Renal Interstitium and Major Features of Chronic Tubulointerstitial Nephritis

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A s a rule, diseases of the kidney primarily affect the glomeruli, vasculature, or remainder of the renal parenchyma that consists of the tubules and interstitium. Although the interstitium and the tubules represent separate functional and structural compartments, they are intimately related. Injury initially involving either one of them inevitably results in damage to the other. Hence the term *tubulointerstitial diseases* is used. Because inflammatory cellular infiltrates of variable severity are a constant feature of this entity, the terms *tubulointerstitial diseases* and *tubulointerstitial nephritis* have come to be used interchangeably. The clinicopathologic syndrome that results from these lesions, commonly termed *tubulointerstitial nephropathy*, may pursue an acute or chronic course. The chronic course is discussed here. The abbreviation TIN is used to refer synonymously to chronic tubulointerstitial nephritis and tubulointerstitial nephropathy.

TIN may be classified as primary or secondary in origin. Primary TIN is defined as primary tubulointerstitial injury without significant involvement of the glomeruli or vasculature, at least in the early stages of the disease. Secondary TIN is defined as secondary tubulointerstitial injury, which is consequent to lesions initially involving either the glomeruli or renal vasculature. The presence of secondary TIN is especially important because the magnitude of impairment in renal function and the rate of its progression to renal failure correlate better with the extent of TIN than with that of glomerular or vascular damage.

Renal insufficiency is a common feature of chronic TIN, and its diagnosis must be considered in any patient who exhibits renal insufficiency. In most cases, however, chronic TIN is insidious in onset, renal insufficiency is slow to develop, and earliest manifestations of the disease are those of tubular dysfunction. As such, it is important to maintain a high

CHAPTER

6

index of suspicion of this entity whenever any evidence of tubular dysfunction is detected clinically. At this early stage, removal of a toxic cause of injury or correction of the underlying systemic or renal disease can result in preservation of residual renal function. Of special relevance in patients who exhibit renal insufficiency caused by primary TIN is the absence or modest degree of the two principal hallmarks of glomerular and vascular diseases of the kidney: salt retention, manifested by edema and hypertension; and proteinuria, which usually is modest and less than 1 to 2 g/d in TIN. These clinical considerations notwithstanding, a definite diagnosis of TIN can be established only by morphologic examination of kidney tissue.

Structure of the Interstitium

C—Cortex
IS—Inner stripe of outer medulla
OS—Outer stripe of outer medulla
IZ—Inner zone of medulla

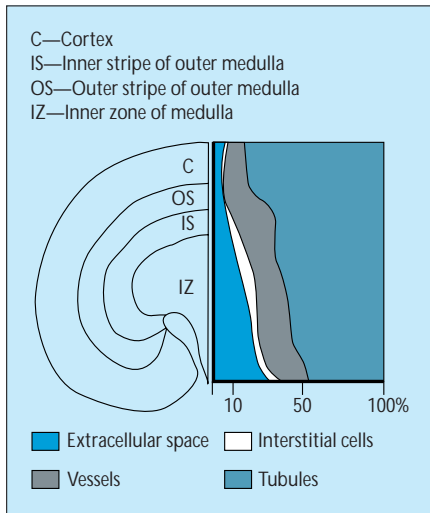Extracellular space Interstitial cells
Vessels Tubules

FIGURE 6-1

Diagram of the approximate relative volume composition of tissue compartments at different segments of the kidney in rats. The interstitium of the kidney consists of peritubular and periarterial spaces. The relative contribution of each of these two spaces to interstitial volume varies, reflecting in part the arbitrary boundaries used in assessing them, but increases in size from the cortex to the papilla. In the cortex there is little interstitium because the peritubular capillaries occupy most of the space between the tubules. The cortical interstitial cells are scattered and relatively inconspicuous. In fact, a loss of the normally very close approximation of the cortical tubules is the first evidence of TIN. In the medulla there is a noticeable increase in interstitial space. The interstitial cells, which are in greater evidence, have characteristic structural features and an organized arrangement. The ground substance of the renal interstitium contains different types of fibrils and basementlike material embedded in a glycosaminoglycan-rich substance. (*From* Bohman [1]; with permission.)
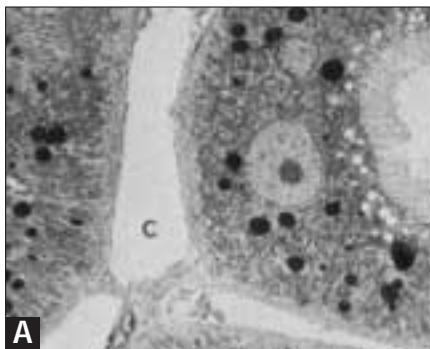
Cortex

FIGURE 6-2

A, Electron micrograph of a rat kidney cortex, where *C* is the cortex. **B,** Schematic rendering, where the narrow interstitium is shown in black and the wide interstitium is shown by dots. The relative volume of the interstitium of the cortex is approximately 7%, consisting of about 3% interstitial cells and 4% extracellular space. The vasculature occupies another 6%; the remainder (*ie,* some 85% or more) is occupied by the tubules. The cortical interstitial space is unevenly distributed and has been divided into narrow and wide structural components. The tubules and peritubular capillaries either are closely apposed at several points, sometimes to the point of sharing a common basement membrane, or are separated by a very narrow space.

This space, the so-called *narrow interstitium*, has been estimated to occupy 0.6% of cortical volume in rats. The narrow interstitium occupies about one-half to two-thirds of the cortical peritubular capillary surface area. The remainder of the cortical interstitium consists of irregularly shaped clearly discernible larger areas, the so-called *wide interstitium.* The wide interstitium has been estimated to occupy 3.4% of cortical volume in rats. The capillary wall facing the narrow interstitium is significantly more fenestrated than is that facing the wide interstitium. Functional heterogeneity of these interstitial spaces has been proposed but remains to be clearly defined. (*From* Bohman [1]; with permission.)
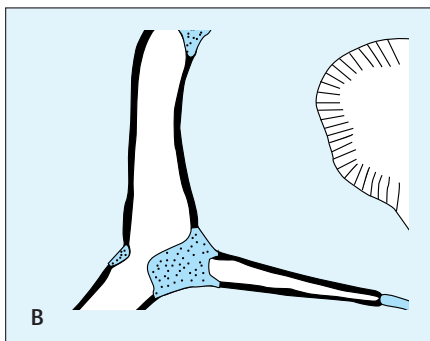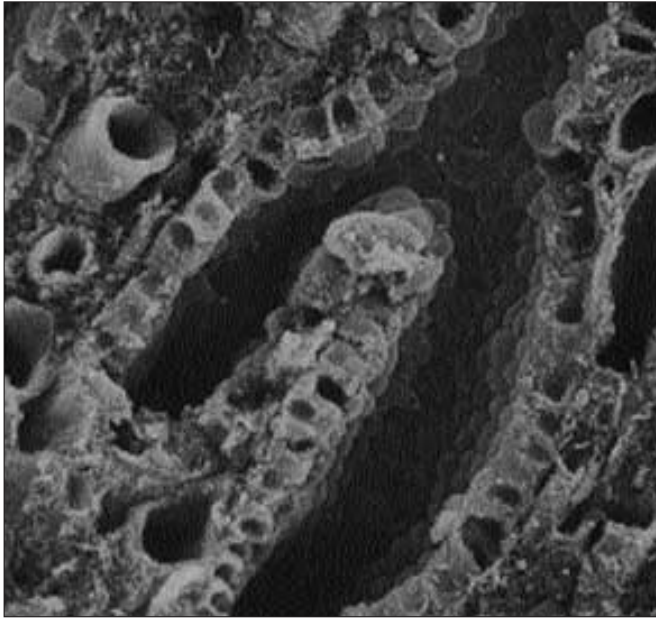
Medulla

Scanning electron micrograph of the inner medulla, showing a prominent collecting duct, thin wall vessels, and abundant interstitium. A gradual increase in interstitial volume from the outer medullary stripe to the tip of the papilla occurs. In the outer stripe of the outer medulla, the relative volume of the interstitium is slightly less than is that of the cortex. This volume has been estimated to be approximately 5% in rats. It is in the inner stripe of the outer medulla that the interstitium begins to increase significantly in volume, in increments that gradually become larger toward the papillary tip.

The inner stripe of the outer medulla consists of the vascular bundles and the interbundle regions, which are occupied principally by tubules. Within the vascular bundles the interstitial spaces are meager, whereas in the interbundle region the interstitial spaces occupy some 10% to 20% of the volume. In the inner medulla the differentiation into vascular bundles and interbundle regions becomes gradually less obvious until the two regions merge. A gradual increase in the relative volume of the interstitial space from the base of the inner medulla to the tip of the papilla also occurs. In rats, the increment in interstitial space is from 10% to 15% at the base to about 30% at the tip. In rabbits, the increment is from 20% to 25% at the base to more than 40% at the tip.
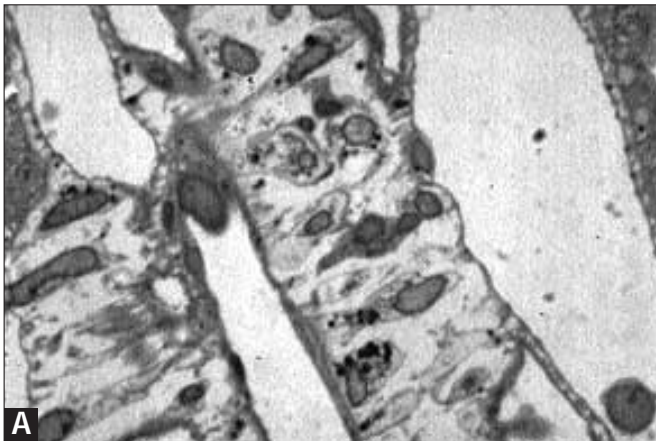
Cell types

B. RENAL INTERSTITIAL CELLS

Cortex	Outer medulla	Inner medulla
Fibroblastic cells	Fibroblastic cells	Pericytes
Mononuclear cells	Mononuclear cells	Lipid-laden cells
		Mononuclear cells

cells are important in antigen presentation. Their cytokines contribute to recruitment of infiltrating cells, progression of injury, and sustenance of fibrogenesis.

In the cortex and outer zone of the outer medulla, type I cells are more common than are type II cells. In the inner zone of the medulla, some type I cells form pericytes whereas others evolve into specialized lipid-laden interstitial cells. These specialized cells increase in number toward the papillary tip and are a possible source of medullary prostaglandins and of production of matriceal glycosaminoglycans. A characteristic feature of these medullary cells is their connection to each other in a characteristic arrangement, similar to the rungs of a ladder. These cells have a distinct close and regular transverse apposition to their surrounding structures, specifically the limbs of the loop of Henle and capillaries, but not to the collecting duct cells.

A, High-power view of the medulla showing the wide interstitium and interstitial cells, which are abundant, varied in shape, and arranged as are the rungs of a ladder. **B,** Renal interstitial cells. The interstitium contains two main cell types, whose numbers increase from the cortex to the papilla. Type I interstitial cells are fibroblastic cells that are active in the deposition and degradation of the interstitial matrix. Type I cells contribute to fibrosis in response to chronic irritation. Type II cells are macrophage-derived mononuclear cells with phagocytic and immunologic properties. Type II

Matrix

Peritubular interstitium in the cortex at the interface of a tubule (T) on the left and a capillary (C) on the right. The inset shows the same space in cross section, including the basement membrane (BM) of the two compartments. The extracellular loose matrix is a hydrated gelatinous substance consisting of glycoproteins and glycosaminoglycans (hyaluronic acid, heparan sulfate, dermatan sulfate, and chondroitin sulfate) that are embedded within a fibrillar reticulum. This reticulum consists of collagen fibers (types I, III, and VI) and unbanded microfilaments. Collagen types IV and V are the principal components of the basement membrane lining the tubules. Glycoprotein components (fibronectin and laminin) of the basement membrane connect it to the interstitial cell membranes and to the fibrillar structures of the interstitial matrix. The relative increase in the interstitial matrix of the medulla may be important for providing support to the delicate tubular and vascular structures in this region. (*From* Lemley and Kriz [2]; with permission.)

