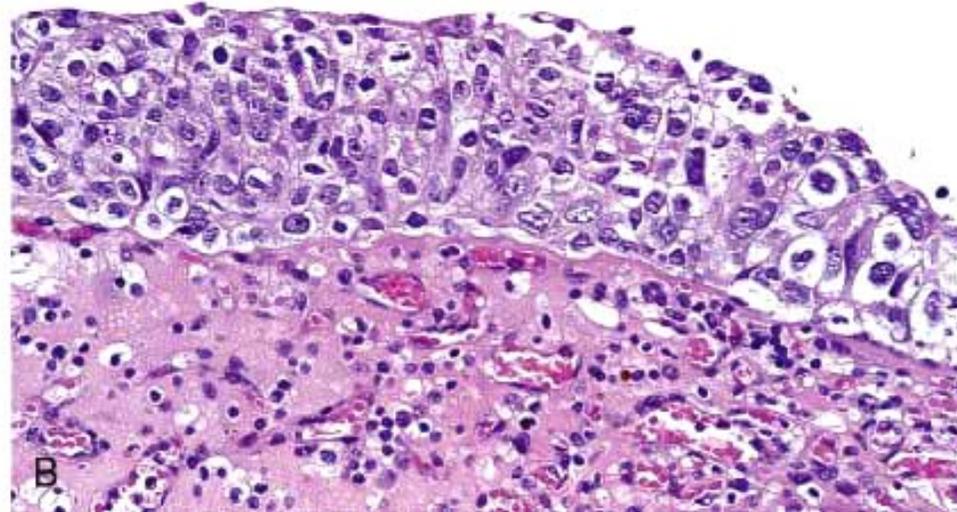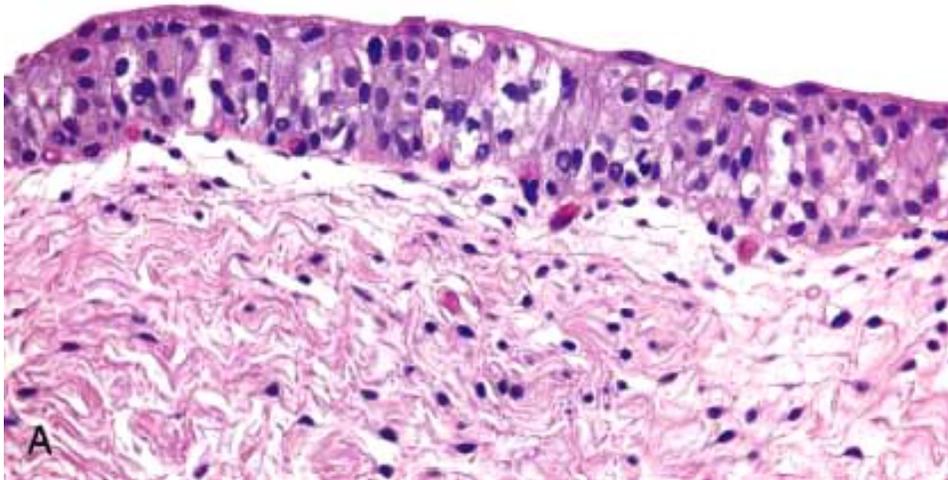


**TABLE 21-4** -- Pathologic T (Primary Tumor) Staging of Bladder Carcinoma

| AJCC/UICC | Depth of Invasion |
| --- | --- |
| Noninvasive, papillary | Ta |
| Carcinoma in situ (noninvasive, flat) | Tis |
| Lamina propria invasion | T1 |
| Muscularis propria invasion | T2 |
| Microscopic extravesicle invasion | T3a |
| Grossly apparent extravesicle invasion | T3b |
| Invades adjacent structures | T4 |

**carcinomas with areas of squamous carcinoma** are more frequent than pure squamous cell carcinomas. Most are invasive, fungating tumors or infiltrative and ulcerative. True papillary patterns are almost never seen. The level of cytologic differentiation varies widely, from the highly differentiated lesions producing abundant keratohyaline pearls to anaplastic giant

**Figure 21-12** Opened bladder showing a high-grade invasive urothelial cell carcinoma at an advanced stage. The aggressive multinodular neoplasm has fungated into the bladder lumen and spread over a wide area. The yellow areas represent areas of ulceration and necrosis.



