Cellular and fluid exudation in the interstitial tissue was noted by Councilman in 1898, while he studied kidneys of patients who died of scarlet fever and diphtheria (1). Councilman also determined that these kidneys did not contain bacteria (they were sterile). He called the condition acute interstitial nephritis (AIN). The term interstitial nephritis connotes predominant involvement of the renal interstitium and tubules by inflammatory cells, often with edema or fibrosis and tubular atrophy. Because interstitial nephritis is commonly accompanied by variable tubular damage, the term tubulointerstitial nephritis, or tubulointerstitial nephropathy, is preferable and is often used interchangeably with interstitial nephritis. TIN has two common clinical presentations: sudden onset and rapid decline in renal function—acute TIN—and protracted onset with slow decline in renal function—chronic TIN. Because chronic TIN may present with prominent fibrosis and few inflammatory cells, the term chronic tubulointerstitial fibrosis, or chronic tubulointerstitial nephropathy, is used by some. Tubulitis refers to infiltration of the tubular epithelium by leukocytes, usually mononuclear cells. Acute TIN, with time, can evolve into chronic TIN; therefore, overlaps between these two entities often exist.
The term primary TIN refers to cases where the inflammation is essentially limited to the tubules and interstitium; glomeruli and vessels are uninvolved or show minor changes. Secondary TIN implies tubulointerstitial inflammation associated with a primary glomerular, vascular, or systemic disease. Idiopathic TIN is a primary TIN whose etiologic agent or cause is unknown.

Reactive TIN connotes tubulointerstitial inflammation from the effects of systemic infections; the kidneys usually are sterile. Infection TIN denotes tubulointerstitial inflammation from the effects of localization of live microorganisms in the kidney, where they can be identified and from which they often can be cultured.

Interstitial nephritis is commonly secondary to infection. These include acute and chronic pyelonephritis by bacteria or fungus, viral infection, and protozoal infections. Infection-associated interstitial nephritis is discussed in Chapter 24.

INCIDENCE

The exact incidence of TIN is unknown. Available figures vary by geographical area, entry criteria, and mode of diagnosis. While renal biopsy remains the gold standard for diagnosis of TIN, nephrologists are less likely to biopsy patients with clinical signs and symptoms of TIN than patients with glomerular diseases. Therefore, the diagnosis of TIN is often based on epidemiologic, clinical, and laboratory evaluations rather than renal biopsy findings (2). Also, mild forms of TIN may be overlooked, because of the absence or vagueness of clinical symptoms. Acute TIN accounts for approximately 3% of kidney biopsies, but this figure may be as high as 25% to 27% in adult patients with acute kidney injury (AKI) (3). In children, acute TIN may account for up to 7% of patients with AKI (4).

It is important to establish the diagnosis of TIN through kidney biopsy for the following reasons: (a) Clinical and laboratory data alone often do not differentiate between TIN and other renal diseases attended by renal insufficiency or renal failure; (b) most acute tubulointerstitial nephritides can be successfully treated; (c) untreated acute TIN may result in interstitial fibrosis and irreversible renal injury; and (d) the use of molecular and other techniques discloses possible genetic abnormalities and the underlying mechanisms of tissue injury (5).

ETIOLOGIC AGENTS, CAUSES, AND CLASSIFICATION

TIN is best classified according to the underlying etiology. The classification that we follow in our outline has been modified from those of Churg et al. (6) and Colvin and Fang (7). Some causes of TIN, including infectious etiologies, are covered in other chapters. TIN is often multifactorial, and several etiologic agents or causes, such as concurrent infection and obstruction, may contribute to tubulointerstitial renal disease in the same patient. Drug-induced TIN is the most common type determined by kidney biopsy, accounting for more than two thirds of the cases. Infection-related TIN may account for up to 15% of cases, whereas idiopathic forms of TIN represent approximately 10% of cases (3,8–10). The etiologic agents and causes of TIN are varied but can be grouped into broad categories. Baker and Pusey (8) pooled their data with two series from the literature (11,12). They found that the most frequent etiology of interstitial nephritis is drug related (71.1%), with antibodies accounting for about a third of these cases. Infection caused 15.6% of interstitial nephritis cases, and 7.8% were idiopathic. TIN and uveitis syndrome (TINU) was responsible for 4.7% of cases, and only 0.8% of the biopsies were due to sarcoidosis. Similar data were observed by other authors as well (9). Among autoimmune interstitial nephritis, more and more attention is paid to IgG4-related TIN (13). The exact incidence of autoimmune interstitial nephritis, including IgG4-related TIN, is unknown, but it is likely that many of the so-called idiopathic interstitial nephritides represent a form of autoimmune interstitial nephritis.

The main etiologic/pathogenetic factors responsible for TIN are shown on Table 25.1.

CLINICAL FEATURES OF PRIMARY TUBULOINTERSTITIAL NEPHRITIS

Various nonspecific clinical and laboratory findings may occur depending, in part, on the underlying cause or portion of the nephron that is affected. AIN may develop at any age and may be associated with variable degrees of acute renal insufficiency. Acute renal failure tends to be more prominent in the elderly. Systemic manifestations of hypersensitivity, such as erythema, maculopapular skin rash, arthralgias, fever, and peripheral eosinophilia, may occur primarily in drug-induced AIN, but these findings are frequently absent. Urinalysis usually reveals microscopic hematuria. Very rarely, gross hematuria or red blood cell (RBC) casts may be seen. Typically, these patients have white blood cells (WBCs) in the urine, and urine cultures are negative (sterile pyuria). Eosinophils in the urine, particularly if this number is greater than 1% of the cells, are thought to be a very characteristic finding in AIN. However, recent publications suggest that the specificity of urine eosinophils may be overestimated. Thus, out of 62 patients with eosinophiluria, only 13 patients had acute TIN, with the sensitivity of 25% and positive predictive value of 3% (14). Ruffing et al. (15) addressed the diagnostic accuracy of this test. In a selected group of patients, in which the diagnosis of AIN was suspected by the nephrologist, the sensitivity of eosinophiluria was 40% and the specificity was 72% with a positive predictive...
value of only 38%. The same authors also examined consecutive patients with WBC in the urine who did not have interstitial nephritis. Four of these patients had urinary eosinophils greater than 1%. Eosinophiluria is not uncommon in secondary forms of interstitial nephritis, particularly in those that are associated with crescentic glomerulonephritis (vasculitis).

Mild proteinuria, usually less than 1 g/24 hours, is frequently seen, but nephrotic-range proteinuria is rare. Nephrotic syndrome may occur if interstitial nephritis is associated with minimal change disease secondary to nonsteroidal anti-inflammatory drugs (NSAIDs). If the inflammation affects primarily the proximal tubule, it may result in renal glucosuria, aminoaciduria, phosphaturia, and uricosuria. If the distal tubule is primarily damaged, potassium secretion and sodium balance regulation suffer. Renal tubular acidosis may follow the damage of both distal and proximal tubules. It is worth noting that in many instances both the proximal and distal tubules are equally undergoing injury. Medullary inflammation may be associated with inappropriate urinary concentration and polyuria.

PATHOLOGY OF PRIMARY TUBULOINTERSTITIAL NEPHRITIS

The details of gross and histologic features underlying the pathology of tubulointerstitial nephritides associated with various agents or conditions are provided in the following sections.

In this section, we present an overview of the pathology of primary TIN. Pyelonephritis and other infection-related interstitial nephrites are discussed in Chapter 24.

**Acute Tubulointerstitial Nephritis**

Grossly, the kidneys are pale, edematous, and enlarged, with the degree of enlargement proportional to the extent of involvement. The external surface is smooth.

Microscopically, the cellular infiltration and edema are multifocal and vary in intensity. Although neutrophils are common in acute TIN, mononuclear cells, including lymphocytes and macrophages, also participate in inflammation and are usually the predominant cell types (Fig. 25.1). Drug reactions, such as those to antibiotics, are often associated with mononuclear cell infiltrates, including lymphocytes and frequently eosinophils. Most mononuclear cells in the inflammatory infiltrate are T cells (Fig. 25.2) (16,17). Overall, CD4+ T cells predominate relative to CD8+ T cells (17). However, in the report of Bender et al. (16), nine patients with drug-induced TIN had nephrotic-range proteinuria and predominance of CD8+ T cells in the interstitial infiltrate. Similarly, in the report of D’Agati et al. (18), CD8+ T cells outnumber CD4+ T cells in the interstitium in 22 of 26 biopsies of patients with lupus nephritis. It appears that CD8+ T cells are effectors of injury, whereas CD4+ cells play a predominantly regulatory role (19).

In later stages of progressive tubulointerstitial disease, monocytes/macrophages tend to predominate (20). Eosinophils are

**FIGURE 25.1 Interstitial nephritis in a 66-year-old patient who did not have any identifiable underlying etiology but had peripheral eosinophilia.** A: Interstitial mononuclear cell infiltrate with edema. (PAS, ×100.) B: Focally large numbers of eosinophils were present in the interstitium. (H&E, ×400.) C: In several foci, the inflammatory cells infiltrated the tubular epithelium (tubulitis). (PAS, ×600.)
common in drug-induced cases, but their absence does not exclude a drug-induced form of interstitial nephritis (21). After a few days or weeks have elapsed, a variable accumulation of plasma cells and histiocytes may be present (Fig. 25.3). Although not a common component of acute TIN, granuloma formation may occur in drug reactions, sarcoidosis, and idiopathic forms (Fig. 25.4) (3). If many plasma cells are seen, the diagnosis of IgG4-related interstitial nephritis should be considered, and an immunostain for IgG4 should be performed (13) (Fig. 25.5).

Tubular injury includes tubulitis (see Fig. 25.1C), breaks of tubular basement membrane (TBM), necrosis of tubular cells, and, later, atrophy and loss of tubules, depending on the stage of the disease. According to Ivanyi et al. (22), tubulitis more often involves the distal nephron. Biopsies taken several days after the initial insult show features of tubular cell regeneration, manifesting as flattening of the epithelial lining, cytoplasmic basophilia, and enlarged nuclei with frequent and prominent nucleoli. Nuclear changes may also be observed due to direct drug toxicity or in association with viral infections. Although not a common component of acute TIN, some interstitial fibrosis, as a part of the reparative process, may be seen in late biopsies. The presence of monocytes/macrophages and granulomas and some degree of fibrosis, encountered in some forms of acute TIN, emphasizes the overlap that exists between acute and chronic TIN (Figs. 25.4 and 25.6). Tamm-Horsfall protein (THP) may find its way into the interstitium following tubular rupture (Fig. 25.7). Interstitial THP is commonly found in nephron obstruction, but it is not exclusive to obstructive nephropathy.

Immunofluorescence and immunohistochemical techniques may be helpful in the determination of the underlying etiology. Linear deposits of an immunoglobulin (usually IgG) and complement along the TBM suggest an antibody directed to or cross-reactive with the TBM. Granular deposits of an immunoglobulin and complement in the TBM, interstitium, or both suggest an immune complex pathogenesis. This is common in systemic lupus erythematosus (SLE) and IgG4-related interstitial nephritis (13,23). However, granular or linear TBM staining for complement (particularly C3) is a frequent nonspecific finding, especially in the basement membrane of atrophic tubules.

Electron microscopy is also of limited value in the diagnosis of interstitial nephritis. Ultrastructural examination may occasionally reveal electron-dense immune-type deposits along the TBM or in the interstitium, particularly if there is underlying SLE or IgG4-related disease. Crystalline inclusions in tubular epithelial cells or finely granular electron-dense deposits along the TBM indicate monoclonal immunoglobulin deposition. Crystalline inclusions may also be seen with cystinosis. Rarely, electron microscopy may be helpful in detecting viral particles in infected tubular epithelial cells.

In acute TIN, the glomeruli are mostly spared. Arterial and arteriolar changes are usually absent. When present in
older persons, they are unrelated to the primary tubulointerstitial process and reflect aging, associated hypertension, or both. The morphology of AIN is nonspecific, and only in rare instances is it possible to define the exact etiology. If typical viral inclusions are present or other microorganisms can be identified or if characteristic immune complex deposits are present, an etiologic diagnosis may be possible. A more detailed description of the morphologic findings will be given in this chapter in the section describing the different forms of AIN.

**Chronic Tubulointerstitial Nephritis**

Common causes of chronic TIN are infections, drug reactions (e.g., analgesics, lithium), urinary tract obstruction, sterile reflux of urine, some forms of immune-mediated TIN, plasma cell dyscrasias, metabolic disorders, exposure to heavy metals, hereditary diseases, and various chronic nephropathies, including idiopathic TIN. Chronic TIN always develops if a progressive chronic primary glomerular disease is present. It is also a common finding in systemic disorders involving the kidney, including systemic autoimmune diseases, monoclonal gammopathies, and metabolic diseases. Vascular diseases are also frequently associated with chronic TIN, particularly vasculitis and chronic forms of thrombotic microangiopathies, but also ischemia secondary to atherosclerosis and hypertension can induce chronic tubulointerstitial injury with some degree of inflammation.

Grossly, kidneys with chronic TIN appear small, contracted, and pale. Variable papillary involvement, including papillary necrosis, sclerosis, and calcification, may be evident. The external surface is usually scarred, or finely granular from small vessel disease, compensatory hypertrophy of residual nephrons, or both. The corticomedullary junction is usually poorly demarcated. The intrarenal vessels are prominent and may have thickened walls.
Microscopically, the inflammatory cell infiltrates are made up of variable numbers of lymphocytes, monocytes/macrophages, and plasma cells. Granulomas may be seen in TIN associated with drugs; infections with mycobacteria, fungi, and parasites; sarcoidosis; and vasculitis. Some are idiopathic (24–26). Tubular atrophy and interstitial fibrosis are the histologic hallmarks of chronic interstitial nephritis, usually associated with some degree of interstitial mononuclear cell infiltrate. Tubular atrophy has different morphologic subtypes (27) (Fig. 25.8). The most common type is the “classic” type: atrophic tubule with prominently thickened, frequently wrinkled, and lamellated basement membrane (see Fig. 25.8A). The “endocrine”-type atrophic tubule has a narrow lumen or no lumen at all, is usually prominently reduced in diameter, and has simplified epithelium and a thin basement membrane (see Fig. 25.8B). These “endocrine”-type atrophic tubules usually occur in clusters. The “thyroid”-type atrophic tubule has only mildly thickened basement membrane, a simplified flattened epithelium, and a lumen filled with eosinophilic Periodic acid–Schiff (PAS)-positive homogeneous proteinaceous material; therefore, the tubule resembles a thyroid follicle (see Fig. 25.8C). These “thyroid”-type atrophic tubules also occur in clusters, and, in occasional cases of renal scarring, the parenchyma resembles thyroid gland. The diagnostic significance of these different types of atrophic tubules is somewhat limited. The endocrine-type atrophic tubule is frequently seen in chronic ischemia, including renal artery stenosis. The thyroid-type atrophic tubule is a common finding in chronic pyelonephritic scars, but we have also frequently observed thyroidization of tubules in ischemic scars, including kidneys with interstitial fibrosis secondary to antiphospholipid antibodies.

In chronic tubulointerstitial injury, tubules frequently undergo compensatory hypertrophy, whatever the etiology. These hypertrophic tubules are lined usually with tall proximal-appearing tubular epithelial cells. The lumen is dilated and commonly irregular (Fig. 25.9). Microcystic dilation of tubules in scarred interstitial areas may also occur. These microcystic tubules usually have a thin simplified epithelium and are filled by proteinaceous homogeneous material. Sometimes, the microcysts may have a scalloped outline (Fig. 25.10).

Interstitial fibrosis, a characteristic feature of chronic TIN, must be considered according to location. In the cortex, the interstitial volume is uniform and composes approximately 7% of the cortical volume (29), whereas in the medulla, the interstitial space increases from the outer stripe of the inner medulla to the tip of the renal papilla. For example, in the rat kidney, the interstitial space at the base of the inner medulla is about 10% of the medullary space but attains 30% of the interstitial space at the tip of the papilla (30). Interstitial fibrosis may be multifocal or diffuse, and the deposited extracellular matrix is a combination of various types of collagens, including types I, III, and V, derived from interstitial fibroblasts. Other cells,
including tubular epithelial cells and endothelial cells, also contribute to the extracellular matrix deposition by producing fibronectin, type IV collagen, and a variety of other matrix proteins (31). Interstitial fibrosis and tubular atrophy are cardinal features for the diagnosis of chronic TIN because inflammatory cells may be scarce or absent.