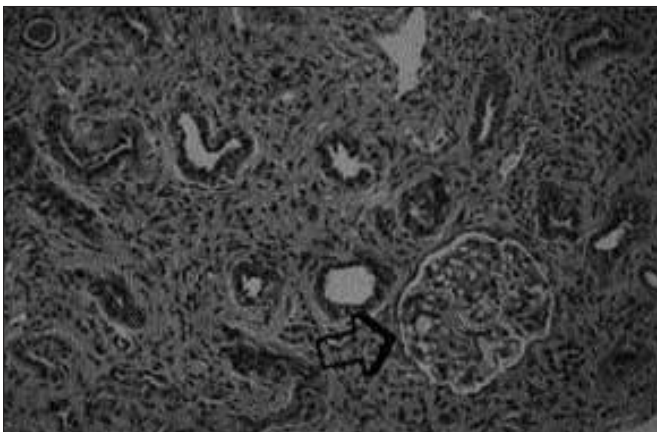# Pathologic Features of Chronic TIN

FIGURE 6-6

Primary chronic TIN. The arrow indicates a normal glomerulus. Apart from providing structural support, the interstitium serves as a conduit for solute transport and is the site of production of several cytokines and hormones (erythropoietin and prostaglandins). For the exchange processes to occur between the tubules and vascular compartment, the absorbed or secreted substances must traverse the interstitial space. The structure, composition, and permeability characteristics of the interstitial space must, of necessity, exert an effect on any such exchange. Although the normal structural and functional correlates of the interstitial space are poorly defined, changes in its composition and structure in chronic TIN are closely linked to changes in tubular function. In addition, replacement of the normal delicate interstitial structures by fibrosclerotic changes of chronic TIN would affect the vascular perfusion of the adjacent tubule, thereby contributing to tubular dysfunction and progressive ischemic injury.
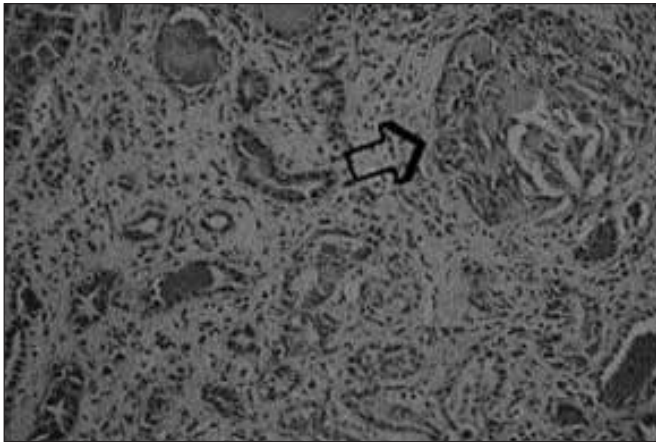
FIGURE 6-7

Secondary chronic TIN. The arrow indicates a glomerulus with a cellular crescent. The diagnosis of TIN can be established only by morphologic examination of kidney tissue. The extent of the lesions of TIN, whether focal or diffuse, correlates with the degree of impairment in renal function.

Tubular atrophy and dilation comprise a principal feature of TIN. The changes are patchy in distribution, with areas of atrophic chronically damaged tubules adjacent to dilated tubules displaying compensatory hypertrophy. In atrophic tubules the epithelial cells show simplification, decreased cell height, loss of brush border, and varying degrees of thickened basement membrane. In dilated tubules the epithelial cells are hypertrophic and the lumen may contain hyalinized casts, giving them the appearance of thyroid follicles. Hence the term *thyroidization* is used.

The interstitium is expanded by fibrous tissue, in which are interspersed proliferating fibroblasts and inflammatory cells comprised mostly of activated T lymphocytes and macrophages. Rarely, B lymphocytes, plasma cells, neutrophils, and even eosinophils may be present.

The glomeruli, which may appear crowded in some areas owing to tubulointerstitial loss, usually are normal in the early stages of the disease. Ultimately, the glomeruli become sclerosed and develop periglomerular fibrosis.

The large blood vessels are unremarkable in the early phases of the disease. Ultimately, these vessels develop intimal fibrosis, medial hypertrophy, and arteriolosclerosis. These vascular changes, which also are associated with hypertension, can be present even in the absence of elevated blood pressure in cases of chronic TIN.

CONDITIONS ASSOCIATED WITH PRIMARY CHRONIC TIN

Immunologic diseases	Urinary tract obstructions	Hematologic diseases	Miscellaneous	Hereditary diseases	Endemic diseases
Systemic lupus erythematosus	Vesicoureteral reflux	Sickle hemoglobinopathies	Vascular diseases	Medullary cystic disease	Balkan nephropathy
Sjögren syndrome	Mechanical	Multiple myeloma	Nephrosclerosis	Hereditary nephritis	Nephropathia epidemica
Transplanted kidney		Lymphoproliferative disorders	Atheroembolic disease	Medullary sponge kidney	
Cryoglobulinemia		Aplastic anemia	Radiation nephritis	Polycystic kidney disease	
Goodpasture's syndrome			Diabetes mellitus		
Immunoglobulin A nephropathy			Sickle hemoglobinopathies		
Amyloidosis			Vasculitis		
Pyelonephritis					
Infections	**Drugs**	**Heavy metals**	**Metabolic disorders**	**Granulomatous disease**	**Idiopathic TIN**
Systemic	Analgesics	Lead	Hyperuricemia-hyperuricosuria	Sarcoidosis	
Renal	Cyclosporine	Cadmium	Hypercalcemia-hypercalciuria	Tuberculosis	
Bacterial	Nitrosourea		Hyperoxaluria	Wegener's granulomatosis	
Viral	Cisplatin		Potassium depletion		
Fungal	Lithium		Cystinosis		
Mycobacterial	Miscellaneous				

FIGURE 6-8

Tubulointerstitial nephropathy occurs in a motley group of diseases of varied and diverse causes. These diseases are arbitrarily grouped together because of the unifying structural changes associated with TIN noted on morphologic examination of the kidneys.
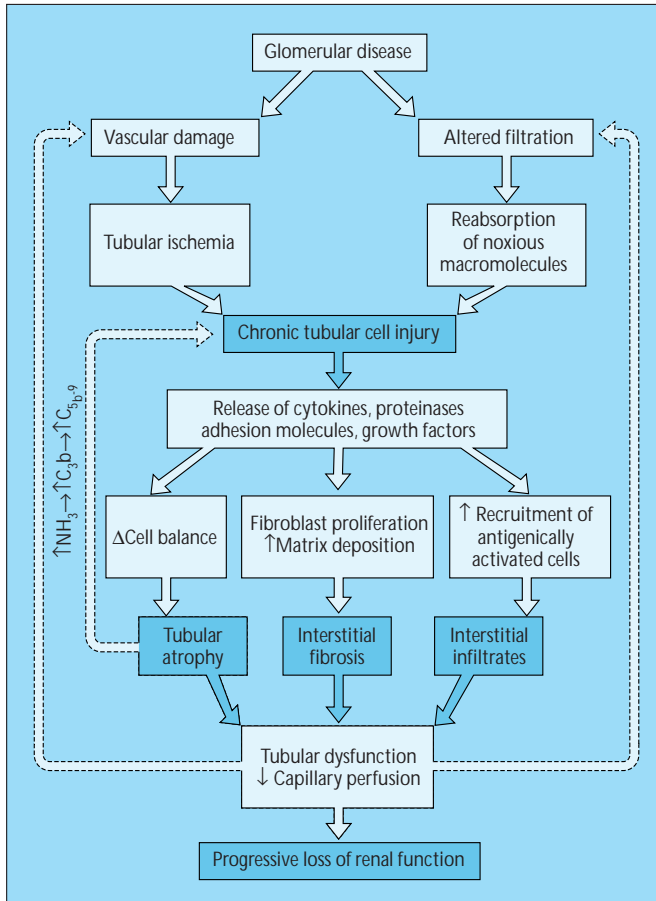
Pathogenesis of Chronic TIN

Schematic presentation of the potential pathways incriminated in the pathogenesis of chronic TIN caused by primary tubular injury (dark boxes) or secondary to glomerular disease (light boxes). The mechanism by which TIN is mediated remains to be elucidated. Chronic tubular epithelial cell injury appears to be pivotal in the process. The injury may be direct through cytotoxicity or indirect by the induction of an inflammatory or immunologic reaction. Studies in experimental models and humans provide compelling evidence for a role of immune mechanisms. The infiltrating lymphocytes have been shown to be activated immunologically. It is the inappropriate release of cytokines by the infiltrating cells and loss of regulatory balance of normal cellular regeneration that results in increased fibrous tissue deposition and tubular atrophy. Another potential mechanism of injury is that of increased tubular ammoniagenesis by the residual functioning but hypertrophic tubules. Increased tubular ammoniagenesis contributes to the immunologic injury by activating the alternate complement pathway.

Altered glomerular permeability with consequent proteinuria appears to be important in the development of TIN in primary glomerular diseases. By the same token, the proteinuria that develops late in the course of primary TIN may contribute to the tubular cell injury and aggravate the course of the disease.

In primary vascular diseases TIN has been attributed to ischemic injury. In fact, hypertension is probably the most common cause of TIN. The vascular lesions that develop late in the course of primary TIN, in turn, can contribute to the progression of TIN. (*From* Eknoyan [3]; with permission.)

ROLE OF TUBULAR EPITHELIAL CELLS

Chemoattractant cytokines	Pro-inflammatory cytokines	Cell surface markers	Matrix proteins
Monocyte chemo-attractant peptide-1	Interleukin-6 (IL-6), IL-8	Human leukocyte antigen class II	Collagen I, III, IV
Osteopontin	Platelet-derived growth factor-β	Intercellular adhesion molecule-1	Laminin, fibronectin
Chemoattractant lipids	Granulocyte -macrophage colony-stimulating factor	Vascular cell adhesion molecule-1	
Endothelin-1	Transforming growth factor-β1		
RANTES	Tumor necrosis factor-α		

The infiltrating interstitial cells contribute to the course TIN. However, increasing evidence exists for a primary role of the tubular epithelial cells in the recruitment of interstitial infiltrating cells and in perpetuation of the process. Injured epithelial cells secrete a variety of cytokines that have both chemoattractant and pro-inflammatory properties. These cells express a number of cell surface markers that enable them to interact with infiltrating cells. Injured epithelial cells also participate in the deposition of increased interstitial matrix and fibrous tissue. Listed are cytokines, cell surface markers, and matrix components secreted by the renal tubular cell that may play a role in the development of tubulointerstitial disease.
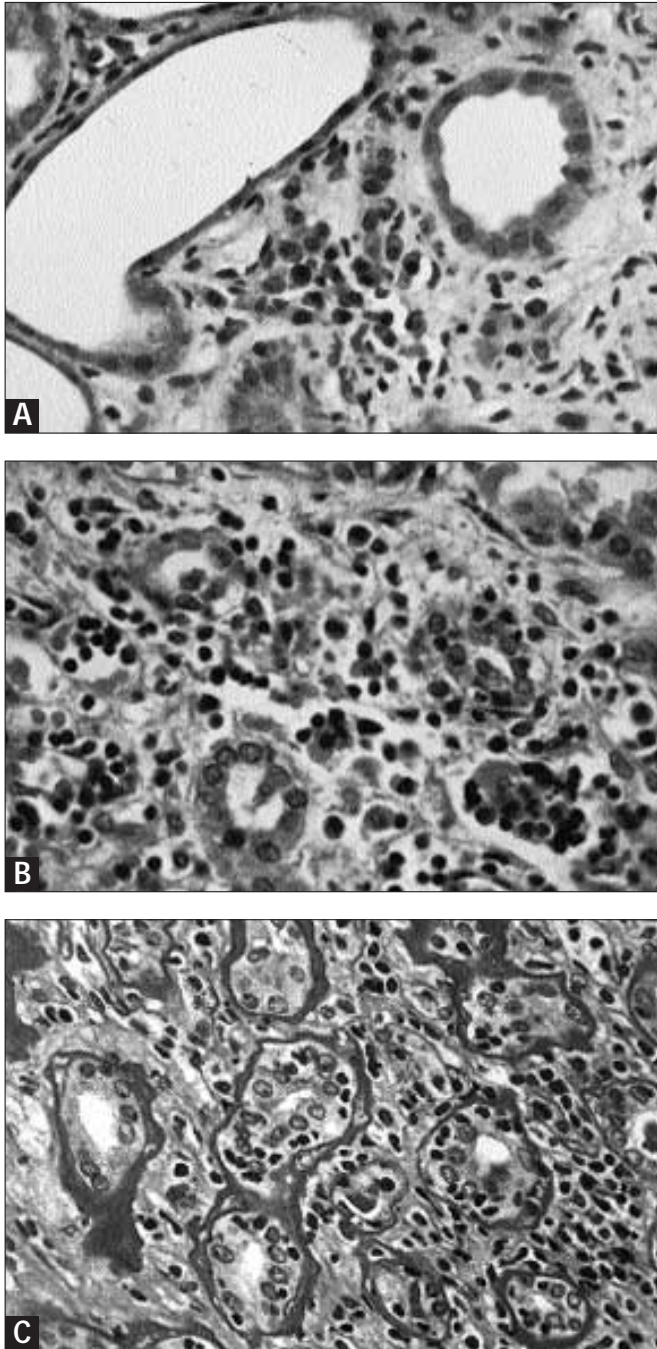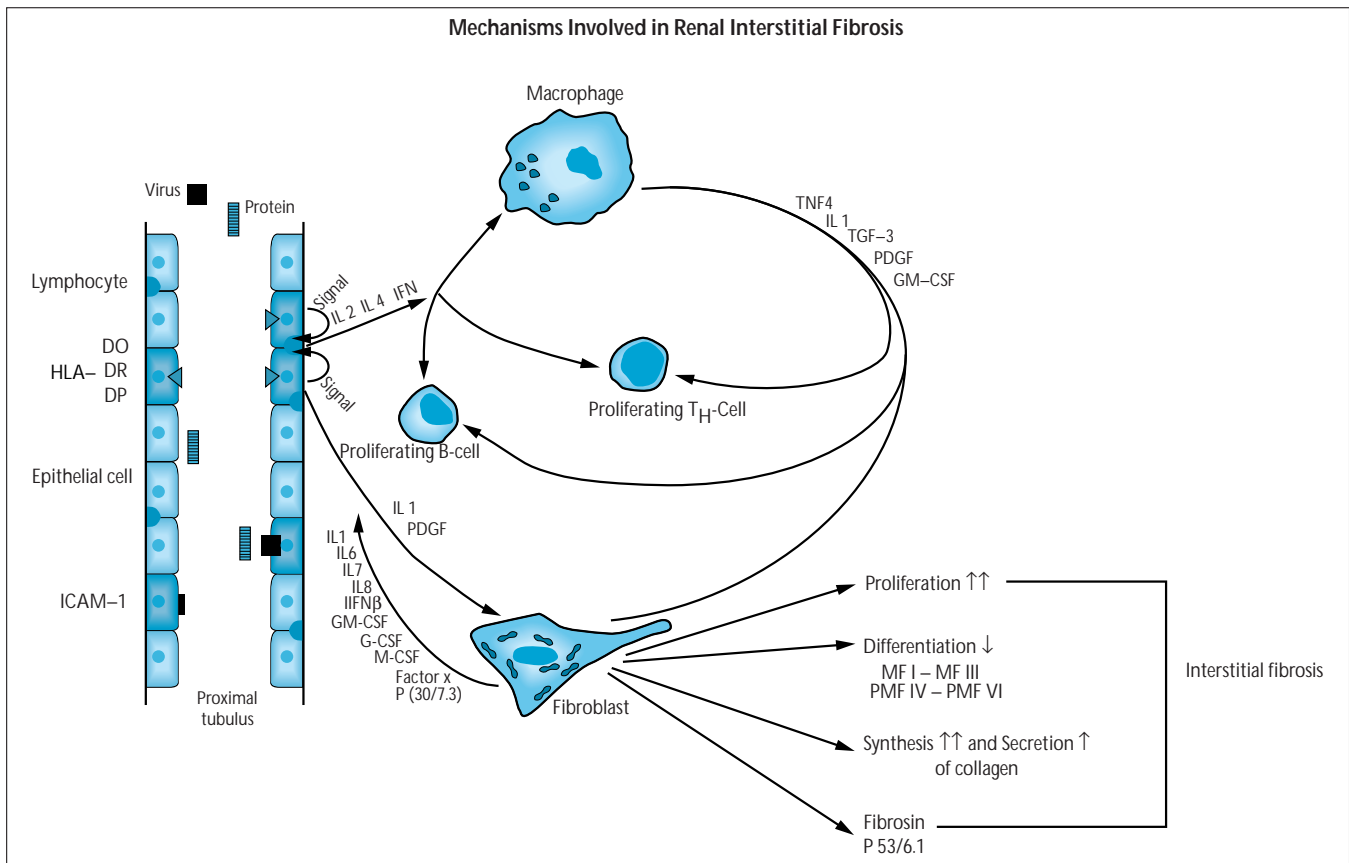
Role of Infiltrating Cells