**Figure 21-13** Hypertrophy and trabeculation of bladder wall secondary to polypoid hyperplasia of the prostate.
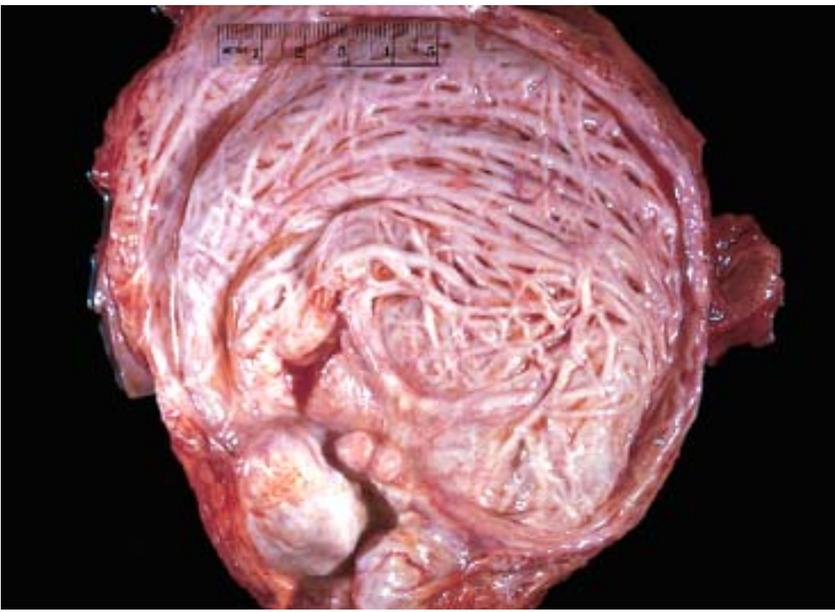
**Figure 21-14** Carcinoma of urethra with typical fungating growth.
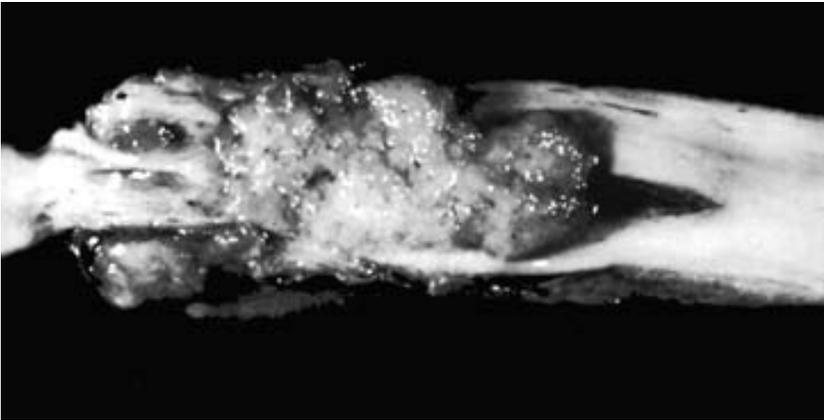


**Figure 21-15** Condyloma acuminatum of the penis.

**Figure 21-16** Condyloma acuminatum of the penis. Low magnification reveals the papillary (villous) architecture.
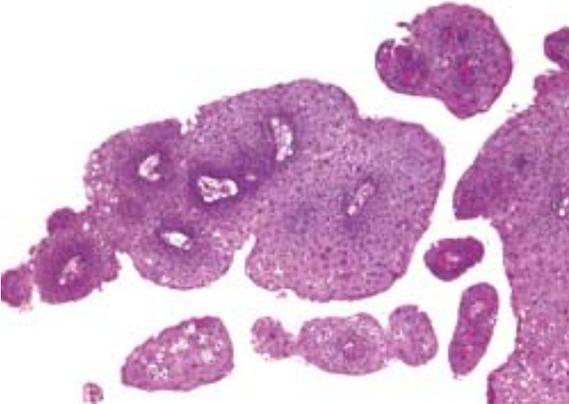