Immunofluorescence and immunohistochemical techniques may be helpful in delineation of the pathogenic mechanisms in a few cases, in a manner similar to that already described for acute TIN. Granular deposits of immunoglobulin and complement along the TBM and interstitium may indicate tubulointerstitial injury mediated by immune complexes. But one has to remember that C3 deposition is a very common nonspecific finding in the basement membrane of atrophic tubules. Immunohistochemical techniques also can be used to identify the segment of the nephron that is involved (32) to develop functional correlates of tissue injury. For example, when TIN involves predominantly the proximal tubules, proximal renal tubular acidosis (type II) develops owing to loss of proximal tubule resorbate (e.g., glucose, phosphate, uric acid, organic acids, low molecular weight proteins), with or without Fanconi syndrome. When distal tubules are predominantly involved, distal renal tubular acidosis (type I) develops, caused by failure of lowering the urinary pH, with or without hyperkalemia and salt wasting. When collecting ducts and papillary involvement predominate, water conservation is compromised by the decreased ability to concentrate urine. Molecular techniques have enabled the detection of deletions of genetic material as a possible cause of certain tubulointerstitial nephritides, such as the defect in the tubulointerstitial antigen gene in some children with progressive TIN (see later section in this chapter) (33).

Electron microscopy in chronic TIN has limited diagnostic value, as indicated above in the discussion of AIN. The basement membrane of atrophic tubules is not only thickened on ultrastructural examination but is frequently also lamellated. This lamellation is probably the result of repeated tubular epithelial injury and regeneration. The regenerating renal epithelium probably creates newer and newer thinner layers of basement membrane material, which will lend a lamellated pattern to the thickened TBM (Fig. 25.11). Aggregates of granular to microspherical material in the thickened basement membranes of atrophic tubules are not uncommon (Fig. 25.12). This material should not be misinterpreted as immune complex deposition.

In contrast to acute TIN, in which glomeruli are usually spared, glomeruli in chronic TIN often show changes. These glomerular changes are frequently secondary to poor glomerular blood perfusion and include tuft wrinkling and collapse, thickening of the Bowman capsule, periglomerular fibrosis, and glomerular obsolescence. Glomeruli with periglomerular fibrosis are frequently, but not always, atubular (34). Occasionally, segmental glomerulosclerosis may develop. Arterial and arteriolar changes, such as intimal thickening and medial hyperplasia, are usually present and reflect aging and associated hypertension.
The pathogenic mechanisms operative in tubulointerstitial nephritides associated with various agents or conditions are provided in the sections to follow. In this section, we present a brief overview of pathogenic mechanisms that are specific for certain tubulointerstitial nephropathies and that are common to most forms of chronic tubulointerstitial nephropathies.

Reactive TIN appears to result from systemic release of lymphokines that are filtered and reabsorbed by the kidneys, thereby promoting chemoattraction and activation of mononuclear cells in the kidneys (1,7,35,36). Infectious TIN results from three basic mechanisms of tissue injury (37): microbial release of degradative enzymes and toxic molecules, direct contact or penetration of host cells by the microbe, and the inflammatory response mediated by antibodies, T cells, or both. The pathogenesis of infectious TIN and vesicoureteral reflux is covered in Chapter 24. Drug-induced TIN is most likely immunologically mediated. The most widely accepted theory is that drugs behave as haptons after binding to extrarenal proteins that later will be planted in the kidneys or to renal proteins (38). This will be discussed in detail in the following section of this chapter. Drug-induced AIN occurs in only a small percentage of patients taking a medication and is not dose dependent, and exacerbation occurs after reexposure to the drug. Also, systemic signs of hypersensitivity may be evident.

TIN owing to anti-TBM antibodies involves predominantly IgG antibodies directed against different autoantigens in basement membranes, including a 54-kDa protein called TIN antigen, localized to chromosome 6p11.2-12 whose molecular composition has been cloned and sequenced (39). However, in our experience, true anti-TBM antibody-mediated interstitial nephritis is extremely rare, and we believe that the anti-TBM antibodies may form secondary to the tubular damage rather than causing it.

TIN owing to immune complex involves predominantly IgG antibodies, which probably are generated against a variety of tubular antigens. It is possible that antibodies may form against THP or megalin (a protein, localized in the brush border of proximal tubular epithelial cells), because immunization of rabbits or rats with those proteins resulted in AIN (40). IgG4-containing immune complexes are present along the TBM in IgG4-related interstitial nephritis; the pathologic role of these immune complexes is unclear (41). Tubulointerstitial injury may depend on complement activation by antibody (42), release of chemotactants, and activation of leukocytes with release of chemokines, cytokines, proteases, and toxic oxygen radicals (36). In many forms of interstitial nephritis, eosinophils are prominent in the interstitium, which may be related to a chemotactic cytokine, eotaxin, produced locally by renal parenchymal cells (43).

TIN due to cell-mediated mechanisms encompasses two types of reactions. First, delayed-type hypersensitivity reaction, which requires prior sensitization and is caused by CD4+ T cells and macrophages, results in production of various lymphokines and may induce a granulomatous reaction. Second, cytotoxic T-cell injury, which requires no prior sensitization, is mediated by CD4+ and CD8+ T cells (26).

Tubulointerstitial inflammation, fibrosis, and tubular atrophy, common to most chronic tubulointerstitial nephropathies, can be induced by various agents and causes. If the underlying etiology is persistent and cannot be eliminated, eventually all etiologic agents will cause chronic tubulointerstitial injury. Various pathogenetic factors are involved in the generation of interstitial fibrosis and tubular atrophy, including ischemia, reactive oxygen species, toxic agents, or immunologic injury (44). It is likely that an important role in the common final pathway leading to fibrosis can be attributed to the transforming growth factor beta (TGF-β)/Smad3 signaling pathway (45–47). TGF-β is up-regulated in response to injurious stimuli by angiotensin II (47). This accounts, at least in part, for the beneficial effect of angiotensin convertase inhibition slowing the progression of chronic renal injury. TGF-β membrane receptors transduce downstream signals via cytoplasmic latent transcription factors called Smad proteins. Smad 2 and 3 are phosphorylated, and they bind to Smad 4 and translocate to the nucleus, where they act as transcriptional regulators of target genes. Disruption of the TGF-β/Smad signaling pathway inhibits interstitial fibrosis in experimental animals (45). Connective tissue growth factor (CTGF) is a downstream mediator of the profibrotic effects of TGF-β. Recent data indicate that CTGF may play a pivotal role in the pathogenesis of TGF-β–dependent interstitial fibrosis (48). There is growing evidence that TGF-β is also capable of inducing epithelial to mesenchymal transdifferentiation of renal tubular epithelial cells (Fig. 25.13) (49,50). The theory is that during tubular injury, activated, injured tubular epithelial cells migrate through TBM ruptures into the interstitium, where they lose their epithelial characteristics and gain mesenchymal markers, such as smooth muscle specific actin, and turn into myofibroblasts. This transdifferentiation process of the injured tubular epithelial cells may be a key pathogenetic step in the development of chronic interstitial nephritis; however, convincing in vivo evidence for tubular epithelial cell to mesenchymal transdifferentiation is still missing (50–52). Based on lineage analysis of mesenchymal cells during nephrogenesis in a mouse model, Humphreys et al. (52) recently proposed that expansion of pericytes is primarily responsible for the development of interstitial fibrosis.
Tubulointerstitial Nephritis Associated with Drug Reactions

The kidney is adversely affected by a wide variety of therapeutic and diagnostic agents and toxic compounds. However, there are only a limited number of patterns of injury produced in the kidney. These may affect any of the compartments of the kidney including tubulointerstitial, glomerular, and vascular pathology (53,54). In the following section, we will focus only on acute and chronic TIN induced by drugs. Other patterns of renal injury associated with drug reaction, including acute tubular necrosis (ATN) and glomerular and vascular changes, will be discussed in other chapters.

It should be recognized that it is often difficult to establish a pathogenetic link between a pathologic lesion and a particular drug or toxin. Several factors contribute to this uncertainty, including concurrent factors that may produce renal injury, such as administration of several potentially nephrotoxic drugs at the same time, lack of or inadequacy of morphologic data in reported cases of drug toxicity, and the fact that some drugs may have multiple effects. Moreover, experimental models of toxicity may not be relevant to a particular clinical context because of interspecies variation and markedly different dosing of drugs in these models. In general, we limit our discussion to those drugs for which toxicity has been well documented in humans by disappearance of toxic effects when the drug is withdrawn, reoccurrence of symptoms on rechallenge, or both.

As pointed out earlier, today the most common form of interstitial nephritis is drug induced. Many drugs, including a range of widely used therapeutic agents, produce unpredictable idiosyncratic systemic reactions that may manifest in the kidney primarily as TIN.

Clinical Features

TIN caused by drug or toxin exposure develops in a few patients who receive the drug; reactions can sometimes be predicted if the patient has had a reaction to the same or a similar agent. The reaction is generally unrelated to the cumulative dose of the drug. Exposure to the offending agent typically occurs days to a few weeks before the clinical presentation (10). Patients may show signs of a systemic syndrome that include fever, skin rash, eosinophilia, and arthralgias. However, only a few patients will have this classic constellation of symptoms (12). Affected individuals may note fluid retention or a fall in urine output, and occasionally, patients may experience back or flank pain (55). Many patients show symptoms of AKI.

Analysis of the urine typically reveals pyuria with numerous mononuclear cells, including lymphocytes and monocytes. There may also be eosinophils, which researchers have touted as a specific marker for allergic interstitial nephritis (56). However, eosinophiluria is not specific for drug-induced interstitial nephritis (14). Eosinophils may best be detected by the use of special stains, such as the Hansel stain (57). Hematuria is not uncommon and is usually microscopic. Mild proteinuria may also be detected, and proteinuria may occasionally be in the nephrotic range, especially in those cases caused by drugs that also produce minimal change disease in the glomeruli. NSAIDs most commonly cause this constellation of symptoms. Urine cultures are routinely negative.

Because the interstitial inflammatory process can result in tubular injury, there may be evidence of tubular dysfunction. Patients may have glycosuria, aminoaciduria, and phosphaturia; occasionally, Fanconi syndrome has been described (58). In addition, tubular acidosis, electrolyte losses, or concentrating defects may be documented. On ultrasound, the kidneys are seen to be of normal size or enlarged. The parenchyma is typically echogenic—a finding that has been correlated with the extent of inflammatory infiltrate (and with the development of long-term changes in the interstitium).

Patients may have renal dysfunction without other accompanying symptoms. Because drug-induced interstitial nephritis is eminently reversible in the early stages, it is important to recognize the etiologic agent, so that long-term damage can be avoided. Some drugs produce more insidious changes, resulting in protracted injury without an obvious acute phase. Classic examples are lithium and analgesic compounds. These patients may show initial signs of salt wasting or acid-base imbalances and evidence of progressive tubular injury.

Pathology

Gross Findings

In acute TIN, the kidney is usually pale and swollen. Areas of congestion and hyperemia may be seen at the corticomedullary junction. In chronic TIN, the kidney is smaller with thinning of the cortex. The surface of the kidney may become granular. Parenchymal cysts may develop as interstitial fibrosis progresses. The cortex may become pale due to a combination of fibrosis and inflammatory cells.

Light Microscopy

Glomeruli

Glomeruli are typically spared. Occasionally, the interstitial inflammatory infiltrate may breach the Bowman capsule. In later stages of chronic interstitial nephritis, glomeruli may show nonspecific ischemic collapse and sclerosing changes. Periglomerular fibrosis is common in chronic cases.
**INTERSTITIUM**

In AIN, there are patchy or diffuse edema and inflammatory infiltrates. The infiltrate is predominantly mononuclear (see Fig. 25.1). Both CD4⁺ and CD8⁺ T cells have been detected in varying proportions. B cells and monocyte/macrophages can also be found. Eosinophils typically make up to 10% or less of the infiltrating cells. The eosinophils in the infiltrate may be focal and, rarely, they form clusters resembling a microabscess (see Fig. 25.1B) (56). Eosinophils are typically seen in reactions to antibiotics, especially penicillins, sulfonamides, and rifampicin, more than in response to various other drugs. Neutrophils are usually rare. Mast cells, which are difficult to detect without special stains, have been reported to constitute 1% to 2% of infiltrating cells (59). There is correlation between the number of interstitial mast cells and the degree of interstitial fibrosis in interstitial nephritis (60). Steroid treatment may reduce the severity of the inflammation and, in particular, lessen accompanying edema.

Granulomatous features are seen in the inflammatory reaction to many drugs (Table 25.2) (see Fig. 25.4). Granulomas, typically noncaseating and composed of epithelioid histiocytes, lymphocytes, and giant cells, may be scattered in the interstitium. They resemble the epithelioid granulomas of sarcoidosis, but the granulomas in drug-induced granulomatous interstitial nephritis are frequently less well defined than in sarcoidosis.

**TABLE 25.2 Causes of granulomatous interstitial nephritis**

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<tr>
<th>Infection (see Chapter 24)</th>
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<td>Fungal infections</td>
<td>Brucellosis</td>
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<td>Parasites</td>
<td>Drugs</td>
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<td>Nonsteroidal anti-inflammatory drugs (NSAIDs)</td>
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<td>Bisphosphonates (alendronate)</td>
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<td>Diphenylhydantoin</td>
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<td>Oxycodeine</td>
<td>Sarcoidosis</td>
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<td>Tubulointerstitial nephritis and uveitis syndrome (TINU)</td>
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<td>Granulomatous vasculitis (Wegener’s)</td>
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<td>Oxalosis (see Chapter 27)</td>
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<td>Gout (see Chapter 27)</td>
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<tr>
<td>Cholesterol granuloma</td>
<td>Idiopathic</td>
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In chronic drug-induced interstitial nephritis, the defining feature is interstitial fibrosis. An interstitial inflammatory infiltrate often persists, but it is usually mild and composed largely of nonactivated lymphocytes, plasma cells, and macrophages. These infiltrates are often nodular and localized to fibrotic areas. Although drug-induced acute TIN occasionally may persist and lead to chronic interstitial nephritis, some drugs have a propensity to produce subclinical progression to chronic renal failure. These drugs include analgesics, lithium, and calcineurin inhibitors.

**TUBULES**

Accompanying acute TIN, there may be evidence of tubular cell injury, which may include vacuolation, loss of brush border, and exfoliation and loss of tubular cells. The tubular epithelium is often infiltrated by inflammatory cells, usually lymphocytes (tubulitis) (see Fig. 25.1C). Although these characteristics are often described in the proximal nephron, a few investigators have reported that tubular injury and tubulitis may be more severe in the distal nephron (21,22). With a severe inflammatory reaction, the TBM may be disrupted. In the circumstance of chronic interstitial nephritis, tubular atrophy is typically seen to be associated with fibrosis in the interstitium.

**VESSELS**

Vessels are usually uninvolved, though a few drugs may produce vasculitis or thrombotic microangiopathy (see Chapters 16 and 18).

**Immunopathology**

Fibrin is often detected in the interstitium by immunofluorescence, reflecting interstitial edema. IgG and C3 have been reported to be deposited in a linear pattern along the TBM in some cases of apparent drug-induced interstitial nephritis, including cases induced by penicillins (56,61–63) and rifampicin (64). Such linear TBM staining may be nonspecific. Minetti et al. have also reported granular peritubular IgG in one case due to rifampicin (65). In cases of methicillin-induced AIN, a drug antigen has been immunolocalized along the TBM as well (61,62).

**Electron Microscopy**

Ultrastructural examination is usually of limited informative value in drug-induced interstitial nephritis. Electron microscopy of the interstitium in cases of drug-induced interstitial nephritis reveals edema, infiltrating inflammatory cells, and tubulitis. Olsen et al. (66) have described severe reduction of the proximal tubular brush border and proximal and distal tubular basolateral infoldings in this context, reflecting tubular injury. In some areas, there may be thinning or disruption of the TBM. Electron-dense immune-type deposits are usually not present in TBMs.

**Etiology and Pathogenesis**

Three major types of immune mechanisms may lead to TIN in response to drugs. These include hypersensitivity/allergic, immune complex, and cell-mediated reactions. Each of these types is discussed in turn. In a few individual cases, mechanisms of action are clearly defined, but for others, pathogenetic mechanisms are assumed, often based on morphologic
and clinical findings. It is possible that several mechanisms of action are at work in an individual patient.