FIGURE 6-11

TIN showing early phase with focal (*A*) and more severe and diffuse (*B*) interstitial inflammatory cell infiltrates. Late phase showing thickened tubular basement membrane, distorted tubular shape, and cellular infiltration of the tubules, called *tubulitis* (*C*). The extent and severity of interstitial cellular infiltrates show a direct correlation with the severity of tubular atrophy and interstitial fibrosis. Experimental studies show the sequential accumulation of T cells and monocytes after the initial insult. Accumulation of these cells implicates their important role both in the early inflammatory stage of the disease and in the progression of subsequent injury.

Immunohistologic examination utilizing monoclonal antibodies, coupled with conventional and electron microscopy, indicates that most of the mononuclear inflammatory cells comprising renal interstitial infiltrates are T cells. These T cells are immunologically activated in the absence of any evidence of tubulointerstitial immune deposits, even in classic examples of immune complex–mediated diseases such as systemic lupus erythematosus. The profile of immunocompetent cells suggests a major role for cell-mediated immunity in the tubulointerstitial lesions. The infiltrating cells may be of the helper-inducer subset or the cyotoxic-suppressor subset, although generally there seems to be a selective prevalence for the former variety. Lymphocytes that are peritubular and are seen invading the tubular epithelial cells, so-called *tubulitis*, are generally of the cytotoxic (CD8+) variety.

The interstitial accumulation of monocytes and macrophages involves osteopontin (uropontin). Osteopontin is a secreted cell attachment glycoprotein whose messenger RNA expression becomes upregulated, and its levels are increased at the sites of tubular injury in proportion to the severity of tubular damage. The expression of other cell adhesion molecules (intercellular adhesion molecule-1, vascular cellular adhesion molecule-1, and E-selectin) also is increased at the sites of tubular injury. This increased expression may contribute to the recruitment of mononuclear cells and increase the susceptibility of renal cells to cell-mediated injury.

Fibroblastic (type I) interstitial cells, which normally produce and maintain the extracellular matrix, begin to proliferate in response to injury. They increase their well-developed rough endoplasmic reticulum and acquire smooth muscle phenotype (myofibroblast). Growth kinetic studies of these cells reveal a significant increase in their proliferating capacity and generation time, indicating hyper-proliferative growth.

Mechanisms Involved in Renal Interstitial Fibrosis

FIGURE 6-12

Expression of human leukocyte antigen class II and adhesion molecules released by injured tubular epithelial cells, as well as by infiltrating cells, modulate and magnify the process to repair the injury (Figure 6-10). When the process becomes unresponsive to controlling feedback mechanisms, fibroblasts proliferate and increase fibrotic matrix deposition. The precise mechanism of TIN remains to be identified. A number of pathogenetic pathways have been proposed to operate at different stages of the disease process. Each of these individual pathways usually is part of a recuperative process that works in concert in response to injury. However, it is the loss of their controlling feedback in chronic TIN that seems to account for the altered balance and results in persistent cellular infiltrates, progressive fibrosis, and tubular degeneration.

Patterns of Tubular Dysfunction

PATTERNS OF TUBULAR DYSFUNCTION IN CHRONIC TIN

Site of injury	Cause	Tubular dysfunction
Cortex		
Proximal tubule	Heavy metals Multiple myeloma Immunologic diseases Cystinosis	Decreased reabsorption of sodium, bicarbonate, glucose, uric acid, phosphate, amino acids
Distal tubule	Immunologic diseases Granulomatous diseases Hereditary diseases Hypercalcemia Urinary tract obstruction Sickle hemoglobinopathy Amyloidosis	Decreased secretion of hydrogen, potassium Decreased reabsorption of sodium
Medulla	Analgesic nephropathy Sickle hemoglobinopathy Uric acid disorders Hypercalcemia Infection Hereditary disorders Granulomatous diseases	Decreased ability to concentrate urine Decreased reabsorption of sodium
Papilla	Analgesic nephropathy Diabetes mellitus Infection Urinary tract obstruction Sickle hemoglobinopathy Transplanted kidney	Decreased ability to concentrate urine Decreased reabsorption of sodium

FIGURE 6-13

The principal manifestations of TIN are those of tubular dysfunction. Because of the focal nature of the lesions that occur and the segmental nature of normal tubular function, the pattern of tubular dysfunction that results varies, depending on the major site of injury. The extent of damage determines the severity of tubular dysfunction. The hallmarks of glomerular disease (such as salt retention, edema, hypertension, proteinuria, and hematuria) are characteristically absent in the early phases of chronic TIN. The type of insult determines the segmental location of injury. For example, agents secreted by the organic pathway in the pars recta (heavy metals) or reabsorbed in the proximal tubule (light chain proteins) cause predominantly proximal tubular lesions. Depositional disorders (amyloidosis and hyperglobulinemic states) cause predominantly distal tubular lesions. Insulting agents that are affected by the urine concentrating mechanism (analgesics and uric acid) or medullary tonicity (sickle hemoglobinopathy) cause medullary injury.

The tubulointerstitial lesions are localized either to the cortex or medulla. Cortical lesions mainly affect either the proximal or distal tubule. Medullary lesions affect the loop of Henle and the collecting duct. The change in the normal function of each of these affected segments then determines the manifestations of tubular dysfunction. Essentially, the proximal nephron segment reabsorbs the bulk of bicarbonate, glucose, amino acids, phosphate, and uric acid. Changes in proximal tubular function, therefore, result in bicarbonaturia (proximal renal acidosis), β_2-microglobinuria, glucosuria (renal glucosuria), aminoaciduria, phosphaturia, and uricosuria.

The distal nephron segment secretes hydrogen and potassium and regulates the final amount of sodium chloride excreted. Lesions primarily affecting this segment, therefore, result in the distal form of renal tubular acidosis, hyperkalemia, and salt wasting. Lesions that primarily involve the medulla and papilla disproportionately affect the loops of Henle, collecting ducts, and the other medullary structures essential to attaining and maintaining medullary hypertonicity. Disruption of these structures, therefore, results in different degrees of nephrogenic diabetes insipidus and clinically manifests as polyuria and nocturia.

Although this general framework is useful in localizing the site of injury, considerable overlap may be encountered clinically, with different degrees of proximal, distal, and medullary dysfunction present in the same individual. Additionally, the ultimate development of renal failure complicates the issue further because of the added effect of urea-induced osmotic diuresis on tubular function in the remaining nephrons. In this later stage of TIN, the absence of glomerular proteinuria and the more common occurrence of hypertension in glomerular diseases can be helpful in the differential diagnosis.

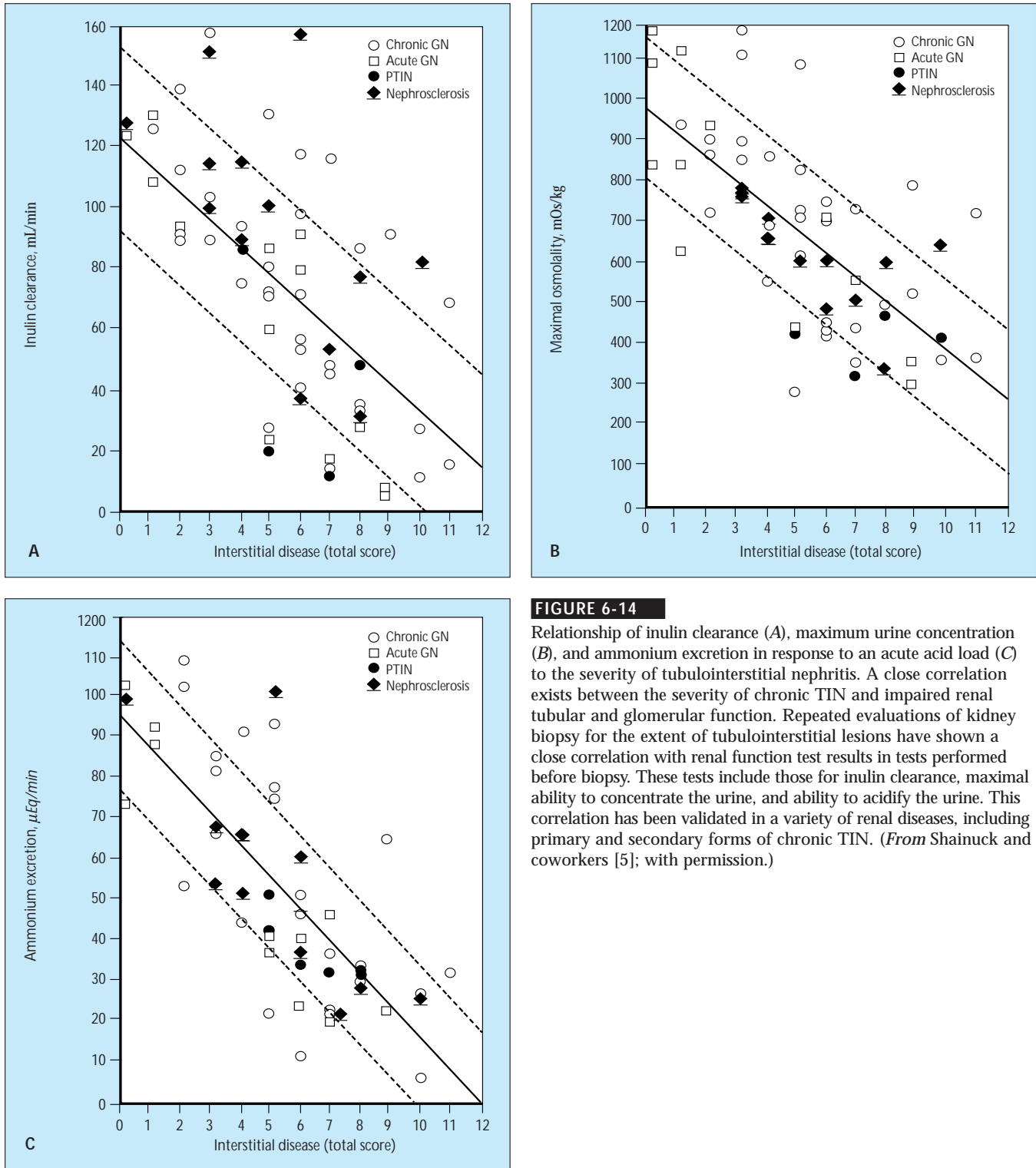# Correlates of Tubular Dysfunction with Severity of Chronic TIN

FIGURE 6-14

Relationship of inulin clearance (*A*), maximum urine concentration (*B*), and ammonium excretion in response to an acute acid load (*C*) to the severity of tubulointerstitial nephritis. A close correlation exists between the severity of chronic TIN and impaired renal tubular and glomerular function. Repeated evaluations of kidney biopsy for the extent of tubulointerstitial lesions have shown a close correlation with renal function test results in tests performed before biopsy. These tests include those for inulin clearance, maximal ability to concentrate the urine, and ability to acidify the urine. This correlation has been validated in a variety of renal diseases, including primary and secondary forms of chronic TIN. (*From* Shainuck and coworkers [5]; with permission.)