**Figure 21-17** Condyloma acuminatum of the penis. The epithelium shows vacuolization (koilocytosis), characteristic of human papillomavirus (HPV) infection.
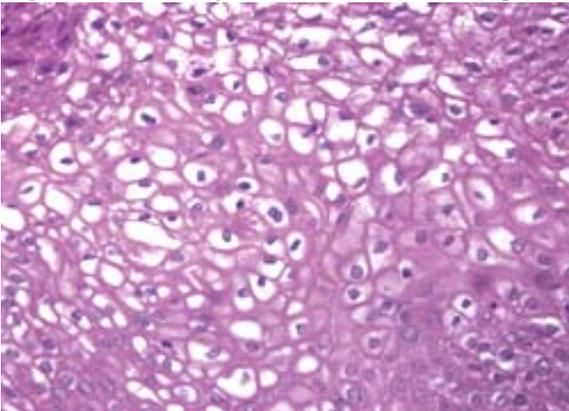
**Figure 21-18** Bowen disease (carcinoma in situ) of the penis. The epithelium above the intact basement membrane (*not seen in this picture*) shows hyperchromatic, dysplastic dyskeratotic epithelial cells with scattered mitoses above the basal layer.
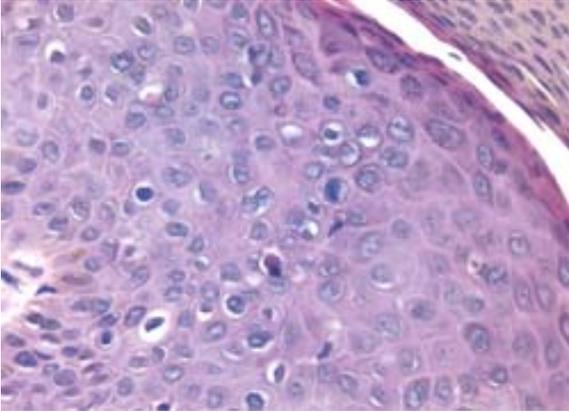


**Figure 21-19** Carcinoma of the penis. The glans penis is deformed by a firm, ulcerated, infiltrative mass.
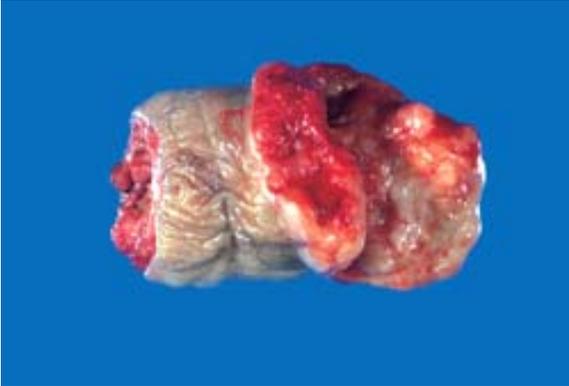