Allergic-type hypersensitivity reactions are idiosyncratic and not related to dose. The reaction to the agent is presumably caused by previous sensitization, and, indeed, patients may give a history of exposure to the ingested drug or a similar compound. The reaction in the kidney is often part of a systemic hypersensitivity reaction, which may include fever, arthralgias, and skin rash. Eosinophils are often a significant component of cells in the inflammatory infiltrate, and, as noted earlier, there is often a peripheral eosinophilia as well.

Reactions involving immune complex deposition are of two types: those with formation of immune complexes that are deposited around tubules and those due to formation of antibodies directed against antigens at or in the TBM. In a few cases, antigens from the drug have been immunolocalized to the TBM. The inciting drug may serve as a hapten, leading to antibody formation. Thus, granular TBM IgG and C3 deposits were reported in a patient after NSAID treatment (67). In a few patients, anti-TBM antibodies have been found; Colvin and Fang (7) reported that these antibodies are frequently found in patients with different forms of AIN if they are sought. In many cases, however, it is unclear whether these antibodies are of clinical significance, and the specificity of the methodologies to detect these antibodies is not always high.

The finding of linear staining for IgG along the TBM is not a specific test to detect anti-TBM antibodies; proof of presence of anti-TBM antibodies requires demonstration of the antibody in the serum or renal eluates. Complexing of antibody to antigen may lead to complement binding and activation, triggering a cascade of events that result in inflammatory infiltrates and tissue injury.

Cell-mediated immunity has also been implicated in the genesis of drug-induced interstitial nephritis. The presence of granulomas in the kidney, in a number of cases of interstitial inflammatory reaction to drugs, is consistent with the delayed-type hypersensitivity. Recent data indicate that drug-specific T cells may be activated locally in the kidneys, and this T-cell activation may mediate a local inflammation via secretion of various cytokines, the type of which depends on the cytokine pattern secreted. This T-cell-mediated inflammation may be responsible for the renal damage (17). Cytotoxic lymphocytes, which were reactive against autologous renal cell line, have been isolated from one patient being treated with recombinant interleukin-2 (IL2) (68).

Chronic interstitial nephritis with fibrosis resulting from a prolonged inflammatory process is likely mediated by inflammatory cells and the cytokines released by them. It appears that interstitial mast cells facilitate the development of interstitial fibrosis (60). Some drugs appear to produce persistent tubulointerstitial damage without an acute injury phase. They include analgesics and lithium. Persistent changes produced by analgesics presumably result in part from ischemia produced by imbalances in the vasodilatory versus vasoconstrictor prostaglandins (PGs) over a prolonged period (see later section on “Analgesics and Nonsteroidal Antiinflammatory Drugs”). Chronic TIN is associated with prominent loss of the peritubular capillaries, which may further aggravate the ischemic injury (69). As pointed out earlier, certain cytokines, such as TGF-β, enhance production and release of matrix from epithelial and mesenchymal cells and likely also play a role in bringing about interstitial fibrosis through promoting epithelial-mesenchymal transdifferentiation of renal tubular epithelial cells (67).

Clinical Course

Drug-induced interstitial nephritis is generally reversible by withdrawal of the offending agent. Steroid therapy may enhance the rate of recovery and is frequently given along with withdrawal of the drug. A typical and diagnostic feature of drug-induced interstitial nephritis is its recurrence on reexposure to the drug or a related compound. Although recovery of renal function is the rule if the drug is withdrawn immediately, a study from Germany indicates that permanent renal insufficiency remained in 88% of drug-induced acute TIN cases if the suspected drug was taken for more than a month before the diagnosis of drug-induced interstitial nephritis was made (70). Also, the same authors suggest that NSAID-induced interstitial nephritis has a worse outcome as compared to other drug-induced forms.

Specific Agents

**Antimicrobial Agents**

**CEPHALOSPORINS**

The cephalosporin group of antibiotics comprises several “generations” of these useful agents, defined on the basis of antimicrobial activity. The first generation includes cefazolin, cephalothin, and cephalaxin. Cefamandole, cefonicid, cefuroxime, cefaclor, cefoxitin, and cefotetan are second generation, whereas the third generation includes cefazidime, cefotaxime, and ceftriaxone. Cefepime is a fourth-generation cephalosporin more resistant to beta-lactamases than the previous agents. The newest, fifth generation of cephalosporins includes ceftobiprole (with stronger anti–*Pseudomonas* activity) and ceftaroline. These drugs may be nephrotoxic, particularly in patients with preexisting renal insufficiency. Cephalexin, the most toxic of the group, is no longer available in the United States but is used experimentally for toxicity studies.

Clinical Presentation

The cephalosporins are most likely to produce renal failure in patients with preexisting renal insufficiency (71,72), in those with drug overdose (73), and in those receiving other antibiotics (73,74). Patients simultaneously receiving furosemide (73) are also at increased risk, which is probably related to the ability of furosemide to prolong the half-life of the cephalosporins (75). Many of the patients reported to have nephrotoxicity due to cephalosporins are elderly and acutely ill with severe infections.

*Cephaloridine* has been reported to cause AKI, often as the result of oliguria (75,76). *Cephalothin* given alone (72) or with gentamicin, tobramycin (76,77), or other substances (78) can cause AKI in humans or can worsen preexisting renal insufficiency (71). The AKI is usually reversible. *Cephalaxin* is less likely to cause nephrotoxicity than cephalexin or cephalothin, but hematuria, eosinophilia, and a transient rise in BUN have been reported (79). Clinical features suggest an immunologic basis. Hypersensitivity reactions have been reported in patients treated with *cephalexin* as well (77,80). Rare cases of skin rash, eosinophilia, fever, and renal insufficiency with *ceftriaxone* have been reported (81).

Pathology

Renal biopsies have been obtained in relatively few cases of cephalosporin-induced renal injury, usually in those in which the older cephalosporins were given. Biopsies
have shown a picture of interstitial edema with variable numbers of mononuclear cells, accompanied by variable degree of acute tubular injury (76,82,83). Granulomas may be seen in some cases (84). No immunoglobulins or complement have been seen with immunofluorescence techniques.

Pathogenesis Cephalosporins appear to be capable of producing direct toxic injury to tubular cells. Tune and Hsu (85) have shown that cephalosporins interfere with mitochondrial function in the renal tubule. Cephaloridine has structural homology to carmine, and it has toxic effects on carmine transport and fatty acid metabolism in rabbit renal cortical mitochondria; in vivo/in vitro effects on pyruvate metabolism have been seen, albeit at very high concentrations (85). Cephaloridine also produces lipid peroxidation and acylation and inactivation of some tubular cell proteins. Other cephalosporins, which lack cephaloridine’s side group constituents, largely affect tubular cell proteins and especially mitochondrial anionic substrate transporters (85). In vitro, proximal tubular cells show evidence of cytotoxicity on exposure to cephaloridine, cephalexin, and cephalothin, whereas distal tubules do not. These studies provide evidence of the role of oxidative stress, cytochrome P450 activation, and mitochondrial dysfunction in tubular cell toxicity (86). It is important to note that preexisting chronic renal failure (the degree of which is not accurately represented by serum creatinine [Scr] levels alone) is a very important risk factor for the development of progressive renal failure following the use of nephrotic medications.

In addition, cephalosporins are known to cause hypersensitivity reactions. In some cases, there has been resolution with drug withdrawal and, in a few cases, recurrence on rechallenge (82). The cephalosporins are structurally similar to the penicillins, which produce similar reactions (see later), and cross-reactivity may occur in 1% to 20% of patients (87). No specific cephalosporin is more likely than others to cause such a reaction.

Fluoroquinolones Clinical Presentation Fluoroquinolones belong to a family of synthetic broad-spectrum antibiotics. Ciprofloxacin, the most widely used of these drugs, has been reported to produce AKI with interstitial nephritis. Levofloxacin, norfloxacin, tosufloxacin, and moxifloxacin have also been associated with interstitial nephritis (88–91). There is typically fever, eosinophilia, and skin rash (92–96), but systemic manifestations may not be present (97). Onset of symptoms is generally within 2 to 12 days of beginning either oral or intravenous therapy. Patients have responded to withdrawal of the drug and, generally, concomitant treatment with immunosuppressive agents.

Pathology Renal biopsies in cases of fluoroquinolone-associated renal dysfunction have revealed interstitial nephritis. In a few cases, there were granulomatous features in the interstitial inflammatory infiltrate (69,96,98). Shih et al. have reported a necrotizing vasculitis in the kidney in two patients being treated with ciprofloxacin (96). An interesting case from Japan was reported in which a patient developed crystal-forming chronic interstitial nephritis following long-term exposure to tosufloxacin (90). The crystals were present in interstitial macrophages, but the crystals did not contain immunoglobulin. The patient’s renal function improved following discontinuation of the drug.

Pathogenesis The mechanism of pathogenesis appears to be a hypersensitivity reaction, with evidence of a cell-mediated process in the few cases with granulomatous features. As with many drug reactions, the possibility that another drug or underlying disease process may have produced the renal effects cannot be ruled out in several of these cases.

Penicillins In the following section, adverse reactions to ampicillin, methicillin, and penicillin are discussed in detail. AIN has been reported with other penicillins as well, including chloramphenicol (99) and piperacillin (100,101).

Clinical Presentation Several cases are recorded in which ampicillin appears to have provoked renal dysfunction (102–105). Fever, skin rash, and eosinophilia may be found and may antedate renal symptoms. Renal manifestations may be mild, with hematuria and a small amount of proteinuria, or severe, with acute oliguric renal failure. Rapid recovery is the rule. Time to onset varies, but renal symptoms generally appear within a few days of administration of ampicillin; other manifestations, such as fever and skin rash, develop within 24 hours. In several cases, there had been prior treatment with penicillin, methicillin, or tetracycline.

There are many reports of renal damage caused by methicillin. Nephrotoxicity with methicillin is not dose dependent. Onset of toxic reactions usually begins within 5 weeks after initiation of the drug. Patients typically manifest fever and skin rash, and 73% of patients in a review of 68 patients were male (106). Patients of all ages are at risk, though renal failure appears to be more common in older patients. Eosinophilia is a typical feature and may reach very high levels (56). Hematuria may occur; it is often the first sign of renal involvement. Proteinuria is seen in some cases but is generally mild. WBCs are frequently found in the urine, which is usually sterile, and eosinophils are present in the urine in a high proportion of patients (56,106). Azotemia occurs in over half of patients and oliguria in one third. Complete recovery of renal function is the rule, though azotemia may persist in less than 10% of patients (107).

Penicillin has been widely used for more than 50 years, and there have been several reports of nephrotoxicity ascribed to the drug. Appel and Neu (108) summarized the reported adverse reactions to penicillin under three main headings: various vascular and glomerular lesions, acute anuric renal failure after a single injection, and AIN. In a number of cases, there is fever, skin rash, and eosinophilia, suggesting a hypersensitivity reaction. The patients have hematuria with varying degrees of proteinuria, and renal failure may ensue.

Pathology Histologic changes in interstitial nephritis associated with penicillin and its derivatives do not differ from other forms of drug-induced interstitial nephritis. Eosinophils, however, are frequently abundant. Occasionally, granulomas (63,109) and vasculitis lesions (56,110) were recorded, but these are rare. Immunofluorescence is usually nonspecific; however, occasional investigators describe linear staining along the TBM for IgG (61,62,111,112). Such staining, in many instances, is probably nonspecific; however, antibodies to TBM antigens were reported in a few cases (62). Ultrastructural examination is also usually noncontributory. Association of minimal change disease with penicillin-induced interstitial nephritis has been
reported (113). A few investigators described fibrillar deposits along distal convoluted tubules and in glomerular epithelial cells (102,105), but the relevance of these fibrils is unclear, and they may merely represent procollagen.

Morphologic examination cannot differentiate between interstitial nephritides caused by different penicillins. In fact, the histology does not even indicate whether the interstitial nephritis is secondary to penicillin or some other drug or injurious agent. Pirani et al. (114) compared beta-lactam–induced interstitial nephritis with NSAID-induced interstitial nephritis and found that the beta-lactam–induced cases contained more eosinophils. Both types contained primarily mononuclear cells with some plasma cells in the infiltrate. Still, these are histologic findings of low specificity.

**Pathogenesis** Nephrotoxicity of the penicillins is not dose dependent, and the clinical picture overall is that of a hypersensitivity reaction. In several studies, immunofluorescence microscopy raises the possibility that anti-TBM antibodies may play a role in the pathogenesis of TIN, but the evidence is weak (61,62,111). Cell-mediated mechanisms may also be involved in some cases, based on the nature of the inflammatory infiltrate, and the absence of antibody and complement deposition. Gilbert et al. (102) have reported exacerbation of the reaction to methicillin by inadvertent exposure to ampicillin, a closely related drug. In addition, some case histories suggest that ampicillin can trigger a hypersensitivity reaction in patients who might have been sensitized to other penicillins. In one of these cases, antibodies against ampicillin were detected in the patient’s serum (104). In some studies, hypo-complementemia provided additional evidence of an immune reaction (102).

**Rifampicin**

**Clinical Presentation** Rifampicin is a drug used in the treatment of tuberculosis. When it is given intermittently, it causes various adverse reactions, including fever, chills, dizziness, nausea, and diarrhea (115,116). There have been several reports of acute oliguric renal failure during intermittent rifampicin therapy (115–118). The most common clinical scenario is AKI following a single dose of rifampicin. The average time between the initiation of therapy and clinical presentation is less than 3 weeks (119). Clinical manifestations may include gastrointestinal symptoms. Usually, no skin rashes are observed. Hematuria without any significant proteinuria is common. Anemia is often present, sometimes with associated thrombocytopenia (119). Most patients recover when the drug is withdrawn (116), a few cases have been reported to result in permanent renal damage (119,120).

**Pathology** Renal biopsies in cases of rifampicin toxicity typically show interstitial edema with variable numbers of mononuclear cells, and eosinophils have also been found (64). Rarely, granulomas may be seen (121). There may be patchy necrosis of the tubular epithelium. Even patchy cortical necrosis has been described (120); in that case, there was residual renal dysfunction. However, the degree of tubular necrosis is often not severe, and in one case, the tubules were described as unaffected (115). In addition, pigmented casts may be evident. Although glomeruli and vessels are usually normal, rarely glomerulonephritis, including crescentic and necrotizing glomerulonephritis, has been noted (64,116). On immunofluorescence microscopy, it has usually not been possible to establish the presence of immunoglobulins or complement (117,118), although C3 has been found in the mesangium and in the TBM (64,122) (common nonspecific findings).

**Pathogenesis** Antibodies to rifampicin have been detected in patients (123,124); in one study, they were present in one third of 49 patients (123). The various adverse reactions reported in this series, including renal dysfunction, were found more commonly in patients with antibodies than in patients without them. These authors suggest that the drug acts as a hapten, which, after it has become bound to macromolecules in the plasma, becomes antigenic with the formation of antibodies. The antibodies are considered to be directed against the drug, with formation of hapten-antibody complexes when the drug is given again.

**Sulfonamides**

The sulfonamides have been widely used, with relatively few renal complications. Alleged hypersensitivity reactions in the early days of their use were associated with polyarteritis or AIN (125,126). However, AIN secondary to sulfonamides has become a rare event, and only a few cases have been reported (127,128). In one case, acute oliguric renal failure developed in a patient being treated with sulfadiazine. The patient recovered after 6 weeks of oliguria (128). Cotrimoxazole (sulfamethoxazole and trimethoprim) has occasionally been found to cause deterioration of renal function (129,130). A case of delayed acute TIN in a patient who developed “drug rash” with eosinophilia and systemic symptoms (DRESS syndrome) secondary to sulfasalazine was described (131).

Patients in whom crystalline precipitates develop with the use of sulfonamides have microscopic or gross hematuria, crystalluria, and renal colic, and in some cases, they become oliguric or anuric (108,132). Occasionally, urothelitis may evolve. In one series of 40 patients, the urinary bladder was the most common location of stones (133). Sulfasalazine (a combination of 5-amino salicylic acid and sulfapyridine) has been reported to cause obstructive uropathy secondary to calculi (134). Less soluble forms, including sulfapyridine, sulfathiazole, and sulfadiazine, are most frequently associated with crystalline obstruction (135). Fortunately, this complication became rarer when sulfonamides of greater solubility became available. Rapid improvement may take place with discontinuation of the drug, fluid administration, and alkalinization of the urine.

The typical pathologic finding is interstitial nephritis. Eosinophils are a typical component of the infiltrate (127,130,136). Granulomas have occasionally been described (136). In patients with crystallization of sulfonamide in the kidney, some pathologic changes are due to obstruction as a consequence of crystal formation.