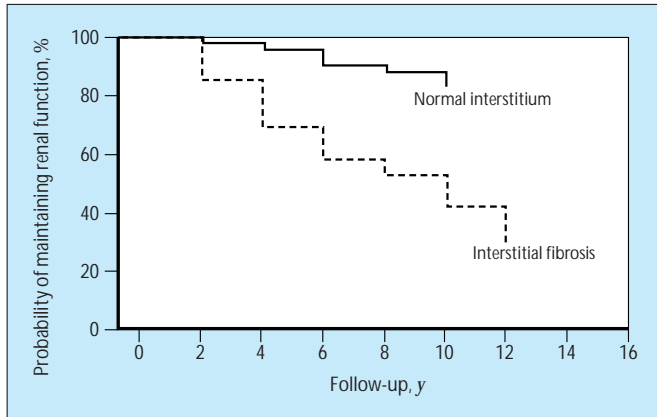# Correlates of Chronic TIN with Progressive Renal Failure

FIGURE 6-15

Effect on long-term prognosis of the presence of cortical chronic tubulointerstitial nephritis in patients with mesangioproliferative glomerulonephritis (n = 455), membranous nephropathy (n = 334), and membranoproliferative glomerulonephritis (n = 220). The extent of tubulointerstitial nephritis correlates not only with altered glomerular and tubular dysfunction at the time of kidney biopsy but also provides a prognostic index of the progression rate to end-stage renal disease. As shown, the presence of interstitial fibrosis on the initial biopsy exerts a significant detrimental effect on the progression rate of renal failure in a variety of glomerular diseases. (*From* Eknoyan [3]; with permission.)

Drugs
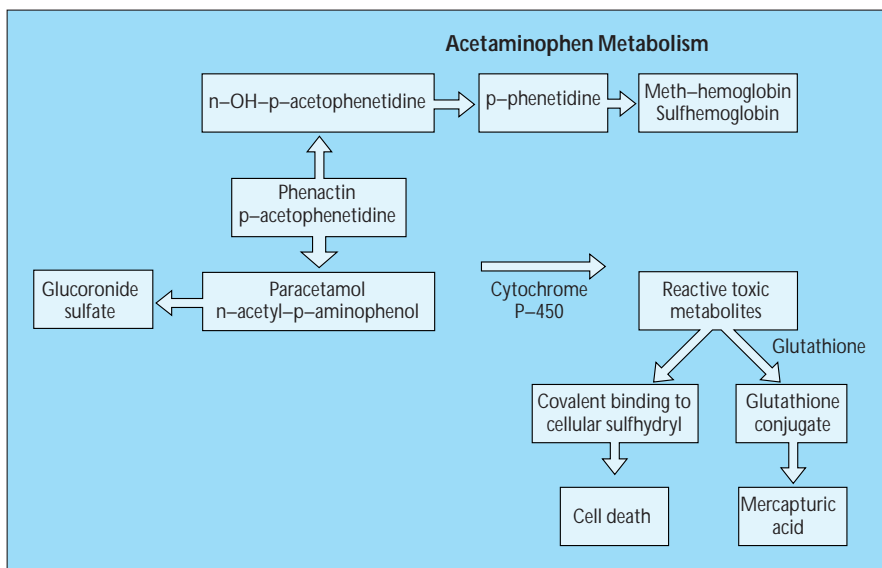
Analgesic Nephropathy

FIGURE 6-16

Metabolism of acetaminophen and its excretion by the kidney. Prolonged exposure to drugs can cause chronic TIN. Although a number of drugs (*eg,* lithium, cyclosporine, cisplatin, and nitrosoureas) have been implicated, the more commonly responsible agents are analgesics. As a rule, the lesions of analgesic nephropathy develop in persons who abuse analgesic combinations (phenacetin, or its main metabolite acetaminophen, plus aspirin, with or without caffeine). Experimental evidence indicates that phenacetin, or acetaminophen, plus aspirin taken alone are only moderately nephrotoxic and only at massive doses, but that the lesions can be more readily induced when these drugs are taken together. In all experimental studies the extent of renal injury has been dose-dependent and, when examined, water diuresis has provided protection from analgesic-induced renal injury. Relative to plasma levels, both acetaminophen (paracetamol) and its excretory conjugate attain significant (fourfold to fivefold) concentrations in the medulla and papilla, depending on the state of hydration of the animal studied. The toxic effect of these drugs apparently is related to their intrarenal oxidation to reactive intermediates that, in the absence of reducing substances such as glutathione, become cytotoxic by virtue of their capacity to induce oxidative injury. Salicylates also are significantly (sixfold to thirteenfold above plasma levels) concentrated in the medulla and papilla, where they attain a level sufficient to uncouple oxidative phosphorylation and compromise the ability of cells to generate reducing substances. Thus, both agents attain sufficient renal medullary concentration to individually exert a detrimental and injurious effect on cell function, which is magnified when they are present together. By reducing the medullary tonicity, and therefore the medullary concentration of drug attained, water diuresis protects from analgesic-induced cell injury. A direct role of analgesic-induced injury can be adduced from the improvement of renal function that can occur after cessation of analgesic abuse.
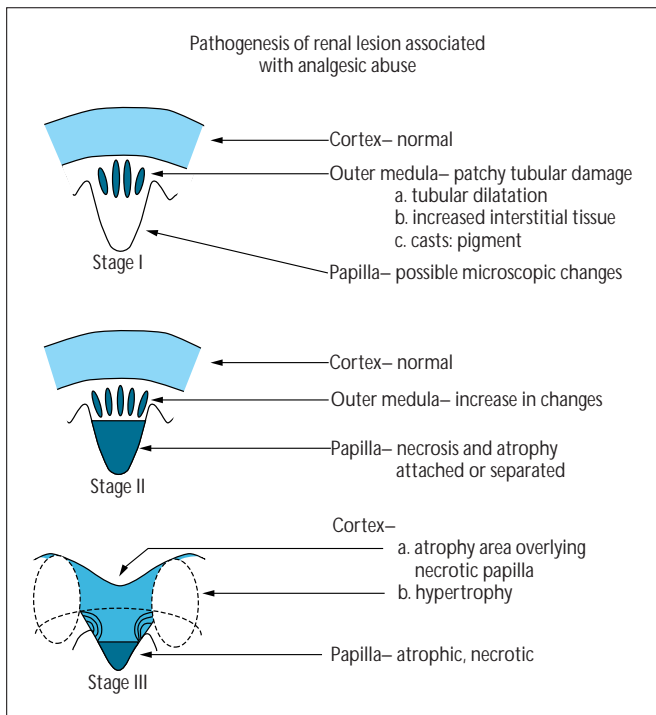
Pathogenesis of renal lesion associated
with analgesic abuse

Stage I

- Cortex– normal
- Outer medula– patchy tubular damage
  - a. tubular dilatation
  - b. increased interstitial tissue
  - c. casts: pigment
- Papilla– possible microscopic changes

Stage II

- Cortex– normal
- Outer medula– increase in changes
- Papilla– necrosis and atrophy attached or separated

Stage III

- Cortex–
  - a. atrophy area overlying necrotic papilla
  - b. hypertrophy
- Papilla– atrophic, necrotic

FIGURE 6-17

Course of the renal lesions in analgesic nephropathy. The intrarenal distribution of analgesics provides an explanation for the medullary location of the pathologic lesions of analgesic nephropathy. The initial lesions are patchy and consist of necrosis of the interstitial cells, thin limbs of the loops of Henle, and vasa recta of the papilla. The collecting ducts are spared. The quantities of tubular and vascular basement membrane and ground substance are increased. At this stage the kidneys are normal in size and no abnormalities have occurred in the renal cortex. With persistent drug exposure the changes extend to the outer medulla. Again, the lesions are initially patchy, involving the interstitial cells, loops of Henle, and vascular bundles. With continued analgesic abuse, the severity of the inner medullary lesions increases with sclerosis and obliteration of the capillaries, atrophy and degeneration of the loops of Henle and collecting ducts, and the beginning of calcification of the necrotic foci. Ultimately, the papillae become entirely necrotic, with sequestration and demarcation of the necrotic tissue. The necrotic papillae may then slough and are excreted into the urine or remain *in situ*, where they atrophy further and become calcified. Cortical scarring, characterized by interstitial fibrosis, tubular atrophy, and periglomerular fibrosis, develops over the necrotic medullary segments. The medullary rays traversing the cortex are usually spared and become hypertrophic, thereby imparting a characteristic cortical nodularity to the now shrunken kidneys. Visual observation of these configurational changes by computed tomography scan can be extremely useful in the diagnosis of analgesic nephropathy.
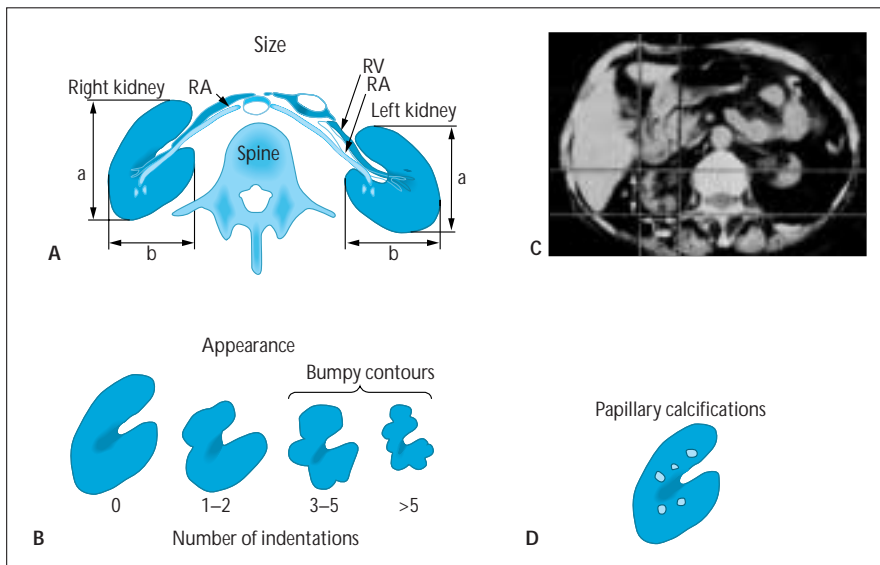

Size

Right kidney RA

RV
RA
Left kidney

Spine

a

a

A b b

C

Appearance

Bumpy contours

0 1–2 3–5 >5

B Number of indentations

Papillary calcifications

D

in men and 96 mm in women. Bumpy contours are considered to be present if at least three indentations are evident (panels *B* and *C*). The scan can reveal papillary calcifications (panels *B* and *D*). Visual observation of the configurational changes illustrated in Figure 6-18 can be extremely useful in diagnosing the scarred kidney in analgesic nephropathy. A series of careful studies using CT scans without contrast material have provided imaging criteria for the diagnosis of analgesic nephropathy. Validation of these criteria currently is underway by a study at the National Institutes of Health.

From studies comparing analgesic abusers to persons in control groups, it has been shown that a decrease in kidney size and bumpy contours of both kidneys provide a diagnostic sensitivity of 90% and a specificity of 95%. The additional finding of evidence of renal papillary necrosis provides a diagnostic sensitivity of 72% and specificity of 97%, giving a positive predictive value of 92%. RA— renal artery; RV— renal vein. (*From* DeBroe and Elseviers [6]; with permission.)