**Figure 21-20** *A*, Normal testis shows tubules with active spermatogenesis. *B*, Testicular atrophy. The tubules show Sertoli cells but no spermatogenesis. There is thickening of basement membranes and an apparent increase in interstitial Leydig cells.
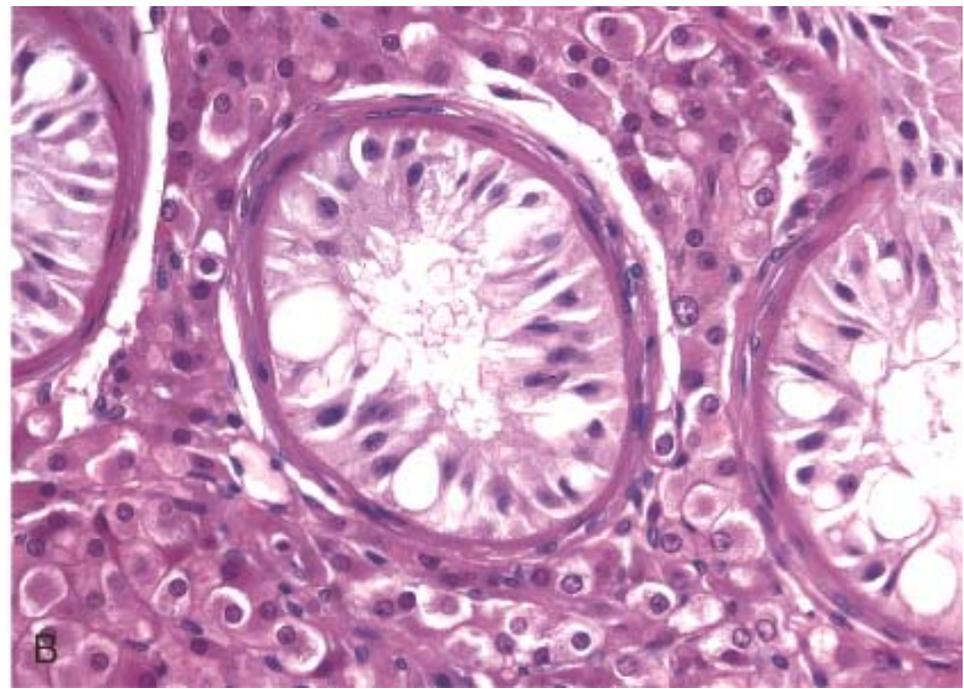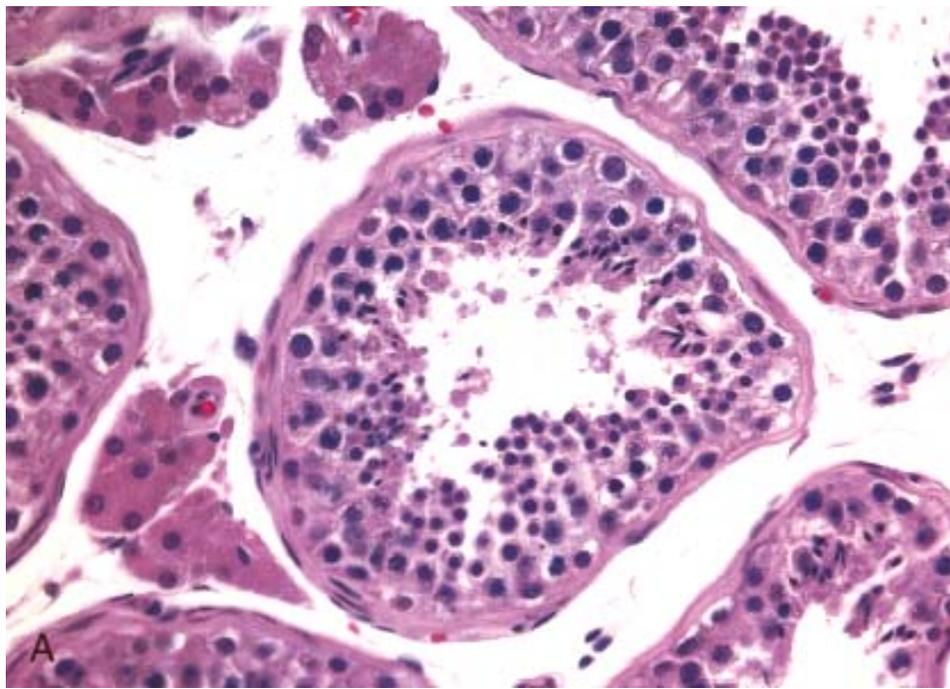
**Figure 21-21** Acute epididymitis caused by gonococcal infection. The epididymis is replaced by an abscess. A normal testis is seen on the right.