**Vancomycin**

Vancomycin is a glycopeptide antibiotic used increasingly to treat infections caused by organisms resistant to other antibiotics such as methicillin-resistant _Staphylococcus aureus_ (MRSA). With the growing number of MRSA infection, the cases of vancomycin-associated TIN have been reported more frequently (137–139). Nephrotoxicity is a known complication of the drugs when given alone or in combination with other drugs, especially aminoglycosides (140,141) or cephalosporins (74). Pediatric patients may be less susceptible to the toxic effects of
vancomycin combination therapy (142). Some patients have an associated rash and eosinophilia, suggesting a hypersensitivity reaction. In addition to these adverse renal effects, in some cases, patients have an anaphylactoid reaction to the drug, with generalized flushing—the so-called red man syndrome.

Pathologic findings in kidney biopsies obtained from patients with vancomycin-associated AKI may include TIN with many eosinophils (137,143). Several case reports described ATN in patients after vancomycin treatment without relevant interstitial inflammation, predominantly in pediatric patients (144–146). Rarely, vancomycin-associated kidney injury may be manifest as granulomatous interstitial nephritis (139). In the last 8 years, we have seen over 50 biopsies with ATN and interstitial nephritis following vancomycin administration. Most of these patients had high vancomycin trough levels and underlying preexisting chronic renal injury. Interestingly, in our experience, the ATN is the predominant finding associated with relatively mild but active interstitial inflammatory cell infiltrate with interstitial edema. In these cases, the lesions are usually reversible unless patients have severe systemic disease, sepsis, or other prominent chronic renal injury such as diabetic nephropathy.

The pathogenesis of renal toxicity is not well defined clinically, but experimental studies suggest that it stems from tubular cell injury. In some patients, the constellation of clinical symptoms and pathologic features indicate a hypersensitivity reaction (147), but many patients do not develop such a syndrome. The potentiation of toxic reactions when vancomycin is used with aminoglycosides may be due, at least in part, to enhancement of aminoglycoside binding to brush border and, presumably, its uptake into tubular cells, with subsequent cellular injury (148).

**Analgesics and Nonsteroidal Anti-Inflammatory Drugs**

Anti-inflammatory agents can be classified as steroidal and non-steroidal. However, by convention, the generic term nonsteroidal anti-inflammatory drugs (NSAIDs) has come to refer to specific PG synthase (cyclooxygenase [COX]) inhibitors, exclusive of aspirin. This causes some conceptual confusion because aspirin, in fact, is a PG synthase inhibitor. These drugs are used for their analgesic, antipyretic, and anti-inflammatory effects. COX has two isoforms. COX-1 is the constitutive isoform normally expressed in the tissues, and COX-2 is the inducible isoform. The hypothesis was that COX-1–derived PGs are responsible for regulating physiologic functions, whereas COX-2–derived PGs play a more important role in the pathogenesis of inflammation and tissue damage. The older generations of NSAIDs block both COX-1 and COX-2. A new generation of drugs selectively inhibits COX-2, and the assumption was made that these would not be associated with serious gastrointestinal and renal side effects. This led to the finding that constitutive tissue expression is present not only for COX-1 but also for COX-2. COX-2 has been detected in normal renal tissue in the medullary interstitial cells, in the macula densa, in the thick ascending limb of Henle, and also in smooth muscle cells and endothelial cells of arteries and veins (149–151).

Importantly, more and more data indicate that renal toxicity, including AKI with interstitial nephritis and also heavy proteinuria, may be associated not only with conventional NSAIDs but also with COX-2 inhibitors (152–158).

There is considerable controversy about COX-2 inhibitors and their cardiovascular side effects, which resulted in the withdrawal of rofecoxib (Vioxx) from the US market. However, celecoxib (Celebrex) is still available. The future of these otherwise promising anti-inflammatory medications is currently uncertain.

Under euolemic conditions, renal PG synthesis is low; however, if the renal blood flow is compromised, PG exerts a compensating influence on renal function. Some PGs induce renal vasodilatation that counterbalances vasoconstrictor effects of angiotensin II and norepinephrine. They also affect sodium excretion and, as a consequence of renal vasodilatation, they may increase the filtered load of sodium. They also increase medullary blood flow and reduce hyperosmotic effects of the loop of Henle. PGs also have a natriuretic effect by direct inhibition of sodium transport in the loop of Henle and distal nephron, and they also oppose the hydrosorotic effects of vasopressin (150). There are a number of different PGs with diverse effects. The above list of the actions of PGs is not complete, highlighting the complexity of their effect on renal function under normal and pathologic conditions.

Acetaminophen is frequently not classified as an NSAID because it has no anti-inflammatory effect, and it is not a PG synthase inhibitor. It is, however, one of the most widely used analgesic and antipyretic drugs and is discussed under the category of NSAIDs by many pharmacology textbooks. For convenience, we discuss acetaminophen with NSAIDs (Table 25.3). The gastrointestinal toxicity of these agents is well known, but their adverse effect on renal function became apparent only in the past three decades.

**INCIDENCE**

The incidence of NSAID nephrotoxicity is not well established. Taking into consideration their over-the-counter availability and the frequency with which people take them for pain relief or fever, the incidence appears to be rather low. On the other hand, because of their widespread use and availability, many patients with renal impairment have a history of NSAID use. In a number of such patients, the association of NSAIDs and renal failure is incidental. A causative relationship between NSAIDs and renal impairment should be considered if the initiation of NSAID therapy and the renal impairment show a close temporal association, if other etiologic factors can be excluded, and if renal function improves following discontinuation of NSAIDs.

Approximately 50 million Americans per year are likely to take NSAIDs, and some 500,000 (1%) of them are thought to experience renal side effects (159–161). Murray and Brater (162), in a prospective study, found renal impairment in 18% of patients treated with ibuprofen. Kleinknecht et al. (163), in a prospective study, collected 2160 cases of AKI, 146 of which (6.8%) were attributed to NSAIDs. AKI was defined as a greater than 50% rise in the Scr level or an increase to greater than 2.4 mg/dL from the baseline value. Data from the Boston Drug Surveillance Program on 122,000 hospitalized patients taking NSAIDs indicate that the Scr did not increase compared with levels in patients not receiving NSAIDs (164). A meta-analysis reviewing 1368 patients taking NSAIDs found only 3 patients in whom the Scr concentration increased to greater than 2 mg/dL (165). Corwin and Bonventre (166) reviewed 26 patients with AKI due to NSAID treatment. The Scr increased from a mean value of 1.6 ± 0.1 to 3.3 ± 0.3 mg/dL.
condition usually develops within a few days to weeks after
nied by varying degrees of proteinuria (10,155,166–168). The
AKI is the typical clinical presentation and may be accompa-
CliniCal presentation
may have risk factors for NSAID toxicity (see later).

hospitalized patients already represent a selected population and
may be overestimated in some of these studies because hos-

the incidence of AKI, defined as the number of rec-
gular cases per inpatient days of therapy, and found it to be
0.001, 0.0003, 0.0001, and 0.0001 for indomethacin, ibupro-
fen, zomepirac, and sulindac, respectively (166). The incidence
may be overestimated in some of these studies because hos-
pitalized patients already represent a selected population and
may have risk factors for NSAID toxicity (see later).

CLINICAL PRESENTATION
AKI is the typical clinical presentation and may be accompa-
nied by varying degrees of proteinuria (10,155,166–168). The
condition usually develops within a few days to weeks after

initiation of therapy. Sodium retention and edema may occur, and occasionally hyperkalemia may develop, presumably as
the result of reduced renal PG production and a subsequent
decline in serum aldosterone (169,170). Calvo-Alén et al.
(171) found that prolonged use of NSAIDs leads to subclinical
renal failure, which manifests first in decreased renal concen-
trating capacity and is correlated with the cumulative intake of
the drug.

Proteinuria is common among patients with NSAID tox-
icity, with approximately 10% to 12% of patients with renal
impairment due to NSAIDs developing nephrotic-range pro-
teinuria (172,173). A group of researchers from Chicago found
that 9% of their adult cases of minimal change nephrotic syn-
drome were associated with NSAIDs (174). Patients usually
take the drugs for several months before the nephrotic syn-
drome develops. It is worth noting that women appear to be
more susceptible (173,174). Rarely, COX-2 inhibitors may
also induce nephrotic syndrome as has been reported with cele-
coxib (155). The proteinuria typically subsides within a few
weeks after discontinuation of the NSAIDs but may worsen
with reexposure to the drug. The usual glomerular lesion is
minimal change disease and is discussed in Chapter 5.

The concurrence of renal insufficiency and severe protein-
uria, particularly if the renal failure is nonoliguric, is strongly
suggesrive of AIN (172,173). Hypersensitivity symptoms (skin
rash, eosinophilia) and fever are less frequently noted than in
cases of antibiotic-induced AIN (114). Hematuria may also be
present. The male-to-female ratio is 1:2. The symptoms usually
appear weeks to months after initiation of NSAID therapy and
may resolve within days or weeks afterward (114,174,175).
Recovery is not always the case for NSAID-associated AIN,
and cases of patients who progress to end-stage renal disease
(ESRD) have been reported (163,175). Approximately 20% of
AIN cases are associated with acetic acid derivatives. However,
other NSAIDs, including mefenamic acid, niflumic acid, and
many others including COX-2 inhibitors, are reported to
induce AIN (114,152–157,174,175).

Oligohydramnios with congenital renal insufficiency may
follow in utero exposure of the fetus to NSAIDs, which also
may cause bleading diathesis, premature closure of the duc-
tus arteriosus, and ileal perforation. Tubular dysgenesis with
incomplete differentiation of the proximal tubules as well as
tubular microcystic dilation has been described (176–178),
and the renal damage is severe and irreversible. Most reported
cases are related to prolonged in utero indomethacin expos-
ure (176,177).

RISK FACTORS
NSAIDs do not alter the glomerular filtration rate (GFR)
in healthy, euvoletic individuals (179), but they reduce the
GFR in patients with chronic renal disease or with preexi-
iting impaired renal function (4,161,179). Elderly and diabetic
patients are particularly vulnerable to the toxic effects of
NSAIDs (162,180,181), which can be explained by the fact
that aging is associated with a progressive decline in the GFR
and impaired pharmacokinetics of NSAIDs (168). Dehydration
and decreased cardiac output are also associated with an increased
risk of nephrotoxicity; diminished GFR may be the main risk
factor in these conditions as well (166). Patients with liver cir-
rhosis are also at higher risk, which may be related, in part,
to the impaired hepatic metabolism of NSAIDs and to renal

### TABLE 25.3 Nonsteroidal anti-inflammatory drugs

| Nonselective PG synthase inhibitors (COX-1 and COX-2) |
| Acetic acids |
| Indomethacin |
| Sulindac |
| Tolmetin |
| Diclofenac |
| Etodolac |
| Nabumetone |
| Ketorolac |
| Propionic acids |
| Ibuprofen |
| Naproxen |
| Fenoprofen |
| Ketoprofen |
| Flurbiprofen |
| Oxaprozin |
| Enolic acids |
| Acetaminophen |
| Para-aminophenols |
| Valdecoxib |
| Celecoxib |
| Piroxicam |
| Selective COX-2 inhibitors |
| Celecoxib |
| Rofecoxib |
| Valdecoxib |
| Non-PG synthase inhibitors |
| Para-aminophenols |
| Acetaminophen |
| Phenacetin |

*(a) Specific anti-rheumatoid arthritis agents and antigout agents are not included.
(b) Withdrawn from the market.*

following 4.2 ± 0.7 days’ mean duration of treatment, and the
Scr returned to normal following withdrawal of NSAIDs. They
estimated the incidence of AKI, defined as the number of rec-
ognized cases per inpatient days of therapy, and found it to be
0.001, 0.0003, 0.0001, and 0.0001 for indomethacin, ibupro-
fen, zomepirac, and sulindac, respectively (166). The incidence
may be overestimated in some of these studies because hos-
pitalized patients already represent a selected population and
may have risk factors for NSAID toxicity (see later).
impairment associated with chronic hepatic failure (168). In addition, cirrhotic patients have enhanced renal PG-E production, which is vasodilatory. Administration of NSAID to these patients may profoundly reduce renal blood flow and GFR (182).

Certain types of NSAIDs are more likely to cause renal injury than others. It has been reported that fenoprofen causes more than 50% of all NSAID-associated AIN (38). Whelton and coworkers in a randomized trial found that in patients with asymptomatic renal failure, ibuprofen is more frequently associated with AKI than are sulindac and piroxicam (170). There are also data that suggest that sulindac has less nephrotoxic potential than other NSAIDs. Sulindac does not reduce the excretion of urinary PGs and appears to be a safe drug even in patients with pre-existing renal failure (168). The kidney has the ability to metabolize sulindac into an inactive sulfone metabolite, thus protecting its own PG metabolism against the drug (168). There is limited literature available regarding nephrotoxicity of COX-2 inhibitors. Ahmad et al. (183) collected data from the U.S. Food and Drug Administration’s (FDA’s) Adverse Event Reporting System and found that 122 and 142 domestic US cases of celecoxib- and rofecoxib-associated renal failure, respectively, were reported by 2002, suggesting that use of both these drugs is associated with renal effects similar to that of conventional nonselective NSAIDs. Acetaminophen and aspirin are usually not associated with acute renal injury, but large doses of these drugs may cause AKI, especially in a combination with other medications or alcohol (184–187).

**Pathology**

In most patients with AKI secondary to NSAIDs, no renal biopsy is performed, and we can assume that in many of these cases, the nephrotoxicity is functional (renal vasoconstriction) and that there are no, or only minor, light microscopic changes. ATN may be present, but the tubular degenerative and regenerative changes are frequently coupled to interstitial nephritis, minimal change disease, or both (Fig. 25.14) (114).

The morphologic features of NSAID-associated AIN are similar to those of other interstitial nephritides and are characterized by a mononuclear interstitial infiltrate. However, minor differences do exist. Pirani et al. compared NSAID and beta-lactam antibiotic–associated renal changes and found that in NSAID-induced interstitial nephritis, there is less intensive infiltrate, and the proportion of eosinophils is substantially smaller. The paucity of eosinophilic cells in the infiltrate was also reported by Bender et al. (16). It is worth noting that routine staining methods may not reveal degranulated eosinophils; thus, the actual number of eosinophils may be underestimated. There are also fewer plasma cells, and tubulitis as well as granulomatous features are less common (114). Although there is agreement that the infiltrate consists mainly of lymphocytes, primarily T lymphocytes, occasionally plasma cells, B lymphocytes, and polymorphonuclear leukocytes may also be present in substantial numbers (16,114,188). There are few data regarding T-lymphocyte subsets, and these are controversial. Initial studies indicated a predominance of cytotoxic/suppressor T cells (16), but other researchers have found a helper/inducer cell predominance (188). The different types of antibodies used and the diverse methodologies, forms of fixation, and selection biases may account for the divergent results.

**Pathogenesis**

There is agreement that NSAIDs exert their toxic effect on the kidney through their interference with renal PG metabolism (149,150). PGI<sub>2</sub> is the most abundant PG in the cortex; it is produced primarily by arterioles and glomeruli. PGE<sub>2</sub> is the most abundant PG synthesized by the tubular epithelium, primarily in the distal nephron segments (distal tubules, collecting ducts) (193). Thromboxane A<sub>2</sub> is produced by the glomeruli, and PGF<sub>2α</sub> is produced by the tubules. The effect of PGs on the renal vasculature is primarily vasodilatory (194). Vasconstrictive mediators, such as angiotensin II, sympathetic stimuli, norepinephrine, arginine vasopressin, and endothelin, also stimulate PGI<sub>2</sub> and PGE<sub>2</sub> synthesis, which, in turn, will counterbalance the vasoconstriction. PGs also inhibit tubular

Occasionally, NSAID-associated interstitial nephritis may have granulomatous features (189). The condition has to be differentiated from sarcoidosis and infectious granulomatous interstitial nephritis, including tuberculosis. The differential diagnosis should not be based on the morphologic characteristics alone, because the histologic changes are usually not distinctive. In NSAID-associated interstitial nephritis, the granulomas are usually, but not always, less distinct than in sarcoidosis. The clinical history is the most important factor in making the correct diagnosis. Discontinuation of NSAIDs usually leads to resolution (189).