FIGURE 6-18

Computed tomography (CT) imaging criteria for diagnosing analgesic nephropathy. Renal size (*A*) is considered decreased if the sum of a and b (panels *A* and *B*) is less than 103 mm

CLINICAL FEATURES

Female predominance, 60–85%

Age, >30 y

Personality disorders: introvert, dependent, anxiety, neurosis, family instability

Addictive habits: smoking, alcohol, laxatives, psychotropics, sedatives

Causes of analgesic dependency: headache, 40–60%; mood, 6–30%; musculoskeletal
pain, 20–30%

FIGURE 6-19

Certain personality features and clinical findings characterize patients prone to analgesic abuse. These patients tend to deny analgesic use on direct questioning; however, their history can be revealing. In all cases, a relationship exists between renal function and the duration, intensity, and quantity of analgesic consumed. The magnitude of injury is related to the quantity of analgesic ingested chronically over years. In persons with significant renal impairment, the average dose ingested has been estimated at about 10 kg over a mean period of 13 years. The minimum amount of drug consumption that results in significant renal damage is unknown. It has been estimated that a cumulative dose of 3 kg of the index compound, or a daily ingestion of 1 g/d over 3 years or more, is a minimum that can result in detectable renal impairment.
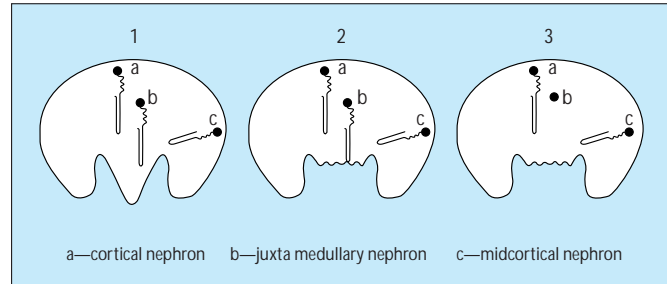

a—cortical nephron　　b—juxta medullary nephron　　c—midcortical nephron

FIGURE 6-20

Diagram of cortical and juxtamedullary nephrons in the normal kidney (1). Papillary necrosis (2) and sloughing (3) result in loss of juxtamedullary nephrons. Cortical nephrons are spared, thereby preserving normal renal function in the early stages of the disease. The course of analgesic nephropathy is slowly progressive, and deterioration of renal function is insidious. One reason for these characteristics of the disease is that lesions beginning in the papillary tip affect only the juxtamedullary nephrons, sparing the cortical nephrons. It is only when the lesions are advanced enough to affect the whole medulla that the number of nephrons lost is sufficient to result in a reduction in filtration rate. However, renal injury can be detected by testing for sterile pyuria, reduced concentrating ability, and a distal acidifying defect. These features may be evident at levels of mild renal insufficiency and become more pronounced and prevalent as renal function deteriorates. Proximal tubular function is preserved in patients with mild renal insufficiency but can be abnormal in those with more advanced renal failure.
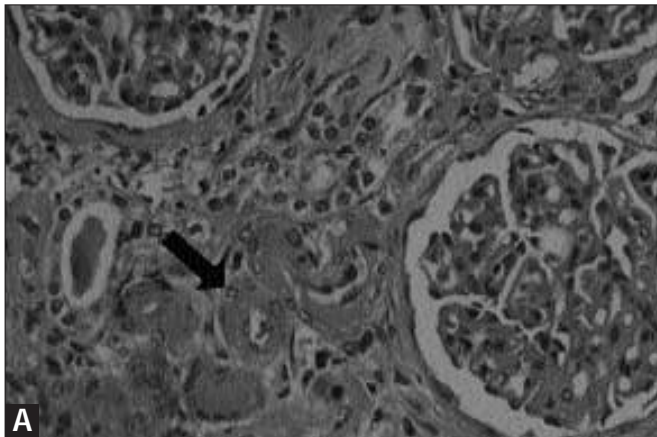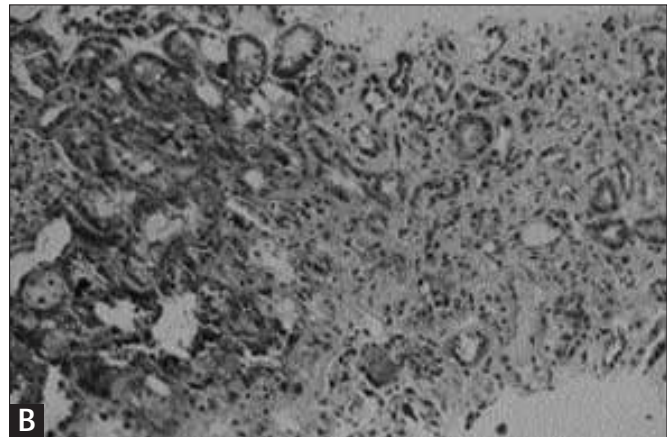
Cyclosporine

FIGURE 6-21

A, Chronic TIN caused by cyclosporine. The arrow indicates the characteristic hyaline-type arteriolopathy of cyclosporine nephrotoxicity. **B,** Patchy nature of chronic TIN caused by cyclosporine. Note the severe TIN on the right adjacent to an otherwise intact area on the left. Tubulointerstitial nephritis has emerged as the most serious side effect of cyclosporine. Cyclosporine-mediated vasoconstriction of the cortical microvasculature has been implicated in the development of an occlusive arteriolopathy and tubular epithelial cell injury. Whereas these early lesions tend to be reversible with cessation of therapy, an irreversible interstitial fibrosis and mononuclear cellular infiltrates develop with prolonged use of cyclosporine, especially at high doses. The irreversible nature of TIN associated with the use of cyclosporine and its attendant reduction in renal function have raised concerns regarding the long-term use of this otherwise efficient immunosuppressive agent.
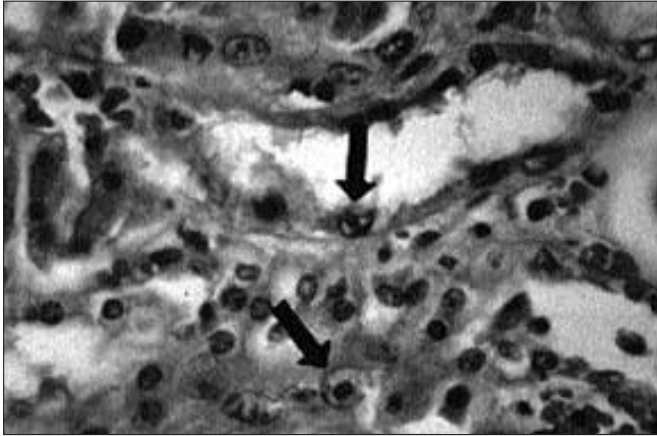
Heavy Metals

Lead Nephropathy

Lead nephropathy. Arrows indicate the characteristic intranuclear inclusions. Exposure to a variety of heavy metals results in development of chronic TIN. Of these metals, the more common and clinically important implicated agent is lead. Major sources of

exposure to lead are lead-based paints; lead leaked into food during storage or processing, particularly in illegal alcoholic beverages (moonshine); and increasingly, through environmental exposure (gasoline and industrial fumes). This insidious accumulation of lead in the body has been implicated in the causation of hyperuricemia, hypertension, and progressive renal failure. Gout occurs in over half of cases. Blood levels of lead usually are normal. The diagnosis is established by demonstrating increased levels of urinary lead after infusion of 1 g of the chelating agent erthylenediamine tetraacetic acid (EDTA).

The renal lesions of lead nephropathy are those of chronic TIN. Cases examined early, before the onset of end-stage renal disease, show primarily focal lesions of TIN with relatively little interstitial cellular infiltrates. In more advanced cases the kidneys are fibrotic and shrunken. On microscopy, the kidneys show diffuse lesions of TIN. As expected from the clinical features, hypertensive vascular changes are prominent.

Other heavy metals associated with TIN are cadmium, silicon, copper, bismuth, and barium. Sufficient experimental evidence and some weak epidemiologic evidence suggest a possible role of organic solvents in the development of chronic TIN.
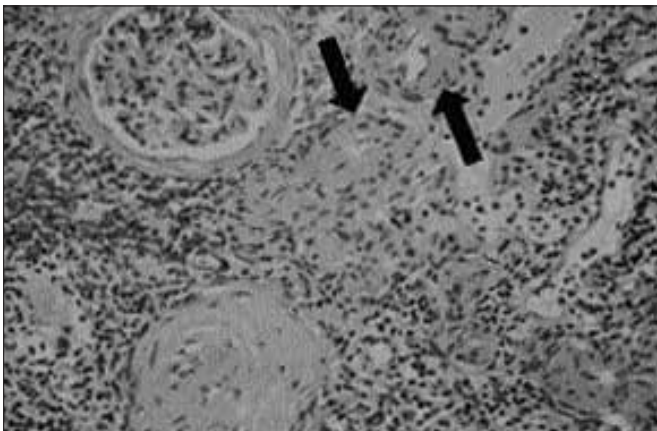
Ischemic Vascular Disease

Hypertensive Nephrosclerosis

Chronic TIN associated with hypertension. The arrows indicate arterioles and small arteries with thickened walls. Tubular degeneration, interstitial fibrosis, and mononuclear inflammatory cell infiltration are part of the degenerative process that affects the kidneys in all vascular diseases involving the intrarenal vasculature with any degree of severity as to cause ischemic injury. Rarely, if the insult is sudden and massive (such as in fulminant vasculitis), the lesions are those of infarction and acute deterioration of renal function. More commonly, the vascular lesions develop gradually and go undetected until renal insufficiency supervenes. This chronic form of TIN accounts for the tubulointerstitial lesions of arteriolar nephrosclerosis in persons with hypertension. Ischemic vascular changes also contribute to the lesions of TIN in patients with diabetes, sickle cell hemoglobinopathy, cyclosporine nephrotoxicity, and radiation nephritis.
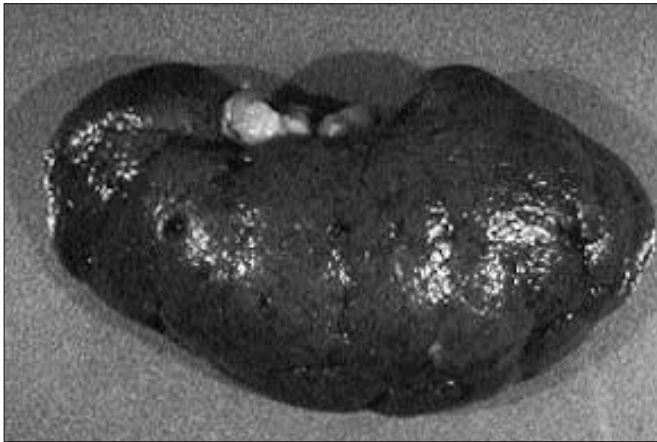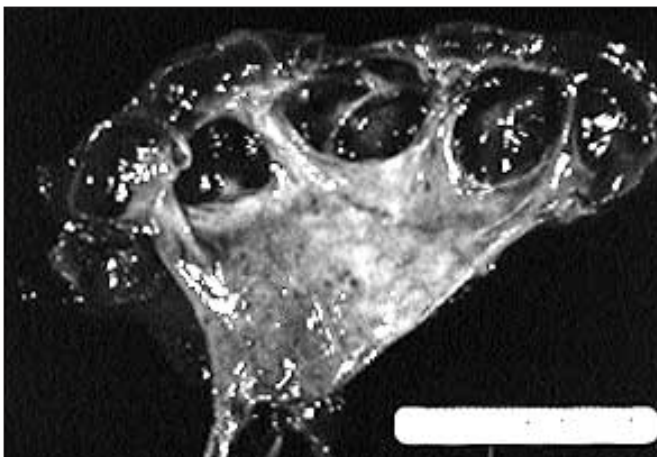
FIGURE 6-24

Gross appearance of the kidney as a result of arteriolonephrosclerosis, showing the granular and scarified cortex.

Obstruction
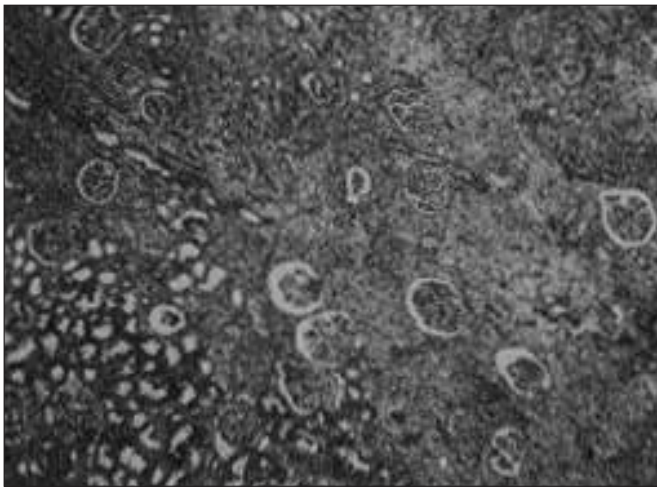
FIGURE 6-25 (*see* Color Plate)

Chronic TIN secondary to vesicoureteral reflux (VUR). Clearly demonstrated is an area that is fairly intact (lower left corner) adjacent to one that shows marked damage. Urinary tract obstruction, whether congenital or acquired, is a common cause of chronic TIN. Clinically, superimposed infection plays a secondary, adjunctive, and definitely aggravating role in the progressive changes of TIN. However, the entire process can occur in the absence of infection.