**Figure 21-22** Torsion of the testis.
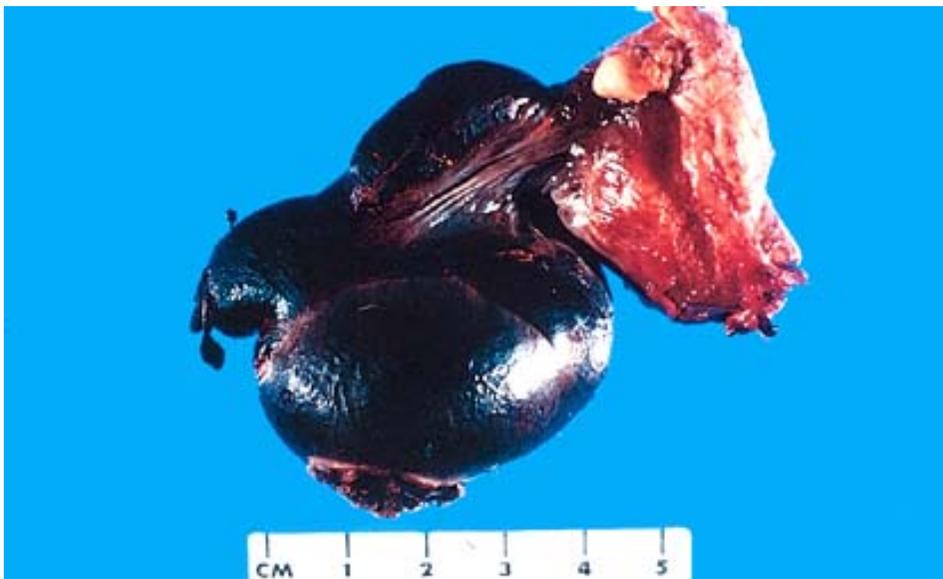
**TABLE 21-5** -- Pathologic Classification of Common Testicular Tumors

| *Germ Cell Tumors* |
| --- |
| Seminoma |
| Spermatocytic seminoma |
| Embryonal carcinoma |
| Yolk sac (endodermal sinus) tumor |
| Choriocarcinoma |
| Teratoma |
| *Sex Cord-Stromal Tumors* |
| Leydig cell tumor |
| Sertoli cell tumor |

Most tumors in this group originate from intratubular germ cell neoplasia (ITGCN).[74] [75] ITGCN is seen adjacent to all germ cell tumors in adults except for spermatocytic seminoma and epidermoid and dermoid cysts. With rare exceptions, it is also not seen in pediatric tumors (teratomas, yolk sac tumors). ITCGN is encountered with a high frequency in the following conditions, listed in order of increasing risk: cryptorchidism, prior germ cell tumors, strong family history of germ cell tumor, androgen insensitivity syndrome, and gonadal dysgenesis syndrome. Untreated ITGCN progresses to invasive germ cell tumor in approximately 50% of cases over 5 years of follow-up. Thus its significance is similar to carcinoma in situ in other organs. If ITGCN is identified, it is treated by low-dose radiotherapy, which destroys the germ cells yet maintains the androgen production of the Leydig cells.

Neoplastic germ cells may differentiate along gonadal lines to give rise to *seminoma* or transform into a totipotential cell population that gives rise to *nonseminomatous tumors*. Such totipotential cells may remain largely undifferentiated to form embryonal carcinoma or may differentiate along extraembryonic lines to form *yolk sac tumors* or *choriocarcinomas*. Teratoma results from differentiation of the embryonic carcinoma cells along the lines of all three germ cell layers. Some studies suggest that seminomas are not end-stage neoplasms.