Either the glomeruli show no changes on electron microscopy, or, if nephrotic-range proteinuria is present, minimal change disease can be seen with the effacement of podocyte foot processes (114,173,174). Baisac reviewed 59 cases of NSAID-induced minimal change nephrotic syndrome and found that interstitial nephritis was also present in 43 patients (190). Occasionally, glomerular lesions other than minimal change disease (e.g., membranous glomerulopathy (191) or glomerular tip lesion (192)) are reported. These NSAID-induced glomerular diseases are discussed in the appropriate chapters (Chapters 5–7).
water and salt reabsorption (168). As mentioned earlier, NSAIDs do not alter the GFR in healthy, euvoeic individuals (179). In contrast, in conditions where the systemic hemodynamic conditions are compromised, NSAIDs may have a deleterious effect on the renal circulation. Owing to the inhibition of COX, the synthesis of vasodilatory PG\textsubscript{1} and PG\textsubscript{2} is diminished, and severe, unbalanced renal vasoconstriction may develop, resulting in AKI (168,195).

The development of AIN is probably related to a delayed-type hypersensitivity response to NSAIDs, which is also reflected in the composition of the infiltrate (16,114). This suggestion is also supported by the prolonged exposure and the infrequency of hypersensitivity symptoms. This condition is somewhat different from antibiotic-associated interstitial nephritides, where hypersensitivity signs are more common and eosinophils are more prominent in the infiltrate.

The pathogenesis of NSAID-associated severe proteinuria is unclear. In fact, there is some evidence that NSAIDs may ameliorate glomerular proteinuria (196). Why in certain patients the opposite happens is unresolved. The fact that nephrotic-range proteinuria and interstitial nephritis are frequently present at the same time suggests the role of mediators such as lymphokines released from interstitial or circulating inflammatory cells, which could alter glomerular permeability. In addition, the inhibition of PG synthesis by NSAIDs may hamper the inhibitory effects of PGs on T-cell function, thus intensifying immune activation and cytokine release. The inhibition of COX may also result in a shift of arachidonic acid metabolism toward the lipoxygenase pathway, which may result in the enhanced production of proinflammatory leukotrienes (164,173).

**Analgesic Nephropathy**

Analgesic nephropathy is a chronic progressive tubulointerstitial disease induced by the prolonged use (abuse) of analgesics and potentially addictive substances, such as caffeine or codeine. Analgesic nephropathy was first described in the 1950s (197) and was further characterized in the following decades (198–202). It became apparent that the chronic use of analgesics, primarily phenacetin, might be associated with the development of renal failure. However, after the withdrawal of phenacetin from the market, the incidence of analgesic nephropathy did not decrease subsequently; therefore, the scientific advisory board of the National Kidney Foundation formed an ad hoc committee who redefined analgesic nephropathy as a disease resulting from the habitual consumption over several years of a mixture containing at least two antipyretic analgesics and usually codeine and caffeine (203).

The definition of analgesic abuse is quite variable and arbitrary in the different studies, but the consumption of daily analgesics for \( \geq 1 \) year or a cumulative intake above 1000 units (tablets) is the minimum criterion required by most investigators. However, true analgesic abuse and subsequent nephropathy are associated with higher cumulative intake (usually above 5000 units).

**INCIDENCE**

The incidence varies greatly from study to study, depending primarily on the timing of the study and on the region or country where the investigation was performed. In Europe, the percentage of analgesic nephropathy among patients with ESRD undergoing long-term dialysis varied widely, from only 0.1% in Ireland, Norway, Poland, and Hungary to 18.1% in Switzerland (204). According to the Analgesic Nephropathy Network of Europe study, the average European incidence of analgesic nephropathy among patients who were started on renal replacement therapy in 1991–1992 was 6.4% (199). In Australia and Canada, 11% and 2.5% incidence rates have been reported, respectively (205,206). In the United States, 1.7% to 10% of the ESRD cases are thought to be the result of analgesic nephropathy in various regions (200,207). These large geographic differences may be explained by differences in local habits, psychosocial factors, availability of these drugs, and the frequency of correct diagnosis and reporting.

The removal of phenacetin from the market as well as other regulations (restricting over-the-counter sales and marketing smaller packages) resulted in a decline of the proportion of patients requiring dialysis therapy for analgesic nephropathy in Australia, Sweden, and Germany (206,208,209). Still, the incidence remains high in many countries, indicating that drugs other than phenacetin, such as acetaminophen and NSAIDs, are responsible for the development of the disease (160,198,208). Some authors believe that combination analgesics (acetaminophen and salicylates or aspirin) are more likely to induce analgesic nephropathy than single drug usage (198). Data on analgesic nephropathy in two highly endemic regions, Belgium and New South Wales, Australia, demonstrated that the downward trend and prevalence of analgesic nephropathy were very similar, despite the fact that the sale of only phenacetin was banned in Belgium, while other combined analgesics remained on the market, and in New South Wales not only phenacetin but all combined analgesics were prohibited. Still, the downward trend and prevalence of analgesic nephropathy were very similar during the follow-up period indicating that nonphenacetin mixed analgesics probably do not play a significant role in the development of analgesic nephropathy (210). Because of the relevance of the cumulative dose of analgesics, the effects of restrictions in the sale of combined analgesic medications show only with a delay. Studies from Australia and Belgium (211,212) indicate a recent decline in the incidence of analgesic nephropathy, particularly in the younger population. The cumulative dose of analgesics appears to be an important factor. Perneger et al. (200) have shown that the odds ratio of ESRD is 2 in patients with a cumulative dose of greater than 1000 pills and 2.4 in patients taking greater than 5000 pills of acetaminophen, compared with that in persons taking less than 1000 pills. They also found that the use of NSAIDs is associated with an increased risk of ESRD in patients taking greater than 5000 pills of NSAIDs (odds ratio 8.8), whereas the use of aspirin is not. It appears that the absolute risk of developing ESRD in analgesic abusers is approximately 1.6 to 1.7/1000 per year (198). However, the true incidence of analgesic nephropathy is quite difficult to determine. An Ad Hoc Committee of the International Study Group on Analgesics and Nephropathy critically reviewed the available data of the association between NSAID and renal disease (213). They found that many studies on analgesic nephropathy are inconclusive because of sparse information and substantial methodologic problems. Also, they emphasized that the diagnosis of analgesic nephropathy in different studies can vary and, in many cases, the diagnosis is based primarily on information about drug ingestion without any specific imaging or histologic studies. Therefore, the committee decided that there is no convincing evidence that...
nonphenacetin combined analgesics are truly associated with nephropathy (213).

A large autopsy study performed on 616 patients in Switzerland indicates that the autopsy prevalence of analgesic nephropathy decreased from 3% in 1980 to 0.2% in 2000. Similarly, capillary sclerosis of the urinary tract, the initiating event in the pathophysiology of papillary necrosis and analgesic nephropathy and the histologic hallmark of the effect of toxic metabolites of phenacetin in analgesic abusers, decreased from 4% of autopsy cases in 1980 to a 0.2% in 2000. Thus, the classic analgesic nephropathy has practically disappeared some 20 years after the removal of phenacetin from the analgesic market. Despite the fact that mixed analgesics containing paracetamol, the main metabolite of phenacetin, have continued to be popular and widely used drugs (214). This study later received some criticism because it was supported by pharmaceutical companies and the ad hoc committee consisted mainly of researchers from Germany, Switzerland, and Austria. Still, later studies from these three countries further indicate that analgesic nephropathy is disappearing and that non–phenacetin-containing analgesics do not cause analgesic nephropathy (214–216). However, as mentioned above, studies from Belgium and Australia contradict these findings, and, in spite of the declining prevalence of analgesic nephropathy, they state that the continuing use of non–phenacetin-containing analgesics (including paracetamol/phenacetin combined with NSAID, codeine, caffeine) is still associated with the development of analgesic nephropathy (211,212,217). Data from the Physicians’ Health Study indicated that analgesic use in healthy male patients is not associated with the risk of subsequent renal failure (218). The study involved 4772 healthy male physicians with normal Scr levels in 1982. During a follow-up period of 14 years, there was no evidence of renal impairment in these patients, not even in those who consumed more than 7000 analgesic pills (218). The studies somewhat contradict previous data, but they emphasize that a preexisting underlying renal condition or other coexisting aggravating pathogenetic factors (such as hypertension, diabetes, obesity) may be important in the pathogenesis of analgesic nephropathy and analgesic intake by itself may not be deleterious to the kidney if no other coexistent or preexistent pathologic factors are present (219). In spite of these contradictory data, considering the widespread use and abuse of analgesics, analgesic nephropathy must be considered an important public health issue.

Clinical Presentation

The typical patient is a middle-aged woman with a variety of symptoms, frequently including headaches and some degree of acute and/or chronic renal failure. The decline in the GFR may be due to vasoconstriction, vascular damage, or tubular obstruction (220). Tubular damage is reflected in defects of urinary concentration, acidification, and sodium retention. Microscopic hematuria occurs in 40% of patients (220). Gross hematuria with loin pain and AKI is suggestive of papillary necrosis (221). Occasionally, full-blown papillary necrosis occurs. If the necrotic papilla is sloughed into the renal pelvis, fragments of necrotic papilla segments may cause obstruction or be voided in the urine. Significant proteinuria (greater than 0.3 g/24 hours) is present in half of the patients, but nephrotic-range proteinuria is uncommon (220). Hypertension develops in a substantial number of patients.

The diagnosis of analgesic nephropathy should not be solely based on renal biopsy. Renal imaging techniques, such as sonography and particularly computed tomography, are the best methods for diagnosis in the appropriate clinical context (199). The Analgesic Nephropathy Network of Europe study showed that shrinkage of renal mass (sensitivity 96%, specificity 37%), bumpy renal contours (sensitivity 57%, specificity 92%), and the presence of papillary calcifications (sensitivity 85%, specificity 93%) are the most useful criteria in diagnosing analgesic nephropathy. The combination of these three criteria resulted in a sensitivity of 85% and a specificity of 93% (199). Radiocontrast examinations may be helpful in the diagnosis of papillary necrosis. The specificity and sensitivity of diagnostic imaging studies have been reviewed by De Broe and Elseviers (222).

Pathologic Findings

Gross Appearance

In the full-blown form, both kidneys are somewhat contracted, and the subcapsular surface shows irregularly alternating depressed areas and raised nodules, the latter sometimes assuming a characteristic ridged form (223,224). The depressed areas correspond to atrophic, scarred portions of the cortex above a necrotic papilla. The nodular areas correspond to the hypertrophic areas of the cortex above the columns of Bertin. The papillae are shrunken and withered and may be pale or brown. Calcification may be present, primarily in the medulla. In early-stage papillary necrosis, yellow stripes radiating outward from the tip of the medulla may be seen, separated by dark zones. This appearance may be confined to the tip or may extend through the entire papilla. Later, the yellow appearance becomes confluent and extends to the border of the inner and outer medullae. In some cases, only the tip of the papilla becomes necrotic. In others, the necrosis is found only in the central part of the papilla. Occasionally, the necrotic papillae become sequestered and may be found lying free in the pelvis. Soft phosphate stones may also be noted in the pelvis in association with papillary necrosis. A characteristic brown pigmentation of the pelvic mucosa may be observed, which is thought to be the result of lipid deposition (225,226).

Light Microscopy

The earliest change is the sclerosis (basement membrane thickening) of capillaries beneath the urothelial mucosa (Fig. 25.15) (224,226,227). This suburothelial capillary calcification was demonstrated in phenacetin abusers and has been reviewed by De Broe and Elseviers (222). The specificity and sensitivity of diagnostic imaging studies have been reviewed by De Broe and Elseviers (222).
abuse–associated analgesic nephropathy, and it is not entirely clear whether non–phenacetin-related cases have the same capillary calcification. This capillary sclerosis increases in intensity toward the pelvic-ureteric junction, is most prominent in the proximal ureter, and then gradually decreases (224). At a more advanced stage (in early stages of papillary necrosis), the capillary sclerosis involves the peritubular capillaries in the papilla and inner medulla. The ascending loop of Henle also exhibits a substantially thickened basement membrane, but the basement membranes of the collecting ducts, descending loop of Henle, and vasa recta are not affected or are only mildly affected. The thickened basement membranes are PAS positive and contain lipid as well as calcium deposits (Fig. 25.16). Ultrastructurally, this basement membrane thickening consists of numerous thin layers of basement membrane material (Fig. 25.17), which probably forms as the result of repeated injury of the capillary endothelium and the epithelium of the thin limb of Henle (224,228). Early on, these changes are confined to the central part of the inner medulla, but as the disease progresses, the affected small foci become confluent and may involve the entire inner medulla.

As full-blown papillary necrosis develops, the collecting ducts and the vasa recta become necrotic as well, and a ghost outline of the original structure is present (Fig. 25.18). Renal papillary necrosis is not associated with an influx of neutrophils into the necrotic areas or the bordering preserved renal parenchyma. There may be focal collections of lymphocytes and macrophages. If the necrotic portion of the papilla sloughs into the lumen of the renal pelvis, the resulting cavity will reepithelialize. The necrotic material may also remain in place, and in such cases, calcification of the necrotic papilla is common, with possible bone formation (Fig. 25.19).

The cortical changes are thought to stem from the alterations in the papilla (229,230). The cortex may be normal in the

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**FIGURE 25.16** Calcium deposits in the basement membranes of the vasa recta in the renal papilla in analgesic nephropathy. (Von Kossa, ×200.)

early and intermediate forms. The cortical changes consist of tubular loss and tubular atrophy with interstitial fibrosis and a varying degree of interstitial infiltration of chronic inflammatory cells (Fig. 25.20). Lipofuscin accumulation is frequently noted in the epithelium of atrophic tubules. These are nonspecific changes and cannot be reliably differentiated from other forms of chronic tubulointerstitial injury. It appears that the necrotic papilla, in some ways analogous to obstructive nephropathy, is responsible for the cortical changes. This is also supported by the fact that the columns of Bertin are often spared.

The glomerular changes are presumably the result of the tubulointerstitial changes and are quite nonspecific as well. In the atrophic suprapapillary cortex, periglomerular fibrosis, glomerular ischemia, obsolescence, and sclerosis may occur. In the columns of Bertin, where compensatory hypertrophy is common, some glomeruli may undergo segmental hyalinosis and sclerosis (224,231). Zollinger (231) called this change “overload glomerulitis,” which is in fact identical to glomerular hyperperfusion injury. Except for the medullary and pelvic capillary sclerosis, there are no vascular changes characteristic of analgesic nephropathy. Arteriolar hyalinosis and varying degrees of arterial intimal fibrosis may develop, particularly in older patients and in patients with arterial hypertension.

**DIFFERENTIAL DIAGNOSIS**

The key to the differential diagnosis is the clinical history. From the point of view of morphology, the gross findings are at least as characteristic as the histologic appearance. The irregular bumpy cortical contours with underlying papillary necrosis and sclerosis are distinct from the medullary and cortical scarring with caliceal deformities in chronic pyelonephritis/reflux nephropathy. Obstructive uropathy with renal pelvis dilation and parenchymal atrophy is easy to recognize. However, analgesic nephropathy predisposes patients to infections, and acute as well as chronic pyelonephritis is much more common than in the normal population (224). Diabetic nephropathy with papillary necrosis may have a similar gross and microscopic appearance with basement membrane thickening of the loop of Henle and peritubular capillaries. However, the capillary sclerosis beneath the urothelium is not seen. Papillary necrosis may occur in sickle cell disease and, rarely, in vasculitis and SLE (221). In these conditions, as well as in diabetes, the characteristic features of the underlying disease assist in making the diagnosis.

**PATHOGENESIS**

One theory is that the papillary changes are caused by insufficient blood supply (232,233). Lagergren and Ljungqvist (234) were unable to demonstrate the postglomerular vessels of juxtamedullary glomeruli, indicating decreased blood supply of the papilla. A reduction in number and dimension of the vasa recta in a rat model of analgesic nephropathy was noted by Kincaid-Smith et al. (232) as well. Molland (233) suggested that the reduced medullary blood flow in analgesic nephropathy is the consequence of disturbed autoregulation.

Certainly, capillary sclerosis can compromise the medullary blood flow, but it appears that capillary sclerosis itself is the consequence of toxic effects (235). The concentric lamellated ultrastructure of the thickened basement membranes of the peritubular and pelvic capillaries and the loop of Henle suggests repeated injury and subsequent repair of the capillary endothelium and
loop of Henle epithelium, respectively. Analgesic drugs are highly lipophilic, and they can easily diffuse out of the urine into the medullary and papillary interstitium and cause capillary damage. It has been shown that the concentration of analgesic substances in the renal medulla can be many times higher than in the blood (236). Thus, it appears that the topographic distribution of renal injury is related to the local concentration of analgesics and their metabolites. The primary injury appears to be toxic capillary damage, which in turn, through ischemia, aggravates the injury and leads eventually to papillary necrosis.