As clearly demonstrated in experimental models of obstruction, mononuclear inflammatory cell infiltration is one of the earliest responses of the kidney to ureteral obstruction. The infiltrating cells consist of macrophages and suppressor-cytotoxic lymphocytes. The release of various cytokines by the infiltrating cells of the hydronephrotic kidney appears to exert a significant modulating role in the transport processes and hemodynamic changes seen early in the course of obstruction. With persistent obstruction, changes of chronic TIN set in within weeks. Fibrosis gradually becomes prominent.

FIGURE 6-26

Gross appearance of a hydronephrotic kidney caused by vesicoureteral reflux.
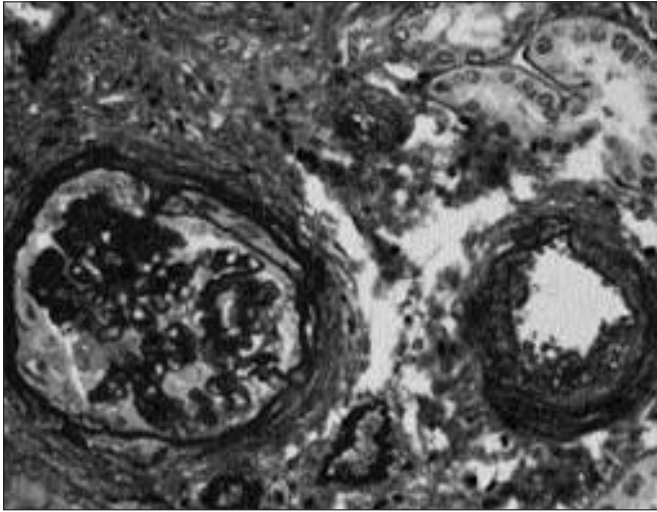
Obstructive Nephropathy

Glomerular lesion of advanced chronic TIN secondary to vesicoureteral reflux in a patient with massive proteinuria. Note the segmental sclerosis of the glomerulus and the reactive proliferation of the visceral epithelial cells. In persons with obstructive nephropathy, the onset of significant proteinuria (>2g/d) is an ominous sign of progressive renal failure. As a rule, most of these patients will have coexistent hypertension, and the renal vasculature will show changes of hypertensive arteriolosclerosis. The glomerular changes are ischemic in nature. In those with significant proteinuria, the lesions are those of focal and segmental glomerulosclerosis and hyalinosis. The affected glomeruli commonly contain immunoglobulin M and C_3 complement on immunofluorescent microscopy. The role of an immune mechanism remains unclear. Autologous (Tamm-Horsfall protein and brush-border antigen) or bacterial antigen derivatives have been incriminated. Adaptive hemodynamic changes (hyperfiltration) in response to a reduction in renal mass, by the glomeruli of remaining intact nephrons of the hydronephrotic kidney, also have been implicated.

Hematopoietic Diseases
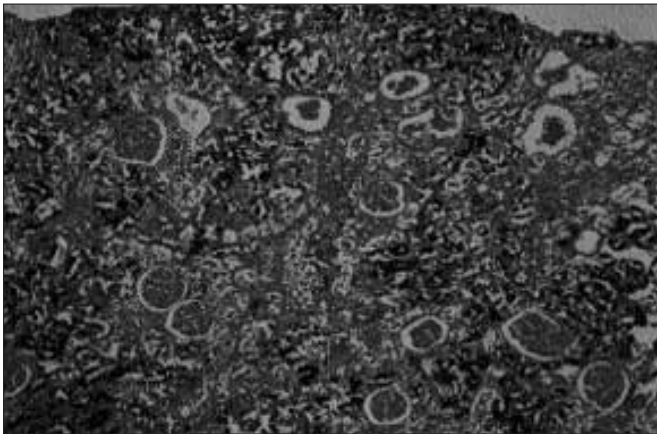
Sickle Hemoglobinopathy

The kidney in sickle cell disease. Note the tubular deposition of hemosiderin. The principal renal lesion of hemoglobinopathy S is that of chronic TIN. By far more prevalent and severe in patients with sickle cell disease, variable degrees of TIN also are common in those with the sickle cell trait, sickle cell–hemoglobin C disease, or sickle cell–thalassemia disease. The predisposing factors that lead to a propensity of renal involvement are the physicochemical properties of hemoglobin S that predispose its polymerization in an environment of low oxygen tension, hypertonicity, and low pH. These conditions are characteristic of the renal medulla and therefore are conducive to the intraerythrocyte polymerization of hemoglobin S. The consequent erythrocyte sickling accounts for development of the typical vascular occlusive lesions. Although some of these changes occur in the cortex, the lesions begin and are predominantly located in the inner medulla, where they are at the core of the focal scarring and interstitial fibrosis. These lesions account for the common occurrence of papillary necrosis.

Examples of tubular functional abnormalities common and detectable early in the course of the disease are the following: impaired concentrating ability, depressed distal potassium and hydrogen secretion, tubular proteinuria, and decreased proximal reabsorption of phosphate, and increased secretion of uric acid and creatinine.
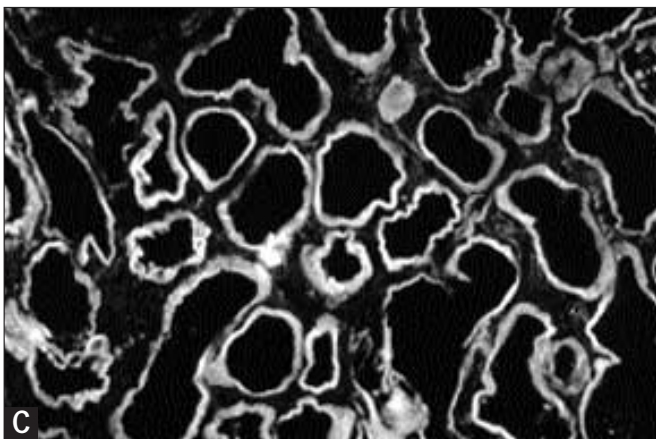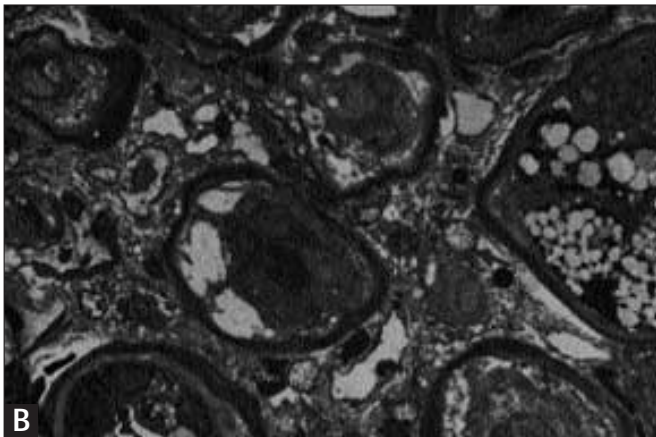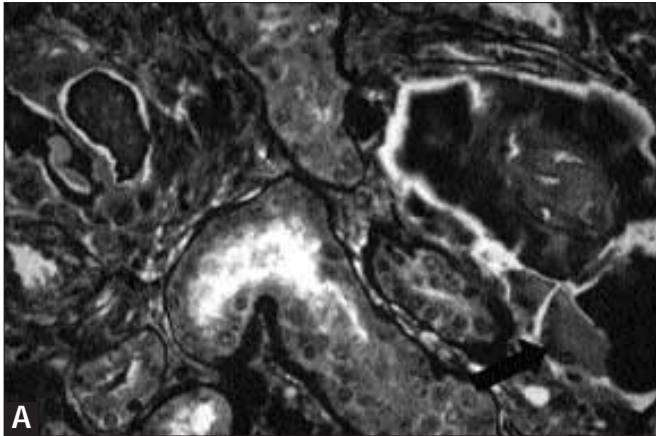
Hematologic Diseases

Plasma Cell Dyscrasias

FIGURE 6-29 (*see* Color Plate)

A, Myeloma cast nephropathy. The *arrow* indicates a multinucleated giant cell. **B,** Light chain deposition disease. Note the changes indicative of chronic TIN and light chain deposition along the tubular basement membrane (dark purple). **C,** Immunofluorescent stain for κ light chain deposition along the tubular basement membrane. The renal complications of multiple myeloma are a major risk factor in the morbidity and mortality of this neoplastic disorder. Whereas the pathogenesis of renal involvement is multifactorial (hypercalcemia and hyperuricemia), it is the lesions that result from the excessive production of light chains that cause chronic TIN. These lesions are initiated by the precipitation of the light chain dimers in the distal tubules and result in what has been termed *myeloma cast nephropathy*. The affected tubules are surrounded by multinucleated giant cells. Adjoining tubules show varying degrees of atrophy. The propensity of light chains to lead to myeloma cast nephropathy appears to be related to their concentration in the tubular fluid, the tubular fluid pH, and their structural configuration. This propensity accounts for the observation that increasing the flow rate of urine or its alkalinization will prevent or reverse the casts in their early stages of formation.

Direct tubular toxicity of light chains also may contribute to tubular injury. λ Light chains appear to be more injurious than are κ light chains. Binding of human κ and λ light chains to human and rat proximal tubule epithelial cell brush-border membrane has been demonstrated. Epithelial cell injury associated with the absorption of these light chains in the proximal tubules has been implicated in the pathogenesis of cortical TIN. Another mechanism relates to the perivascular deposition of paraproteins, either as amyloid fibrils that are derived from λ chains or as fragments of light chains that are derived from kappa chains, and produce the so-called light chain deposition disease.

Of the various lesions, myeloma cast nephropathy appears to be the most common, being observed at autopsy in one third of cases, followed by amyloid deposition, which is present in 10% of cases. Light chain deposition is relatively rare, being present in less than 5% of cases.
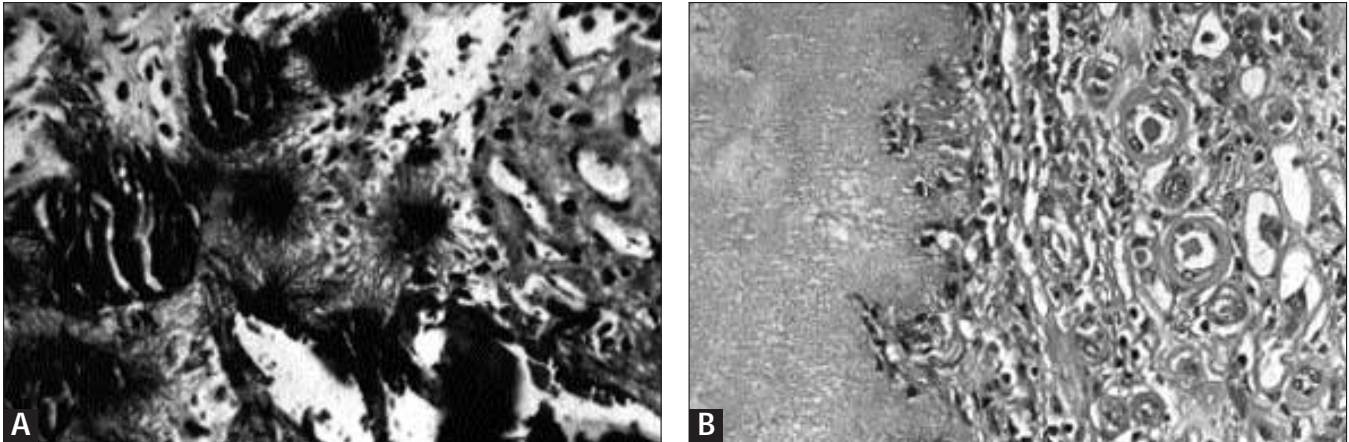
Metabolic Disorders

Hyperuricemia

FIGURE 6-30

A, Intratubular deposits of uric acid. **B,** Gouty tophus in the renal medulla. The kidney is the major organ of urate excretion and a primary target organ affected in disorders of its metabolism. Renal lesions result from crystallization of urate in the urinary outflow tract or the renal parenchyma. Depending on the load of urate, one of three lesions result: acute urate nephropathy, uric acid nephrothiasis, or chronic urate nephropathy. Whereas any of these lesions produce tubulointerstitial lesions, it is those of chronic urate nephropathy that account for most cases of chronic TIN.