Similar to embryonal carcinomas, seminomas may also act as precursors from which other forms of testicular germ cell tumors originate. This view is supported by the fact that cells that form intratubular germ cell neoplasias (the presumed precursors of all types of germ cell tumors) share morphologic and molecular characteristics with tumor cells in seminomas. Despite the fascination of pathologists with the heterogeneity of testicular tumors, from a *clinical standpoint the most important distinction in germ cell tumors is between seminomas and nonseminomatous tumors*. As will be discussed later, this clinical distinction has important bearings on treatment and prognosis.

**Pathogenesis**

As with all neoplasms, little is known about the ultimate cause of germ cell tumors. Several predisposing influences, however, are important: (1) cryptorchidism, (2) testicular dysgenesis, and (3) genetic factors, all of which may contribute to a common denominator: germ cell maldevelopment. Reference has already been made to the increased incidence of neoplasms in *undescended testes*. In most large series of testicular tumors, approximately 10% are associated with cryptorchidism. The higher the location of the undescended testicle (intra-abdominal versus inguinal), the greater is the risk of developing cancer.

Patients with disorders of testicular development (testicular dysgenesis), including testicular feminization and Klinefelter syndrome, harbor an increased risk of developing germ cell tumors. The risk is highest in patients with testicular feminization. In cryptorchid and dysgenetic testes, foci of intratubular germ cell neoplasms can be detected at a high frequency before the development of invasive tumors.

Genetic predisposition also seems to be important, although no well-defined pattern of inheritance has been identified. In support, striking racial differences in the incidence of testicular tumors can be cited. Blacks in Africa have an extremely low incidence of these neoplasms, which is unaffected by migration to the United States. Familial clustering has been reported, and according to one study, sibs of affected individuals have a tenfold higher risk of developing testicular cancer than does the general population.

As with all tumors, genomic changes are undoubtedly important in the pathogenesis of testicular cancers. An *isochromosome of the short arm of chromosome 12*, i(*12p*), *is found in virtually all germ cell tumors*, regardless of their histologic type. In the approximately 10% of cases in which i(12p) is not detected, extra genetic material derived from 12p is found on other chromosomes. Obviously, dosage of genes located on 12p is critical for the pathogenesis of germ cell tumors, and several candidate genes have been identified, including a novel gene, called *DAD-R*, that prevents apoptosis.[76] [77] It is of interest that i(12p) is also noted in ovarian germ cell neoplasms, suggesting that the events leading to this alteration may be critical to the molecular pathogenesis of all germ cell neoplasms.

With this background of pathogenesis, we can discuss the morphologic patterns of germ cell tumors, followed by the clinical features that are common to most germinal tumors.

**Seminoma**

Seminomas are the most common type of germinal tumor (50%) and the type most likely to produce a uniform population of cells. They almost never occur in infants; they peak in the thirties. An identical tumor arises in the ovary, where it is called *dysgerminoma* ( Chapter 22 ).

**Morphology.**

If not otherwise specified, the term "seminoma" refers to "classic" or "typical" seminoma. Spermatocytic seminoma, despite its nosologic similarity, is actually a distinct tumor; it has been segregated into a separate category and will be discussed later.

Seminomas produce bulky masses, sometimes 10 times the size of the normal testis. The typical seminoma has a homogeneous, gray-white, lobulated cut surface, usually devoid of hemorrhage or necrosis ( Fig. 21-23 ). In more than half of cases, the entire testis is replaced. Generally, the tunica albuginea is not penetrated, but occasionally, extension to the epididymis, spermatic cord, or scrotal sac occurs.