The natural history of the medullary/papillary changes is unclear. We had the opportunity to examine a cadaveric donor kidney from a semiprofessional athlete who died because of an automobile accident (Fig. 25.21). Organ donation was considered, but the kidneys were not transplanted because of very poor perfusion on the perfusion pump. Gross examination of the kidney revealed prominent edematous renal papillae (see Fig. 25.21A). Histologically, in the prominently edematous papilla, calcium deposits, including capillary calcification, were noted (Figs. 25.21B and C). Otherwise, the renal parenchyma, including the renal cortex, was normal, and there was no evidence of renal impairment in the donor. After questioning family members, it turned out that the athlete had been taking large amounts of analgesics for several years before his death. There was no evidence of impairment of renal function. Therefore, it is quite possible that this kidney represented an early stage of analgesic nephropathy, which in this particular patient may have been secondary to the combined effect of periodic dehydrations because of the strenuous exercise and the large doses of analgesics.

The pathogenesis of cortical changes is most likely secondary to medullary damage. The nephrons from the columns of Bertin drain into the fornical region of the calyx, which explains their escape from obstruction and subsequent injury in papillary necrosis (223,230). Furthermore, cortical atrophy and chronic interstitial nephritis develop primarily in areas where the underlying papilla remains in situ and undergoes sclerosis with the obstruction of the urine flow. If the separation of the necrotic papilla ensues, the urine flow may persist, and less cortical damage will develop (223,224,230). An alternate theory is that the cortical atrophy in papillary sclerosis/necrosis may be the consequence of the interruption of the limbs of Henle, with subsequent atrophy of the distal and eventually the proximal nephron. The interruption of the peritubular capillaries and vasa recta, by interfering with the blood supply of the tubulointerstitium, may play an important role in the medullary changes and possibly in the cortical changes as well.

The exact pathogenesis of the toxicity of analgesic compounds and the primary target of the toxic reactions are unknown. Inhibition of PG synthesis and immunologic reactions are unlikely causes (224). It is possible that metabolites of phenacetin, aspirin, or paracetamol, under the influence of P450 monooxygenase, bind covalently to cellular proteins and cause toxic damage (220).

Another possible explanation is cellular glutathione depletion with subsequent lipid peroxide production (237). This theory is based on the observation that combination analgesics are more prone to cause damage. Acetaminophen becomes concentrated in the papillae and there undergoes oxidative metabolism, which turns it into a reactive

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**FIGURE 25.21** Nephrectomy specimen from a young athlete who used large doses of analgesic medications for many years and died of an automobile accident. A: Note the edematous papillae. B: Histologic examination revealed prominently edematous renal papillae with compression of the vasa recta. (H&E, ×100.) C: von Kossa stain revealed finely granular calcium deposits in the basement membranes of the vasa recta and collecting ducts. (×400.)
analgesic nephropathy. If acetaminophen is ingested alone, there is sufficient glutathione generated to detoxify the reactive metabolites. If acetaminophen is taken in combination with aspirin or salicylates (aspirin will be converted to salicylate as well), the papillary concentration of salicylates will also be very high. Salicylates potently deplete glutathione, probably through the inhibition of NADPH production. Thus, with the combination of acetaminophen and salicylates or aspirin, glutathione depletion in the papilla may ensue and result in the production of lipid peroxides by the reactive acetaminophen metabolites. This subsequently leads to local tissue damage, resulting in papillary necrosis (237).

There are a few animal models for analgesic nephropathy. Moecnkel et al. (238) administered COX-2 inhibitors to mice and found that COX-2 inhibition dramatically reduced osmolyte accumulation in medullary interstitial cells. Exogenous osmolytes reversed COX-2–induced cell death in cultured renal medullary cells. They proposed that the reduction of osmolytes may have a pathogenic role in analgesic nephropathy (238). In another mouse model of acetaminophen-induced nephrotoxicity, a nitric oxide donor prevented renal injury as measured by blood urea nitrogen levels and renal pathology (interstitial congestion, proximal tubular cell degeneration, and necrosis) (239). The authors proposed that the protective mechanism is secondary to attenuation of lipid peroxidation in the kidney. Ahmed et al. (240) described an animal model with nephropathy following the administration of phenacetin and chloroquine. The renal injury was prevented by the administration of the nitric oxide synthase inhibitor L-nitroarginine methyl ester (L-NAME). A more recent experiment, however, indicated that COX-2 inhibitors may actually be protective against renal injury in an animal model. Administration of COX-2 inhibitor and then an angiotensin 1 receptor inhibitor prevented progressive renal injury in a 5/6 renal ablation model in the rat (241). However, there are clear differences in rodent and human responses to drugs. Chronic aspirin administration can cause renal papillary necrosis in rodents, which has not been reported in humans (242). Therefore, interpreting the somewhat controversial experimental data has to be done with caution. Perhaps nonrodent animals may provide a better model for human analgesic nephropathy.

UROTHELIAL CANCER AND ANALGESIC ABUSE

It is now widely accepted that there is an association between analgesic abuse and transitional cell carcinoma of the renal pelvis and urinary tract (Figure 25.22; (243–245)). The incidence is quite variable, and according to Mihatsch and Knusli (246), it may occur in at least 10% of phenacetin abusers. The latent period can be two or more decades (247). With the decline of phenacetin abuse, the incidence of transitional cell carcinomas of the urinary tract appears to have declined in Australia and Sweden (247,248); however, longer follow-up is needed for definitive proof. Although renal papillary necrosis has been found in a high proportion of patients with transitional cell carcinoma associated with analgesic abuse, it is not a prerequisite for the development of these tumors. Occasional publications also implicate an increased number of renal cell carcinomas in analgesic abusers. However, a study from the National Cancer Institute did not confirm this finding (249).

5-AMINOSALICYLIC ACID

5-Aminosalicylates are anti-inflammatory medications widely used for the treatment of inflammatory bowel disease. Two forms of these medications, mesalazine and sulfasalazine, are used. Based on data from the United Kingdom General Practice Research Database, it appears that the incidence of renal failure in patients on 5-aminosalicylic medications is low (0.17 cases per 100 patients per year) (250). This database indicates that the risk of renal failure is comparable with mesalazine and sulfasalazine use. Examining the renal side effects, Ransford and Langman found that interstitial nephritis was described only following the use of mesalazine (251). This is intriguing because the difference between mesalazine and sulfasalazine is that in sulfasalazine, 5-aminosalicylic acid is combined with sulfapyridine (a sulfonamide). Therefore, theoretically, one might expect a higher prevalence of interstitial nephritis with sulfasalazine. Recently, a case of sulfasalazine-induced hypersensitivity interstitial nephritis was reported (131). Arend and Springate (243) reviewed mesalazine-induced interstitial nephritis, and they concluded that mesalazine-related renal insufficiency occurs in approximately 1 in 100 to 500 patients. In patients with biopsy-proven interstitial nephritis, the frequency of residual renal insufficiency is 61%, and 13% of patients develop ESRD despite discontinuation of the drug (243).

Other Medications

DIPHENYLHYDANTOIN

The drug diphenylhydantoin (Dilantin) is used extensively for the treatment of seizures and arrhythmias. There are several side effects, but adverse reactions involving the kidney are rare. A few cases of oliguric AKI and interstitial nephritis have been reported (244,245,252).

It is well known that vascular changes take place with the use of diphenylhydantoin, and granulomatous arteritis can be seen in patients hypersensitive to this drug (253). Gaffey et al. (253) reviewed eight cases of vasculitis caused by hypersensitivity to Dilantin. The kidney was involved in six cases; three
patients had granulomatous interstitial nephritis. Blood eosinophilia of more than 14% occurred in four patients.

**LITHIUM**

The widespread use of lithium carbonate in psychiatric practice for the treatment of manic-depressive states has been associated with occasional cases of AKI, the more common occurrence of a diabetes insipidus–like state, and permanent impairment of renal function in others.

**Clinical Presentation** Nephrogenic diabetes insipidus (polyuria, polydipsia, and impaired renal concentrating capacity) is the most usual renal complication of maintenance lithium therapy (254). Defective distal tubular acidification owing to low fractional excretion of bicarbonate, with normal serum levels of bicarbonate and phosphate and normal ammonia excretion, is also common. Hypercalcemia may also occur (255). These side effects are usually reversible; however, there are reports that chronic irreversible renal injury may develop following maintenance lithium therapy (256).

The frequency with which chronic renal insufficiency and permanent morphologic damage occur in patients receiving long-term lithium therapy has been considered by several authors (257–259). Walker and Edwards (259) summarized the results of seven longitudinal studies between 1981 and 1988 and found little potential for decreased GFR in lithium-treated patients. In a prospective study of 65 lithium-treated patients, Jorkasky et al. (258) found a mild decline in the GFR in men but not in women. They questioned whether the reduction in the GFR was progressive and would lead to clinically significant renal insufficiency. A study from France indicates that the prevalence of lithium nephrotoxicity among ESRD patients is 2 per 1000 dialysis patients (255). They calculated that the lithium therapy duration until ESRD was 19.8 years and the estimated cumulative lithium salt given was 5231 g per patient. Cases of the nephrotic syndrome have been rarely reported (255,260). Interestingly, a study from the Columbia University indicates that 25% of patients who underwent kidney biopsy and were diagnosed to have lithium nephrotoxicity also had nephrotic syndrome (260). These patients had the light microscopic pattern of focal segmental glomerular sclerosis. Lithium nephrotoxicity appears to be a slowly progressive disease, and discontinuation of lithium will result in improved renal function only if the chronic injury is relatively mild.

**Pathologic Findings** The sparse reports on the renal pathologic features of acute lithium toxicity (261,262) have disclosed little apart from dilated convoluted tubules with some pyknotic nuclei, hyaline droplets, and vacuolated tubular epithelial cells. Chronic lithium nephrotoxicity is associated with progressive chronic TIN.

The original concern about chronic renal disease was raised by the study on the pathologic characteristics of lithium-induced renal disease by Hestbech et al. (256). In this study, renal biopsies were done on 14 patients receiving long-term treatment (1 to 15 years) with lithium carbonate for manic-depressive disease. Thirteen of the biopsies showed pronounced tubular atrophy, interstitial fibrosis, interstitial lymphocytes, and glomerular sclerosis. When the biopsies were assessed by morphometric methods and compared with an age-matched control group without renal disease (transplant donor kidneys for the most part), the lithium patients had twice the amount of interstitial connective tissue, three times the degree of tubular atrophy, and five times the number of sclerotic glomeruli. The intensity of interstitial mononuclear cell infiltrate was relatively mild, compared with the degree of interstitial fibrosis. In addition, two kidneys from patients taking lithium were seen at autopsy, and those had a granular surface and contained small cortical cysts. Renal cortical microcysts, along with fibrosis, have been described in patients on long-term lithium therapy (Fig. 25.23) (260,263). Markowitz et al. (260), using nephron-specific markers, determined that the microcysts are of distal nephron origin. Other investigators questioned the relevance of these findings (257,264). In spite of these controversial studies, there is now agreement that chronic lithium nephrotoxicity is a cause of chronic TIN with the above-described morphologic changes (254,255,260).

Kincaid-Smith et al. (264) and Walker et al. (265) described a peculiar tubular lesion in biopsies from patients treated with lithium. They found this lesion in the distal convoluted tubules and collecting ducts. It consists of cytoplasmic ballooning or vacuolation with strands of PAS-positive material in the vacuolated cytoplasm, sometimes radiating from the nucleus to the periphery of the cells. The change was regarded as unique; it appeared shortly after the start of lithium therapy and disappeared when treatment was stopped. Other investigators only rarely see this tubular lesion (260).

Glomerular changes are usually secondary and include scattered globally sclerotic glomeruli. Rare cases of minimal change disease and focal segmental glomerular sclerosis have been reported (266,267). Interestingly, Markowitz et al. (260) found that 50% of their biopsies from patients with chronic lithium nephrotoxicity had the glomerular pattern of focal segmental glomerular sclerosis. Half of these patients also had nephrotic syndrome.

None of the above-detailed morphologic changes are specific. A characteristic finding is the microcystic dilation of tubules, which is seen in most cases. One has to remember, however, that microcystic dilation of the tubules is a nonspecific

![FIGURE 25.23](image-url) Dilation of a tubule with vacuolated epithelium, in the background of fibrosis, in a patient who developed chronic renal insufficiency following decades of lithium treatment. (PAS, ×400.)
finding and is commonly seen in any chronic tubulointerstitial disorder. Therefore, obviously, chronic lithium nephrotoxicity is not a renal biopsy diagnosis and the correct diagnosis can be made only following careful correlation of the clinical and morphologic findings.  

Pathogenesis The pathogenesis of diabetes insipidus secondary to lithium treatment is most likely the result of the down-regulation of aquaporin-2 expression in the distal nephron (268). The pathogenesis of possible chronic tubulointerstitial injury is much more obscure; it is probably associated with a series of repeated acute injuries and repair. The nephrotic syndrome, seen only occasionally, could be the result of the interaction of lithium with anionic sites on the glomerular basement membranes (GBMs) (267).

Proton Pump Inhibitors Proton pump inhibitors are commonly used in the treatment of acid peptic disorders. More and more publications indicate that AIN may be a complication of these medications (269–273). Torpey et al. (271) found that in 8 out of 14 drug-related AIN cases at their institution, the etiologic agents were probably proton pump inhibitors. Ray et al. (273) found six cases out of 210 kidney biopsies with AIN that were strongly associated with proton pump inhibitors by either temporal association with the injury or response to stopping the drugs. AIN is diagnosed in an average of 2.7 months following administration of proton pump inhibitors (274). Clinical presentation and the morphologic findings do not differ from other forms of drug-induced interstitial nephritides. Among the proton pump inhibitors, omeprazole appears to be the drug most commonly associated with AIN (274).

Protease Inhibitors Protease inhibitors have become the mainstay of current therapy in patients with AIDS. Antiretroviral therapy can contribute to renal dysfunction directly by inducing ATN, AIN, and crystal nephropathy (crystalluria) or indirectly via drug interactions (275). AIN may also be associated with protease inhibitors, primarily with indinavir (276,277). Two patients have been reported who developed AIN with foreign body–type giant cells, presumably secondary to the crystalluria caused by indinavir (278). A few cases of TIN associated with atazanavir and tenofovir use have also been reported (279,280). The kidney biopsies of these patients showed AIN or chronic interstitial nephritis with an acute component. Withdrawal of atazanavir and tenofovir resulted in recovery of renal function (280).

Tubulointerstitial Nephritis With Anti–Tubular Basement Membrane Antibodies The presence of linear deposits of immunoglobulins and complement in the TBM together with tubulointerstitial inflammation is presumptive evidence of anti-TBM antibody disease. However, the significance of TBM deposits of immunoglobulins or complement alone is difficult to ascertain, because such linear TBM staining can occur in diabetes (284) and other advanced chronic renal injuries with tubular atrophy. Complement C3 may be focally present along the TBM even in normal human kidneys (285). Therefore, detection of circulating anti-TBM antibodies in the serum or elution of the antibodies from the renal tissue is necessary to prove the association with interstitial nephritis antibodies. However, the question still remains whether these anti-TBM antibodies are pathogenic or do they merely represent an epiphenomenon secondary to underlying tubular damage. It is theoretically possible that in many forms of severe acute tubulointerstitial injury, tubular and TBM antigens may be exposed, altered, and released in the circulation with subsequent formation of antibodies. Drug-induced TIN with anti-TBM antibodies was discussed earlier in this chapter.