The principal lesion of chronic urate nephropathy is due to deposition of microtophi of amorphous urate crystals in the interstitium, with a surrounding giant-cell reaction. An earlier change, however, probably is due to the precipitation of birefringent uric acid crystals in the collecting tubules, with consequent tubular obstruction, dilatation, atrophy, and interstitial fibrosis. The renal injury in persons who develop lesions has been attributed to hyperacidity of their urine caused by an inherent abnormality in the ability to produce ammonia. The acidity of urine is important because uric acid is 17 times less soluble than is urate. Therefore, uric acid facilitates precipitation in the distal nephron of persons who do not overproduce uric acid but who have a persistently acidic urine.

The previous notion that chronic renal disease was common in patients with hyperuricemia is now considered doubtful in light of prolonged follow-up studies of renal function in persons with hyperuricemia. Renal dysfunction could be documented only when the serum urate concentration was more than 10 mg/dL in women and more than 13 mg/dL in men for prolonged periods. The deterioration of renal function in persons with hyperuricemia of a lower magnitude has been attributed to the higher than expected occurrence of concurrent hypertension, diabetes mellitus, abnormal lipid metabolism, and nephrosclerosis.
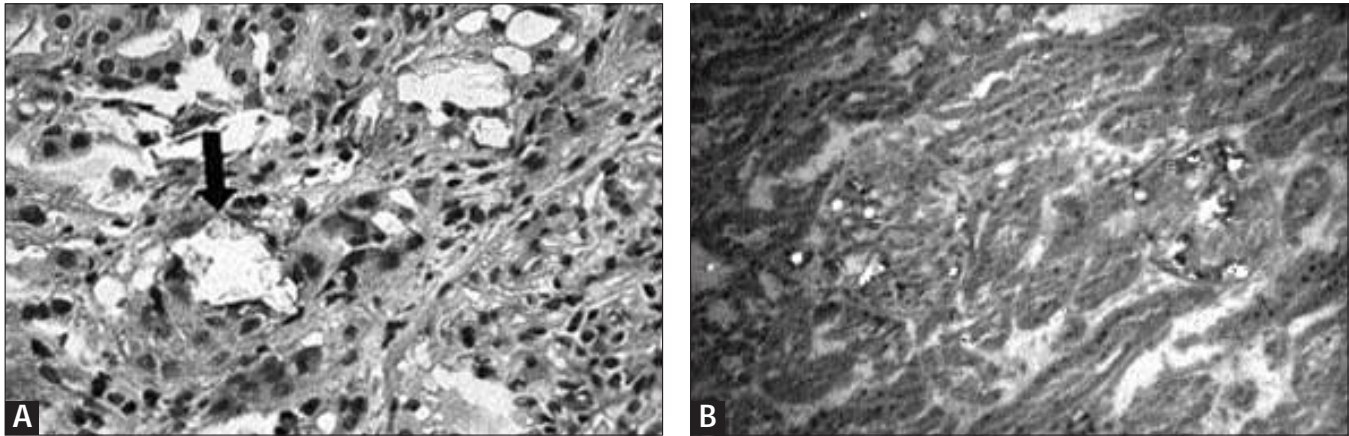
Hyperoxaluria

FIGURE 6-31 (*see* Color Plate)

A, Calcium oxalate crystals (arrow) seen on light microscopy. **B,** Dark field microscopy. When hyperoxaluria is sudden and massive (such as after ethylene glycol ingestion) acute renal failure develops. Otherwise, in most cases of hyperoxaluria the overload is insidious and chronic. As a result, interstitial fibrosis, tubular atrophy, and dilation result in chronic TIN with progressive renal failure. The propensity for recurrent calcium oxalate nephrolithiasis and consequent obstructive uropathy contribute to the tubulointerstitial lesions.

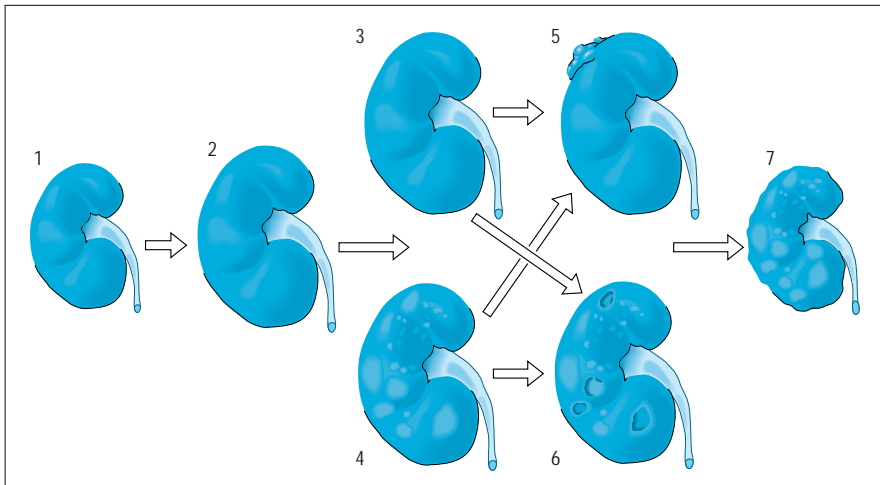# Granulomatous Diseases

Malacoplakia

FIGURE 6-32

Schematic representation of the forms and course of renal involvement by malacoplakia: 1, normal kidney; 2, enlarged kidney resulting from interstitial nephritis without nodularity; 3, unifocal nodular involvement; 4, multifocal nodular involvement; 5, abscess formation with perinephric spread of malacoplakia; 6, cystic lesions; and 7, atrophic multinodular kidney after treatment. Interstitial granulomatous reactions are a rare but characteristic hallmark of certain forms of tubulointerstitial disease. The best-known form is that of sarcoidosis. Interstitial granulomatous reactions also have been noted in renal tuberculosis, xanthogranulomatous pyelonephritis, renal malacoplakia, Wegener's granulomatosis, renal candidiasis, heroin abuse, hyperoxaluria after jejunoileal bypass surgery, and an idiopathic form in association with anterior uveitis.

The inflammatory lesions of malacoplakia principally affect the urinary bladder but may involve other organs, most notably the kidneys. The kidney lesions may be limited to one focus or may be multifocal. In three fourths of cases the renal involvement is multifocal, and in one third of cases both kidneys are involved. The lesions are nodular, well-demarcated, and variable in size. They may coalesce, developing foci of suppuration that may become cystic or calcified. The lesions usually are located in the cortex but may be medullary and result in papillary necrosis. (*From* Dobyan and coworkers [7]; with permission.)
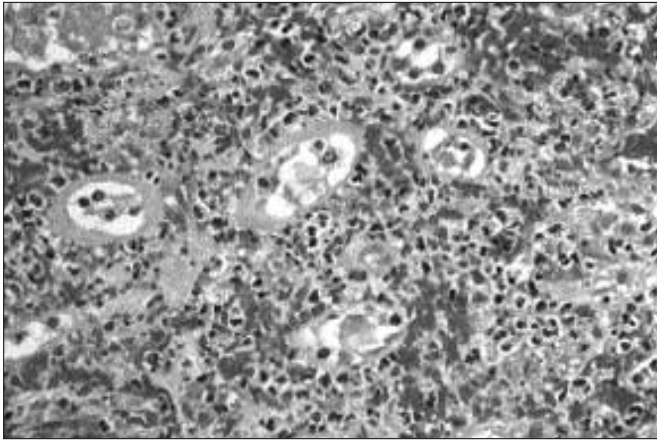
Endemic Diseases

FIGURE 6-33

Hemorrhagic TIN associated with Hantavirus infection. Two endemic diseases in which tubulointerstitial lesions are a predominant component are Balkan nephropathy and nephropathia epidemica. Endemic Balkan nephropathy is a progressive chronic tubulointerstitial nephritis whose occurrence is mostly clustered

in a geographic area bordering the Danube River as it traverses Romania, Bulgaria, and the former Yugoslavia. The cause of Balkan nephropathy is unknown; however, it has been attributed to genetic factors, heavy metals, trace elements, and infectious agents. The disease evolves in emigrants from endemic regions, suggesting a role for inheritance or the perpetuation of injury sustained before emigration.

Initially thought to be restricted to Scandinavian countries, and thus termed *Scandinavian acute hemorrhagic interstitial nephritis*, Nephropathia epidemica has been shown to have a more universal occurrence. It therefore has been more appropriately renamed *hemorrhagic fever with renal syndrome*. As a rule the disease presents as a reversible acute tubulointerstitial nephritis but can progress to a chronic form. It is caused by a rodent-transmitted virus of the *Hantavirus* genus of the Bunyaviridae family, the so-called Hantaan virus. Humans appear to be infected by respiratory aerosols contaminated by rodent excreta. Antibodies to the virus are detected in the serum, and viruslike structures have been demonstrated in the kidneys of persons infected with the virus.

Tubulointerstitial nephropathy caused by viral infection also has been reported in polyomavirus, cytomegalovirus, herpes simplex virus, human immunodeficiency virus, infectious mononucleosis, and Epstein-Barr virus.

Hereditary Diseases

Hereditary Nephritis
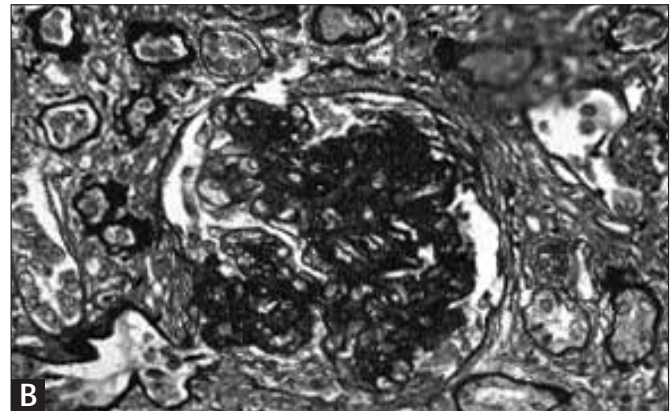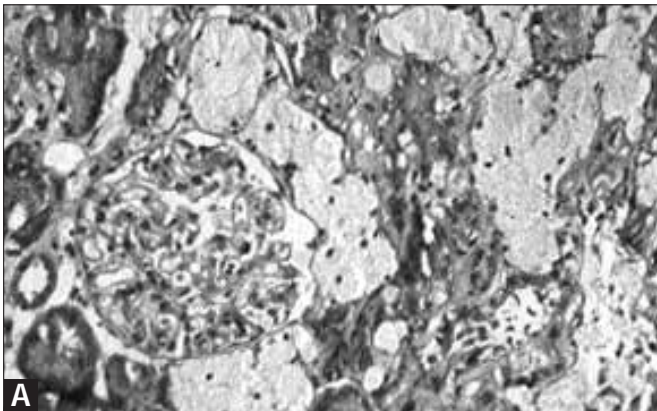
FIGURE 6-34

A, Interstitial foam cells in Alport's syndrome. **B,** Late phase Alport's syndrome showing chronic TIN and glomerular changes in a patient with massive proteinuria. Tubulointerstitial lesions are a prominent component of the renal pathology of a variety of hereditary diseases of the kidney, such as medullary cystic disease, familial juvenile nephronophthisis, medullary sponge kidney, and polycystic kidney disease. The primary disorder of these conditions is a tubular defect that results in the cystic dilation of the affected segment in some patients. Altered tubular basement membrane composition and

associated epithelial cell proliferation account for cyst formation. It is the continuous growth of cysts and their progressive dilation that cause pressure-induced ischemic injury, with consequent TIN of the adjacent renal parenchyma.

Tubulointerstitial lesions also are a salient feature of inherited diseases of the glomerular basement membrane. Notable among them are those of hereditary nephritis or Alport's syndrome, in which a mutation in the encoding gene localized to the X chromosome results in a defect in the α-5 chain of type IV collagen.

Papillary Necrosis

FIGURE 6-35

A, Renal papillary necrosis. The arrow points to the region of a sloughed necrotic papilla. *B,* Whole mount of a necrotic papilla. Arro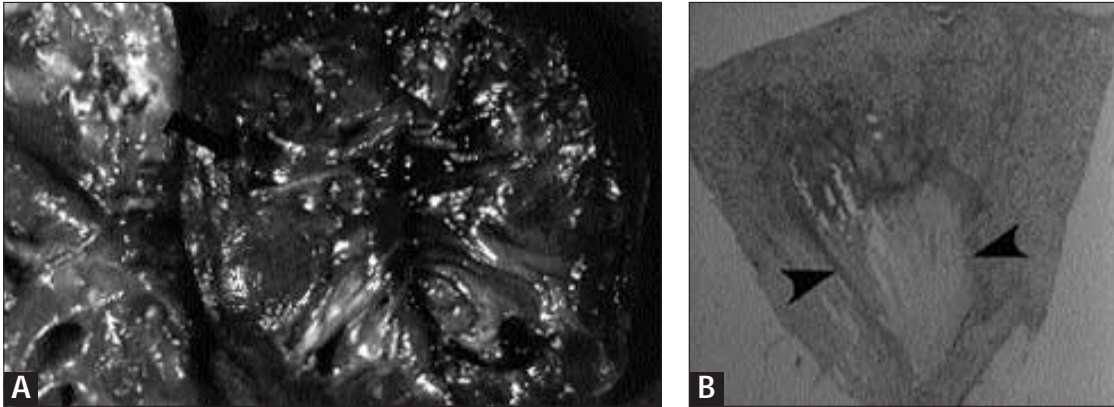ws delineate focal necrosis principally affecting the medullary inner stripe. Renal papillary necrosis (RPN) develops in a variety of diseases that cause chronic tubulointerstitial nephropathy in which the lesion is more severe in the inner medulla. The basic lesion affects the vasculature with consequent focal or diffuse ischemic necrosis of the distal segments of one or more renal pyramids. In the affected papilla, the sharp demarcation of the lesion and coagulative necrosis seen in the early stages of the disease closely resemble those of infarction. The fact that the necrosis is anatomically limited to the papillary tips can be attributed to a variety of features unique to this site, especially those affecting the vasculature. The renal papilla receives its blood supply from the vasa recta. Measurements of medullary blood flow notwithstanding, it should be noted that much of the blood flow in the vasa recta serves the countercurrent exchange mechanism. Nutrient blood supply is provided by small capillary vessels that originate in each given region. The net effect is that the blood supply to the papillary tip is less than that to the rest of the medulla, hence its predisposition to ischemic necrosis.