Microscopically, the typical seminoma presents sheets of uniform cells divided into poorly demarcated lobules by delicate septa of fibrous tissue ( Fig. 21-24*A* ). **The classic seminoma**

**cell is large and round to polyhedral and has a distinct cell membrane; a clear or watery-appearing cytoplasm; and a large,**

1042

**Figure 21-23** Seminoma of the testis appears as a fairly well circumscribed, pale, fleshy, homogeneous mass.



**Figure 21-24** Seminoma. *A*, Low magnification shows clear seminoma cells divided into poorly demarcated lobules by delicate septa. *B*, Microscopic examination reveals large cells with distinct cell borders, pale nuclei, prominent nucleoli, and a sparse lymphocytic infiltrate.
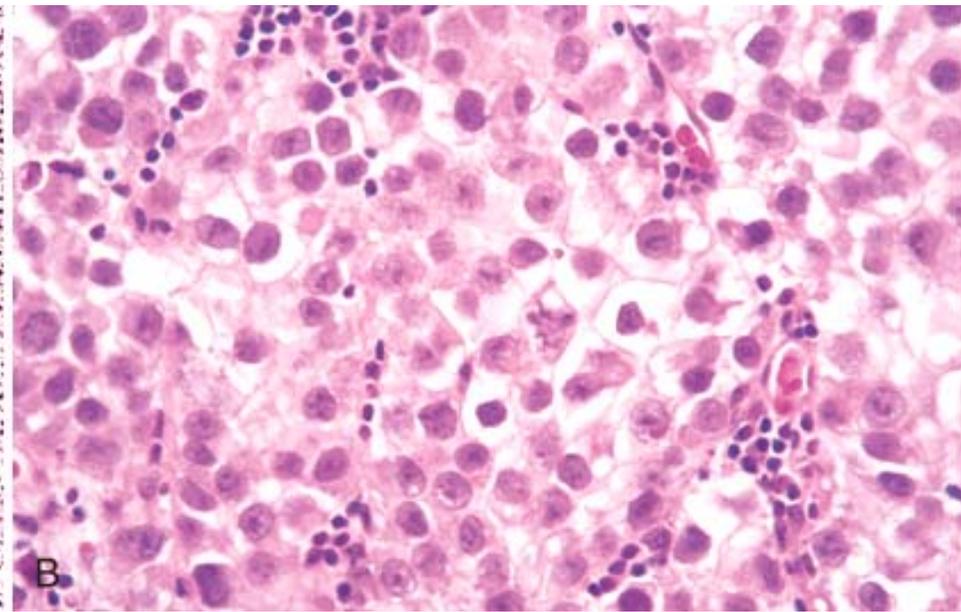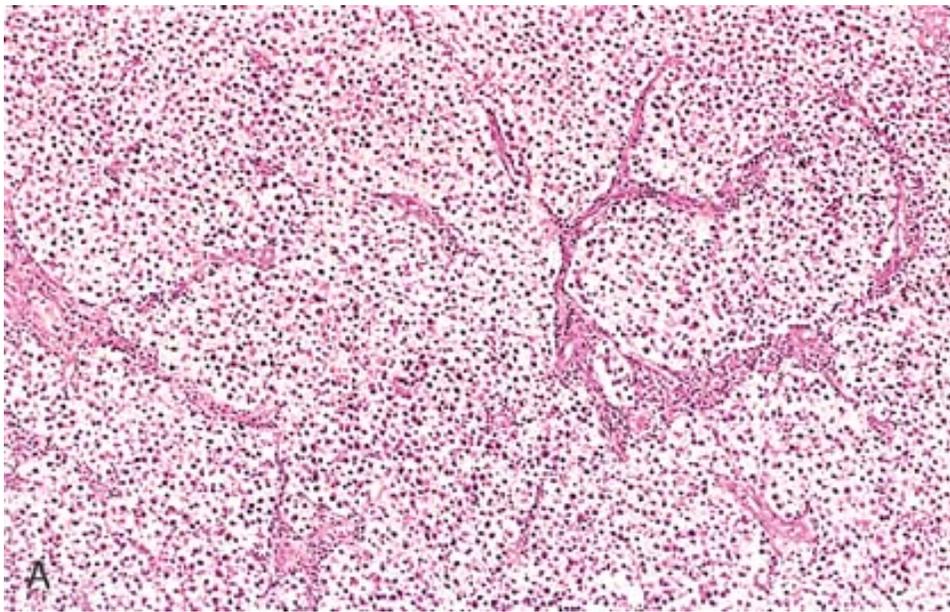
**Figure 21-25** Embryonal carcinoma. In contrast to the seminoma illustrated in Figure 21-23 , the embryonal carcinoma is a hemorrhagic mass.
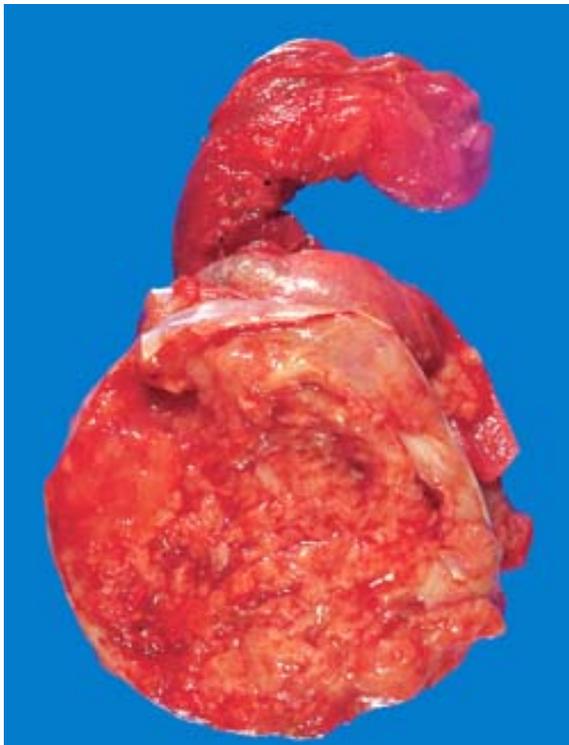