Primary Anti–Tubular Basement Membrane Antibody Nephritis Primary anti-TBM antibody nephritis is a form of TIN with linear deposits of IgG and complement along the TBM, presence of anti-TBM antibodies in serum, mononuclear cell and neutrophilic infiltration of the interstitium and tubules, and edema and tubular cell injury. Glomeruli and vessels are normal or show nonspecific changes. Very few instances of primary anti-TBM nephritis have been reported. The two patients described by Clayman et al. (286) and Brentjens et al. (287) fulfill the criteria delineated earlier. One of the patients, a 27-year-old woman, presented with nausea, vomiting, fever, and generalized body aches. She became rapidly anuric, and a renal biopsy demonstrated intense inflammatory cell infiltrate in the interstitium with neutrophils and mononuclear cells and linear deposits of IgG, C3, and the terminal components of complement in the TBM. Anti-TBM antibodies were detected in the serum. This patient recovered renal function after intensive steroid therapy, but features of renal tubular acidosis persisted. The other patient, a 36-year-old man, presented with ESRD. Both patients had circulating antibodies that were reactive with a 48- to 58-kDa TBM protein, and in both, this antibody activity could be inhibited with a rodent antibody to a cross-reactive antigen. This protein in the TBM was later called TIN antigen (288). The TIN antigen is an extracellular matrix basement protein, which was originally identified as a target antigen involved in anti-TBM antibody-mediated interstitial nephritis. TIN antigen was mapped to chromosome 6p11.2-12 (39). The essential role of TIN antigen in cell survival by utilizing integrin αβ3 and downstream effectors has recently been demonstrated by Xie et al. (289). The case reported by Bergstein and Litman (290), also an instance of primary anti-TBM nephritis, describes a 6-year-old boy who presented with polydipsia, polyuria, microscopic hematuria, proteinuria, and glucosuria. The renal biopsy demonstrated mononuclear cell infiltrate with occasional lymphoid follicles, pronounced interstitial fibrosis, and tubular atrophy and loss associated with linear deposits of IgG and C3 in the TBM (Fig. 25.24).
The glomeruli demonstrated no deposits of immunoreactants. Anti-TBM antibodies were demonstrated in the serum and were not reactive with GBM antigens. The reports of Rakotoarivony et al. (291), Freycon et al. (292), and Helczynski and Landing (293) also include instances of primary TIN with anti-TBM antibodies.

Secondary Anti–Tubular Basement Membrane Antibody Nephritis

Included in the category of secondary anti-TBM antibody nephritis are various types of primary glomerulonephritis and allograft nephropathy in which there is an associated component of TIN with linear deposits of IgG and complement in the TBM.

Anti–glomerular Basement Membrane Antibody Disease

Anti-GBM antibody disease, with or without pulmonary hemorrhage, is an autoimmune disease owing to antibodies reactive exclusively, or principally, with the noncollagenous domain—NC1—of the α3 chain of type IV collagen (294). Anti-TBM antibodies are found in 50% (295) to 70% (296) of patients with anti-GBM nephritis. In general, tubular linear deposits are focal, they are less intense than deposits along the GBM, and they often involve proximal tubules. In the series of Lehman et al. (285), 23 of 26 patients with Goodpasture syndrome (88.4%) and 13 of 21 patients with anti-GBM antibody disease without pulmonary hemorrhage (61.9%) had linear TBM deposits of IgG, sometimes accompanied by C3. In the series of Graindorge and Mahieu (296), 9 of 11 patients with linear deposits of immunoglobulins along the GBM had anti-TBM antibodies by radioimmunoassay (82%), and 8 of these 9 patients showed linear deposits of IgG along the TBM. Anti-TBM antibodies are detected more frequently in kidney eluates than in serum (285).

Although anti-TBM antibodies are usually of the IgG class, Border et al. (297) reported anti-TBM antibodies of the IgA class in a patient with Goodpasture syndrome. The specificity of anti-TBM antibodies in patients with Goodpasture syndrome is unknown, but they probably are nephritogenic. Andres et al. (295) investigated their relative role in the pathogenesis of TIN in three groups of patients with crescentic glomerulonephritis: group 1 with anti-GBM and anti-TBM antibodies, group 2 with anti-GBM antibodies only, and group 3 with neither anti-GBM nor anti-TBM antibodies. Group 1 had the most severe, group 2 the intermediate, and group 3 the mildest form of TIN. These observations were interpreted to suggest that anti-TBM antibodies contribute to the development of TIN in patients with anti-GBM antibody disease. In our opinion, these observations do not prove the pathogenic role of anti-TBM antibodies in anti-GBM disease.

Membranous Glomerulonephritis

Some patients with membranous glomerulonephritis may show evidence of anti-TBM antibodies in kidney biopsies, serum, or both (298,299). Males are more often affected than females, and in most patients, the disease occurs before 5 years of age (300). HLA haplotypes B7 and DRw8 provide susceptibility to disease (299). In the publications of Levy et al. (298), Katz et al. (297), and Makker et al. (300), patients presented with proteinuria or the nephrotic syndrome and tubular dysfunction with features of Fanconi syndrome. Some cases have occurred in families (292,293,301). In the report of Makker et al. (300), the putative antigen in glomerular deposits was determined to be human gp330, the Heymann antigen, or megalin (302). However, in most cases, the target antigen in the TBM is the TIN antigen (299,300,303). The disease progresses to chronic renal failure (300,303). Ivanyi et al. (303) reported a child who developed progressive membranous glomerulopathy with circulating antibodies to the TIN antigen. The patient did not develop recurrent disease in his allograft after a 2-year follow-up.

Renal Allografts

Linear deposits of immunoglobulins and complement in the TBM are found with variable frequency in patients with renal allografts. In the report by Rotellar et al. (304), IgG and complement were present in 18 (2.7%) of 662 biopsies, and they occurred 3 to 13 months after transplantation. Of the 18 patients, circulating anti-TBM antibodies were detected in 10, and in 5 of these 10 patients, anti-TBM antibodies were detected in sera before linear TBM deposits could be found in renal biopsies. Linear deposits of IgG and C3 also were detected in patients who were clinically stable (not rejecting). In 10 of 15 patients who were subjected to sequential biopsies, linear TBM deposits disappeared. Overall, circulating anti-TBM antibodies were detected predominantly in the first 6 months after transplantation; they persisted for an average of 3 months and did not...
present in collagenase digests of TBM. Three antigens have been may arise because of renal damage, and they recognize antigens from experimental models (281,283). The anti-TBM antibodies is inferential and by analogy to data derived antibodies alone. Because only some of these requirements can demonstrate that the antibodies have a pathogenic role, for example, incubation of plasma or eluate with TBM antigen; and to dem-

to establish that TIN is mediated by anti-TBM antibodies, it is necessary to demonstrate linear deposits of immunoglobulins, and malignant hypertension (112).

Pathologic Findings

The tubulointerstitium shows variable degree of mononuclear cell infiltrate and, in more advanced stages of the disease, tubular atrophy, and interstitial fibrosis. The light microscopic changes are not different from other forms of tubulointerstitial fibrosis. In primary anti-TBM nephritis, glomeruli are normal or show nonspecific changes. In secondary anti-TBM nephritis, the glomerular changes vary and include crescentic (285,306), membranous (298,299,301,303), lupus (307), or mesangioproliferative glomerulonephritis or focal segmental glomerulosclerosis (112). Arteries and arterioles may show hypertensive or age-related changes. By immunofluorescence, linear deposits of IgG and rarely other immunoglobulins, often with complement, are detected along the TBM (see Fig. 25.24) (112,285,287). Electron microscopy does not reveal electron-dense immune-type deposits along the TBM.

Etiology and Pathogenesis

To establish that TIN is mediated by anti-TBM antibodies, it is necessary to demonstrate linear deposits of immunoglobulins, commonly IgG, and complement along the TBM (281); to detect antibodies specific for TBM antigens in the circulation (281); to demonstrate that antibodies are concentrated sever-

The antibodies involved are predominantly of the IgG class and, rarely, other immunoglobulins (285,287). Interaction of antigen and antibody results in complement activation and deposition of C3 in TBM. That complement is required for inflammatory infiltration, and tubular epithelial cell injury is indicated by the experimental studies of Hatanaka et al. (322). These authors demonstrated that inhibition of complement activation in a rat model of anti–basement membrane (both glomerular and tubular) disease at the C3 convertase level abrogates tubulointerstitial injury and leukocytic infiltration induced by anti–basement membrane antibodies.

Tubulointerstitial Nephritis With Immune Complexes

TIN with immune complexes implies the presence of granular deposits of immunoglobulins and complement in the TBM, interstitium, or both. Deposits often are associated with an underlying renal disease, usually a form of glomerulonephritis mediated by immune complexes, and the incidence of tubulointerstitial immune complex deposits in renal biopsies varies: 1.5% (16 of 1100 biopsies) in the series of Orfila et al. (112), 6.5% (13 of 200 biopsies) in the Lehman et al. series (285), and 42.9% (6 of 14 biopsies) in the study of Levy et al. (298). In these three series, the underlying conditions were various glomerulonephritides (e.g., lupus, membranous, cryoglobulinemic, membranoproliferative, focal proliferative, crescentic, postinfectious, shunt nephritis), minimal change glomerular disease, allograft rejection, graft versus host reaction, idiopathic TIN, hepatitis B infection, and syphilis. We would like to reiterate that complement

identified to date. The major and best-characterized antigen is a 54-kDa protein localized to chromosome 6p11.2-12 (39), which is the target of autoantibodies in idiopathic anti-TBM disease. The latter is called TIN antigen. Earlier, the TIN antigen was referred to as 48- to 54-kDa protein (308,309), 58-kDa protein (310), or 48- to 58-kDa protein (296) and as 3M-1 antigen (311). Purified 3M-1 protein induces antibodies to the TBM and TIN in susceptible hosts; TBM preparations selectively depleted of 3M-1 protein do not (286). Studies by Yoshioka et al. (311) demonstrated that sera from patients with anti-TBM nephritis bind to both 48- and 54-kDa antigens, and the studies of Miyazato et al. (312) demonstrated that the 48- and 54-kDa glycoproteins share the same epitope but are encoded by differ-

ecent mRNAs. The protein may contribute to basement mem-
brane assembly and cellular adhesion (313) through interaction with α3β1 and αvβ3 integrins (314) and also play an important role in normal renal development (315,316). In spite of its name, it is becoming apparent that TIN antigen may play a more important role in normal renal development than in actual acute TIN later in childhood or in adulthood (33,316–318). Abnormal TIN antigen has been reported in nephropathies (317) and renal dysgenesis/chronic TIN in children (33). Transcription of TIN antigen is down-regulated in obstructive nephropathy, and this down-regulation is mediated by CCAAT/enhancer-binding protein beta (C/EBP-beta) (319). The second antigen, a 70-kDa protein, is the target of autoantibodies present in patients with anti-GBM nephritis and in some patients with lupus nephritis. This antigen is present in the GBM and TBM (285). The third antigen, a 45- to 50-kDa protein, is also target of autoantibodies in some patients with anti-GBM disease (320) and of antibodies that developed in one patient with Alport syndrome after renal transplantation (321).

The antibodies involved are predominantly of the IgG class and, rarely, other immunoglobulins (285,287). Interaction of antigen and antibody results in complement activation and deposition of C3 in TBM. That complement is required for inflammatory infiltration, and tubular epithelial cell injury is indicated by the experimental studies of Hatanaka et al. (322). These authors demonstrated that inhibition of complement activation in a rat model of anti–basement membrane (both glomerular and tubular) disease at the C3 convertase level abrogates tubulointerstitial injury and leukocytic infiltration induced by anti–basement membrane antibodies.
and even IgG staining may occur nonspecifically in the TBM, particularly if the tubules are atrophic and if the patient is diabetic. Granular or finely vacuolar deposits are commonly seen in the basement membranes of atrophic tubules by electron microscopy. On low magnification, these nonspecific deposits may appear as discrete immune-type electron-dense deposits. Therefore, before the diagnosis of immune complex deposits in the TBM is made, careful morphologic examination and correlation of the findings with laboratory results are necessary.

**Primary Tubulointerstitial Nephritis With Immune Complexes**

Primary TIN with immune complexes is very rare because, in most cases of TIN with immune complex deposits, we now recognize the underlying disease. Ellis et al. (323) reported one patient with proximal tubule dysfunction and TIN with granular deposits of immunoglobulins and complement in tubules and interstitium; the glomeruli were normal.

Granular deposits of IgE have been detected in two patients with TIN. The first patient was a 54-year-old woman who presented with anemia, diverticulitis, eosinophilia, and renal insufficiency. The patient had no allergic or drug history and no evidence of systemic connective tissue disease. The kidney biopsy demonstrated TIN with granular TBM deposits for IgE, IgG, IgM, and C3; deposits of IgE predominated (324). The second patient was a 72-year-old man who had a positive antinuclear antibody (ANA) assay but no evidence of SLE. The kidney biopsy demonstrated advanced TIN with prominent granular IgE deposits (7).

Kambham et al. (42) reported eight patients who had interstitial nephritis in their renal biopsies associated with tubulointerstitial immune complex deposition and hypocomplementemia. They used the term “idiopathic hypocomplementemic interstitial nephritis” to designate this entity. None of these patients had evidence of SLE or Sjögren syndrome. In six of their eight patients, complement levels were available. C3 and C4 levels were depressed in all patients except one, in whom C3 was normal and C4 levels were low. In one of their patients, the infiltrate was suggestive of a marginal zone lymphoma, and heavy chain gene rearrangement studies indicated monoclonality (42). Immunofluorescence revealed granular tubular basement deposits for IgG in all cases. C1q was detected in six of eight cases and C3 in only four of the eight cases. Electron microscopy revealed discrete electron-dense immune-type deposits in all biopsies. In two cases, the TBM deposits had a paracrystalline fingerprint-like substructure. None of the patients had evidence of hypocomplementemic urticarial vasculitis syndrome (HUVS). Follow-up data were available in six of their patients, and five of them responded favorably to immunosuppressive medication. Immunosuppression included prednisone and a combination of tacrolimus, prednisone, and mycophenolate mofetil in the patient who had the monoclonal cell population. Rare older and more recent case reports have been published describing very similar primary immune complex tubulointerstitial cases with hypocomplementemia (324–326). Most of these idiopathic hypocomplementemic interstitial nephritis cases probably represent IgG4-related interstitial nephritis (see below).

Markowitz et al. (327) described a patient whose peculiar kidney biopsy showed polyclonal large electron-dense deposits along the TBMIs between the tubular epithelial cells and the basement membrane. These deposits were IgG positive and had a distinctive curvilinear substructure. The patient had underlying diabetic nephropathy, but did not show evidence of active interstitial nephritis.

**Secondary Tubulointerstitial Nephritis With Immune Complexes**

Included in the category of secondary TIN with immune complexes are various systemic diseases, glomerulonephritides, and other renal diseases in which there is tubulointerstitial inflammation associated with granular deposits of immunoglobulins and complement in the interstitium or TBM.

**IgG4-Related Tubulointerstitial Nephritis**

**Introduction**

There is now evidence that some tubulointerstitial nephritides are due to IgG4-related disease. Some patients with IgG4 systemic disease may have TIN with increased number of IgG4-producing plasma cells. Although data are still limited, growing literature suggests that this entity may be overlooked and the number of patients with IgG4-related interstitial nephritis may be substantial.

One of the first reports describing probable cases of IgG4 systemic disease was published more than 50 years ago. Sarles et al. (328) described patients with sclerosing pancreatitis and hyperglobulinemia, and they hypothesized that this may be an autoimmune disease. More recently, this disease was found to be associated with increased IgG4 levels in the serum and the presence of numerous IgG4-positive plasma cells in the affected tissues (329,330). Subsequently, numerous reports described increased number of IgG4-producing plasma cells in a variety of organs associated with IgG4 systemic disease. In addition to “autoimmune pancreatitis,” involvement of the liver (331), lacrimal (332) and salivary (333) glands, lungs (334,335), gastrointestinal system (336), breast (337), lymph nodes (338), retroperitoneum and mediastinum (339,340), and many other organs by IgG4-positive plasma cells was reported. This novel clinical syndrome was proposed to be named IgG4-related disease (41,341). Histologically, patients with IgG4-related disease have infiltration of organs by IgG4-positive plasma cells and progressive fibrosis (342,343). Many questions and problems related to the pathogenesis, diagnostic criteria, and treatment of IgG4-related disease are still to be elucidated. Because of the lack of universal diagnostic criteria, low awareness of the disease among physicians, and high variability of the clinical presentation, the prevalence of IgG4-related disease is unclear. In Japan, the presumed incidence of IgG4-related disease is 0.28 to 1.08/100,000 population (342). Data about incidence and prevalence of the disease elsewhere are scant.

There is growing evidence that the kidney is a frequent target organ in IgG4-related systemic disease (13,344). The main histologic findings in the kidney directly involved by this disease are similar to other organs, namely, TIN with infiltration of the interstitium by IgG4-positive plasma cells and interstitial fibrosis. However, kidney function may also be affected in patients with IgG4-related disease involving retroperitoneum, renal pelvis, or urethra because of urinary outlet obstruction and development of hydronephrosis.