The necrotic lesions may be limited to only a few of the papillae or may involve several of the papillae in either one or both kidneys. The lesions are bilateral in most patients. In patients with involvement of one kidney at the time of initial presentation, RPN will develop in the other kidney within 4 years, which is not unexpected because of the systemic nature of the diseases associated with RPN. RPN may be unilateral in patients in whom predisposing factors (such as infection and obstruction) are limited to one kidney.

Azotemia may be absent even in bilateral papillary necrosis, because it is the total number of papillae involved that ultimately determines the level of renal insufficiency that develops. Each human kidney has an average of eight pyramids, such that even with bilateral RPN affecting one papilla or two papillae in each kidney, sufficient unaffected renal lobules remain to maintain an adequate level of renal function.

As a rule, RPN is a disease of an older age group, the average age of patients being 53 years. Nearly half of cases occur in persons over 60 years of age. More than 90% of cases occur in persons over 40 years of age, except for those caused by sickle cell hemoglobinopathy. RPN is much less common in children, in whom the chronic conditions associated with papillary necrosis are rare. However, RPN does occur in children in association with hypoxia, dehydration, and septicemia.

Total Papillary Necrosis

Renal Papillary Necrosis– Papillary Form

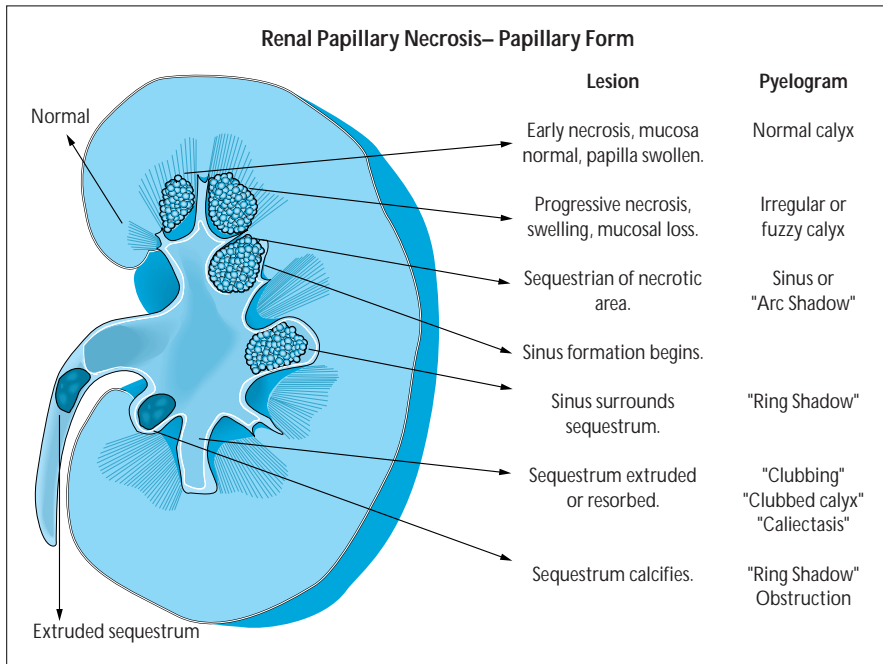|	Lesion	Pyelogram
Normal		
	Early necrosis, mucosa normal, papilla swollen.	Normal calyx
	Progressive necrosis, swelling, mucosal loss.	Irregular or fuzzy calyx
	Sequestrian of necrotic area.	Sinus or "Arc Shadow"
	Sinus formation begins.	
	Sinus surrounds sequestrum.	"Ring Shadow"
	Sequestrum extruded or resorbed.	"Clubbing" "Clubbed calyx" "Caliectasis"
	Sequestrum calcifies.	"Ring Shadow" Obstruction
Extruded sequestrum		

FIGURE 6-36

Schematic of the progressive stages of the papillary form of renal papillary necrosis and their associated radiologic changes seen on intravenous pyelography. Papillary necrosis occurs in one of two forms. In the medullary form, also termed *partial papillary necrosis*, the inner medulla is affected; however, the papillary tip and fornices remain intact. In the papillary form, also termed *total papillary necrosis*, the calyceal fornices and entire papillary tip are necrotic. In total papillary necrosis shown here, the lesion is characterized from the outset by necrosis, demarcation, and sequestration of the papillae, which ultimately slough

Renal Papillary Necrosis – Medullary Form

	Lesion	Pyelogram
Normal		
	Early focal, necrosis of medullary inner stripe.	Normal calyx
	Progressive necrosis, coalescence of necrotic areas. Swelling. Mucosa normal.	Normal calyx
	Mucosal break. Sequestration and sinus formation.	Sinus
	Progressive sequestration, extrusion, or resorption of necrotic tissue.	Irregular sinus
	Healing. Irregular medullary cavity with communicating sinus tract.	Irregular medullary cavity

into the pelvis and may be recovered in the urine. In most of these cases, however, the necrotic papillae are not sloughed but are either resorbed or remain *in situ*, where they becomes calcified or form the nidus of a calculus. In these patients, excretory radiologic examination and computed tomography scanning are diagnostic. Unfortunately, these changes may not be evident until the late stages of RPN, when the papillae already are shrunken and sequestered. In fact, even when the papillae are sloughed out, excretory radiography can be negative.

The passage of sloughed papillae is associated with lumbar pain, which is indistinguishable from ureteral colic of any cause and is present in about half of patients. Oliguria occurs in less than 10% of patients. A definitive diagnosis of RPN can be made by finding portions of necrotic papillae in the urine. A deliberate search should be made for papillary fragments in urine collected during or after attacks of colicky pain of all suspected cases, by straining the urine through filter paper or a piece of gauze. The separation and passage of papillary tissue may be associated with hematuria, which is microscopic in some 40% to 45% of patients and gross in 20%. The hematuria can be massive, and occasionally, instances of exsanguinating hemorrhage requiring nephrectomy have been reported. (*From* Eknoyan and coworkers [8]; with permission.)
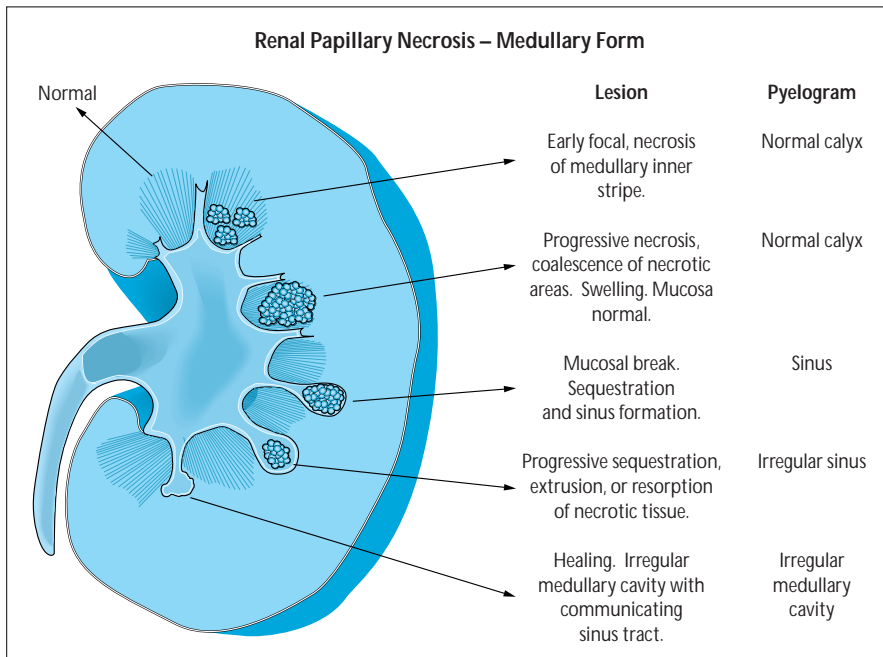
FIGURE 6-37

Schematic of the progressive stages of the medullary form of renal papillary necrosis and their associated radiologic appearance seen on intravenous pyelography. In partial papillary necrosis the lesion begins as focal necrosis within the substance of the medullary inner stripe. The lesion progresses by coagulative necrosis to form a sinus to the papillary tip, with subsequent extrusion or resorption of the sequestered necrotic tissue. The medullary form of papillary necrosis is commonly encountered in persons with sickle cell hemoglobinopathy. The incidence of radiographically demonstrative papillary necrosis is as high as 33% to 65% in such persons.

CONDITIONS ASSOCIATED WITH RENAL PAPILLARY NECROSIS

Diabetes mellitus
Urinary tract obstruction
Pyelonephritis
Analgesic nephropathy
Sickle hemoglobinopathy
Rejection of transplanted kidney
Vasculitis
Miscellaneous

FIGURE 6-38

Diabetes mellitus is the most common condition associated with papillary necrosis. The occurrence of capillary necrosis is likely more common than is generally appreciated, because pyelography (the best diagnostic tool for detection of papillary necrosis) is avoided in these patients because of dye-induced nephrotoxicity. When sought, papillary necrosis has been reported in as many as 25% of cases. Analgesic nephropathy accounts for 15% to 25% of papillary necrosis in the United States but accounts for as much as 70% of cases in countries in which analgesic abuse is common. Papillary necrosis also has been reported in patients receiving nonsteroidal anti-inflammatory drugs.

Sickle hemoglobinopathy is another common cause of papillary necrosis, which, when sought by intravenous pyelography, is detected in well over half of cases.

Infection is usually but not invariably a concomitant finding in most cases of RPN. In fact, with few exceptions, most patients with RPN ultimately develop a urinary tract infection, which represents a complication of papillary necrosis: that is, the infection develops after the primary underlying disease has initiated local injury to the renal medulla, with foci of impaired blood flow and poor tubular drainage. Infection contributes significantly to the symptomatology of RPN, because fever and chills are the presenting symptoms in two thirds of patients and a positive urine culture is obtained in 70%. However, RPN is not an extension of severe pyelonephritis. In most patients with florid acute pyelonephritis, RPN does not occur.

Spectrum of Renal Papillary Necrosis
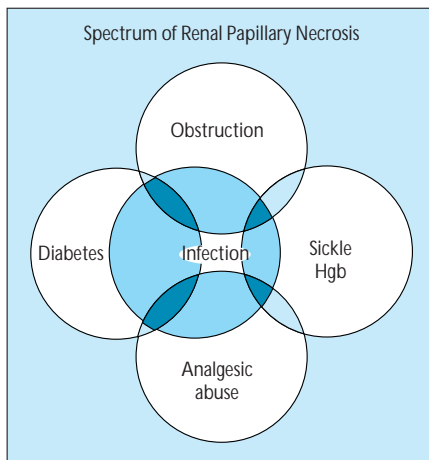
FIGURE 6-39

Spectrum and overlap of diseases principally associated with renal papillary necrosis (RPN). Although each disease can cause RPN, it is their coexistence (darkly shaded areas) that increases the risk, which is even greater after the onset of infection (lightly shaded areas). In most cases of RPN, more than one of the conditions associated with RPN is present. Thus, in most cases, the lesion seems to be multifactorial in origin. The pathogenesis of the lesion may be considered the result of an overlapping phenomenon, in which a combination of detrimental factors appear to operate in concert to cause RPN. As such, whereas each of the conditions alone can cause RPN, the coexistence of more than one predisposing factor in any one person significantly increases the risk for RPN. The contribution of any one of these factors to RPN would be expected to differ among individuals and at various periods during the course of the disease. To the extent that the natural course of RPN itself predisposes patients to development of infection of necrotic foci and obstruction by sloughed papillae, it may be difficult to assign a primary role for any of these processes in an individual patient. Furthermore, the occurrence of any of these factors (necrosis, obstruction, or infection) may itself initiate a vicious cycle that can lead to another of these factors and culminate in RPN.

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