**Figure 21-26** Embryonal carcinoma shows sheets of undifferentiated cells as well as primitive glandular differentiation. The nuclei are large and hyperchromatic.
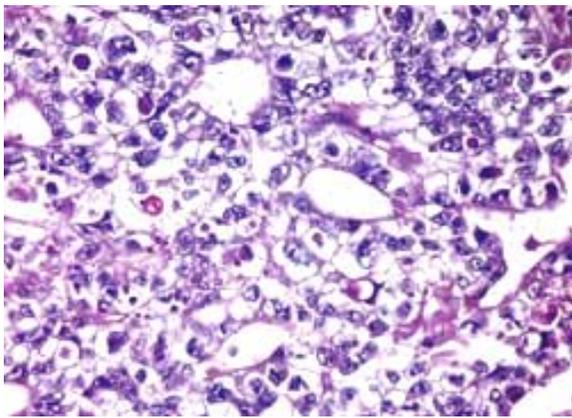
**Figure 21-27** Choriocarcinoma shows clear cytotrophoblastic cells with central nuclei and syncytiotrophoblastic cells with multiple dark nuclei embedded in eosinophilic cytoplasm. Hemorrhage and necrosis are prominent.
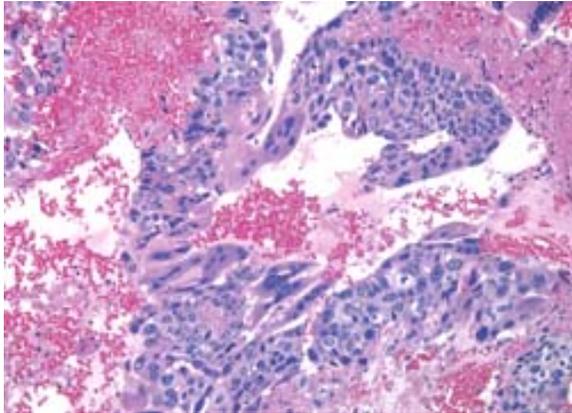


**Figure 21-28** Teratoma of the testis. The variegated cut surface with cysts reflects the multiplicity of tissue found histologically.



**Figure 21-29** Teratoma of the testis consisting of a disorganized collection of glands, cartilage, smooth muscle, and immature stroma.