**Clinical Presentation**

Several authors from Japan, Korea, and the United States describe renal involvement in IgG4-related disease and propose diagnostic criteria for its identification (13,345–347).
The average age of patients with IgG4-related tubulointestinal nephritis is approximately 65 years, ranging from 20 to 83 years (13,346,347). There is a predominance of male patients (from 3:1 in Japan up to 7:1 in the United States). At the time of renal biopsy, the majority of patients have acute or progressive chronic kidney injury. The mean Scr at the time of diagnosis ranges from 1.7 mg/dL (346) to 3.6 mg/dL (13).

Serum total IgG or IgG4 levels are elevated in 79% (13) to 90% (346) of patients. Approximately half of the patients have hypocomplementemia, with decreased C3, C4, or CH50 levels. Peripheral eosinophilia may occur (347). Renal imaging studies reveal different abnormalities, including multiple small low-attenuation lesions, mass lesions, bilaterally markedly enlarged kidneys with bilateral renal swelling, or diffuse thickening of the renal pelvis.

Pathologic Findings

**Light microscopy:** Histologic findings in renal biopsies and nephrectomy specimens include dense interstitial lymphoplasmacytic infiltrates with some eosinophils and variable degree of interstitial fibrosis in the majority of the cases (see Fig. 25.5A). Focal mononuclear cell tubulitis is common, and some biopsies may show mild focal plasma cell tubulitis (13). The cellular composition of inflammatory infiltrates changes with the progression of interstitial fibrosis; lymphocytes with plasma cells are predominant in early stages of fibrosis, whereas plasma cells become more prominent with increasing fibrosis. Inflammatory cell infiltrates are usually attenuated in extensive fibrosis (347). The interstitial fibrosis is usually zonal with clear demarcation between involved and uninvolved areas (Fig. 25.25A). The fibrosis often extends into the deep medulla and may infiltrate extrarenally, involving the renal capsule and retroperitoneal space. The pattern of interstitial fibrosis is characteristic: The collagenous bundles encircle nests of lymphocytes and plasma cells, resembling the “storiform” pattern in autoimmune pancreatitis. Some authors refer to this as the “bird’s-eye” pattern (347). The degree of interstitial fibrosis is variable in the biopsy specimens. Nephrectomy specimens with mass lesions show more fibrotic and less inflammatory areas at the center of the mass with more interstitial inflammation and less fibrosis at the periphery. These data indicate that it is very difficult to evaluate the degree of interstitial fibrosis and proportion of involvement of the renal parenchyma based on kidney biopsy findings alone; sampling error is common. Correlation with imaging studies should be performed in each individual case.

The main histologic feature of IgG4-related TIN is the presence of increased number of IgG4-positive interstitial plasma cells (see Figs. 25.5B and 25.25B). There is no clear quantitative approach available, but many authors agree that the presence of more than 10 IgG4-positive plasma cells per high-power field (HPF) in the densest infiltrates is a diagnostic criterion for IgG4-related interstitial nephritis (13,347). A detailed classification proposes that 11 to 30 IgG4-positive plasma cells per HPF should be considered as moderate increase, whereas more than 30 IgG4-positive plasma cells per HPF are marked increase (13). However, increased numbers of IgG4-positive interstitial plasma cells may be noted in other diseases, such as in anti–neutrophil cytoplasmic antibody (ANCA)–associated glomerulonephritis, diabetic nephropathy, idiopathic TIN, membranous glomerulonephritis, and lupus nephritis (348). Therefore, the presence of numerous IgG4-positive plasma cells in a renal biopsy specimen is not a specific diagnostic finding for IgG4-related TIN.

Several proposals to classify the pattern of interstitial fibrosis and inflammation have been made. The Mayo Clinic group proposes the following patterns of tubulointerstitial inflammation and fibrosis: pattern A, AIN with minimal interstitial fibrosis (less than 10%) without expansive interstitial process; pattern B, more dense interstitial inflammatory lesions with

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**FIGURE 25.25** Light microscopic findings in IgG4-related TIN. A: Zonal appearance of mixed interstitial inflammatory cell infiltrate in IgG4-related interstitial nephritis. Note the demarcation between the inflamed and uninvolved renal cortex. [H&E, ×40.] B: Numerous IgG4-positive plasma cells in the interstitial inflammatory cell infiltrate. (Immunoperoxidase, ×100.)
expansive interstitial fibrosis; and pattern C, collagen-rich paucicellular fibrosis (13). A four-tier classification of the interstitial fibrosis is proposed by a Japanese group: stage A, active cellular infiltration with fine fibrosis; stage B, active cellular inflammation with mild but distinct interstitial fibrosis; stage C, dominant interstitial fibrosis with mild cellular infiltration; and stage D, advanced interstitial fibrosis with little cellular infiltration (347). According to these authors, electron microscopy is the more valuable tool to classify the degree of interstitial fibrosis, when in the early stages, bundles of fine collagen fibrils are sparse among the infiltrating cells, whereas with more advanced fibrosis (stage C), interstitial-type collagen bundles encase each interstitial inflammatory cell. In the advanced stage (D), interstitial-type collagen bundles become thick, and interstitial inflammatory cells are sparse. Distinct collagen bundles are localized around fibroblasts, which are intermingled with inflammatory cells (347). Regarding the value of ultrastructural studies, one has to consider the problem of sampling error, particularly in a renal tubulointerstitial disease with zonal distribution of changes, because the specimen submitted for electron microscopy is usually small and may not be representative. Whether these ultrastructural findings are truly of diagnostic value awaits confirmation. Outside of the inflammatory lesions, the renal parenchyma usually is normal (13).

Glomeruli usually are unremarkable or show mild mesangial expansion. Several recent reports describe membranous glomerulonephritis in patients with IgG4-related TIN (349,350). Indeed, idiopathic or recurrent membranous glomerulonephritis is characterized by IgG4-predominant deposits along the glomerular capillaries (351,352). Even though this association between membranous glomerulonephritis and IgG4-related disease may be not random, the pathogenetic link between the two diseases is unclear.

No specific vascular lesions are identified that are associated with IgG4-related TIN (13,347).

**Immunofluorescence:** Immunofluorescence findings are characteristic. Granular TBM staining for IgG is present in the majority of cases (13) (Fig. 25.26). Notably, glomeruli usually do not show IgG staining. The TBM deposits contain predominantly IgG4 (13). TBM staining for both kappa and lambda light chains is present, often associated with some C3 staining as well. A small number of cases have C1q and IgM staining in the TBM. The TBM deposits are usually present in the areas of inflammation, but not in the normal areas, based on the analysis of nephrectomy specimens. The TBM deposits are more commonly found in specimens with more progressive fibrosis (13). Direct immunofluorescence is an excellent method to detect TBM immune complex deposits and the IgG4 dominance in these deposits, but in our experience, direct immunofluorescence to detect and enumerate the interstitial infiltrating IgG4-positive plasma cells is not the optimal method. A more sensitive immunoperoxidase methodology on paraffin sections should be used to quantify the infiltrating IgG4-positive plasma cells in tissue sections.

**Electron microscopy:** Electron microscopy has limited value in the diagnosis of IgG4-related TIN. Discrete electron-dense immune-type deposits are usually seen within the TBM (Fig. 25.27) (13,347). According to Yamaguchi et al. (347), electron microscopy is a useful tool to determine the degree of interstitial fibrosis (see above). Glomerular changes usually are nonspecific, except for rare cases of membranous glomerulonephritis.

**Diagnostic Criteria** As mentioned above, the diagnosis of IgG4-related TIN should not be made based on the morphologic findings alone. Several diagnostic criteria were proposed recently in order to render the diagnosis of this disease properly (Table 25.4). The Mayo Clinic group (13) proposes the following criteria for IgG4-related TIN: (a) histologic findings of plasma cell–rich TIN with greater than 10 IgG4-positive plasma cells per HPF in the most concentrated areas, TBM...
Involvement with characteristic histologic findings, including nests of lymphocytes and/or plasma cells; and extrarenal organ involvement with infiltrating IgG4-positive plasma cells greater than 40% and characteristic fibrosis surrounding nests of lymphocytes/plasma cells.

**TABLE 25.4** Diagnostic criteria of IgG4-related TIN proposed by two different groups

<table>
<thead>
<tr>
<th>Findings</th>
<th>Mayo Clinic group</th>
<th>Japanese Society of Nephrology&lt;sup&gt;a&lt;/sup&gt;</th>
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<tbody>
<tr>
<td>Light microscopy</td>
<td>Plasma cell–rich interstitial nephritis&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Dense lymphoplasmacytic infiltration with greater than 10 IgG4-positive plasma cells per HPF in the most concentrated areas and/or the ratio of IgG4-to IgG-positive plasma cells &gt;40%</td>
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<tr>
<td>Immunofluorescence</td>
<td>TBM immune complex deposits&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Characteristic fibrosis surrounding nests of lymphocytes/plasma cells</td>
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<tr>
<td>Immunohistochemistry</td>
<td>&gt;10 IgG4-positive plasma cells per HPF in the most concentrated areas</td>
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<tr>
<td>Other organ involvement</td>
<td>Autoimmune pancreatitis, sclerosing cholangitis, sialadenitis, inflammatory aortic aneurysm, retroperitoneal fibrosis, inflammatory mass in any organ</td>
<td>Extrarenal organ involvement with characteristic morphologic findings, including &gt;10 IgG4-positive cells per HPF in the most concentrated areas and/or the ratio of IgG4-to IgG-positive plasma cells &gt;40%</td>
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<tr>
<td>Imaging</td>
<td>Small peripheral low-attenuation cortical nodules, round- or wedge-shaped lesions, diffuse patchy involvement of the kidneys, diffuse marked enlargement of the kidneys by imaging studies; (c) hypovascular solitary mass in the kidney</td>
<td>Multiple low-density lesions on enhanced computer tomography</td>
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<td>Laboratory</td>
<td>Elevated serum IgG4 or total IgG levels</td>
<td>Hypervascular solitary mass in the kidney</td>
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<td>Hypertrophic lesions in the renal pelvic wall without irregularity of the renal pelvic surface</td>
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<td>Kidney injury (abnormal urinalysis, decreased kidney function)</td>
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<td>Hypocomplementemia</td>
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<td>Elevated serum IgE levels</td>
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<td></td>
<td>Elevated serum IgG4 levels &gt;135 mg/dL</td>
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</table>

<sup>a</sup>See the text for diagnostic criteria.

<sup>b</sup>Mandatory criterion.

These two proposed diagnostic algorithms are slightly different, but they both agree that the diagnosis of IgG4-related TIN cannot be made based on the morphologic findings alone and ancillary studies should always be performed.

**Differential Diagnosis** A plasma cell–rich interstitial inflammatory cell infiltrate should invariably raise the possibility of IgG4-related TIN, and immunoperoxidase stains for IgG and IgG4 should be performed to determine the number of infiltrating IgG4-positive plasma cells (and perhaps the ratio of IgG4/IgG-positive plasma cells). As mentioned previously, IgG4-positive plasma cells may occur in other forms of interstitial nephritis as well, not only in IgG4-related interstitial nephritis; therefore, the complex diagnostic criteria mentioned above should be considered. Forms of TIN commonly associated with numerous interstitial plasma cells include Sjögren syndrome; other autoimmune diseases such as lupus nephritis, ANCA-associated vasculitis, and HUVS; and a few cases of drug-induced interstitial nephritis and idiopathic interstitial nephritis. Occasionally, any form of interstitial nephritis can have many interstitial plasma cells. In our experience, sometimes, chronic pyelonephritis can become a differential diagnostic dilemma, particularly in a renal biopsy. In chronic pyelonephritis, the distribution of inflammation is frequently...
Pathogenesis The pathogenesis of IgG4-related disease in general and IgG4-related interstitial nephritis is poorly understood. Most of the available data are observational, and there is no good animal model to study the pathogenesis of this disease. Because of the elevated IgG4 levels in the circulation and in the affected tissue, some authors believe that IgG4-related disease is an autoimmune disease (353). Electron microscopy findings of electron-dense immune-type deposits in the TBM support this hypothesis (354). IgG4 production is controlled primarily by T-helper cells type 2 (Th2) via IL-4 and IL-13 production. Also, interleukin-10 (produced by regulatory T cells), IL-12, and IL-21 shift the balance between IgG4 and IgE production, favoring IgG4 (355,356). Some patients with IgG4-related disease have autoantibodies, including anti-pancreatic trypsin inhibitor, antilactoferrin, and anti-carbonic anhydrase antibodies (41).

An association between Helicobacter pylori (H. pylori) infection and IgG4-related disease has been proposed (357,358). A specific reactivity with a peptide, having homology with the plasminogen-binding protein of H. pylori, was identified in the serum obtained from patients with autoimmune pancreatitis (359). Also, reactivity in the serum from the same patients was found with ubiquitin-protein ligase E3 component n-recongin 2, an enzyme expressed in pancreatic acinar cells. No such reactivity was seen in control serum (359).

Okazaki et al. (360) proposed that the development of autoimmune pancreatitis involves a biphasic reaction, where the first step includes an initial response to autoantigens, such as carbonic anhydrase and lactoferrin, associated with the T-helper cell type 1 (Th1) type cellular immune response. Later, memory T cells, regulatory T cells, and Th2-type cells will predominate and induce increased IL10 production, which eventually will result in B-cell maturation and production of IgG4-producing plasma cells as well as TGF-β production, which will induce progressive fibrosis (360). Proteomic analysis of immune complexes in the serum from patients with IgG4-related disease identified a potential autoantigen, a 13.1-kDa protein, but detailed characteristics of this peptide are not yet available (361).

Several other hypotheses of IgG4-related disease pathogenesis have been advanced, including the possibility of enhanced response of Th2 cells to intestinal microflora (362).

Genetic factors also may play an important role in the pathogenesis of IgG4-related disease. The HLA haplotypes DRB1*0405 and DQB1*0401 are associated with increased susceptibility to IgG4-related disease in the Japanese population (363). In addition, DQB1 with substitution of aspartic acid at position 57 is associated with relapsed autoimmune pancreatitis in a Korean population (364).

Treatment and Outcome IgG4-related TIN usually responds well to steroid or immunosuppressive treatment. Thus, based on the Mayo Clinic data, approximately 90% of the patients who received steroids with or without additional immunosuppressive drugs showed improvement in the Scr levels (13). Approximately 12% of patients with initial response to steroid therapy experienced a relapse with increased Scr upon steroid taper. Approximately 10% of the patients initially treated with steroids progressed to dialysis or expired within 1 year after the kidney biopsy (13). Similar clinical follow-up data in patients with IgG4-related TIN treated with steroids were reported by the Japanese Society of Nephrology (346). Interestingly, patients with IgG4-related TIN showed significantly better response to treatment compared to patients with TIN not related to IgG4 (365).

In summary, there are still many unanswered questions in the recognition, pathogenesis, and proper treatment of IgG4-related TIN. The critical role of a renal pathologist is to consider this entity based on the morphologic findings and to suggest the possibility of IgG4-related TIN in order to initiate further workup and appropriate treatment.

**Systemic Lupus Erythematosus**

SLE is the most common form of tubulointerstitial disease associated with granular deposits of immunoglobulins and complement. Almost one half of the kidney biopsies from patients with SLE have such deposits. The inflammatory infiltrate is variable but includes large numbers of mononuclear cells and occasional neutrophils, with frequent plasma cells (18,366,367). Deposits are predominantly found in proximal tubules but can also be found in other segments of the nephron (368). The deposits include IgG, IgM, rarely IgA, and complement components C3 and C1q (369). The deposits can be found on various locations; interstitial side of the TBM, intramembranous, around peritubular capillaries, and in the interstitium. Rarely, tubulointerstitial immune complex disease may occur in patients with SLE in the absence of significant glomerular disease. We have found that the IgG subclass composition of the glomerular and extraglomerular immune complex deposits is different (23). Thus, IgG subclass distribution was discrepant between glomerular and TBM deposits in 36/52 biopsies and between glomerular and vascular deposits in 27/40 biopsies. Interstitial inflammation did not correlate with the presence of tubulointerstitial immune complex deposits or with the distribution of IgG subclasses in the TBM, but the IgG subclass staining correlated with C1q staining in all the three compartments. These data suggest that immune complex deposits at different sites do not represent the same preformed immune complexes from the circulation (23). It is likely that glomerular and tubulointerstitial immune complex deposits in lupus nephritis form through different pathogeneses as a response to different antigens and some of them probably form in situ. It has been suggested that immune response and tubulointerstitial inflammation in lupus nephritis are mediated by in situ B cells (370). Renal disease, including interstitial nephritis in SLE, is discussed in Chapter 14.

**Sjögren Syndrome**

Sjögren syndrome is an immunologic disorder characterized by progressive destruction of the exocrine glands leading to mucosal and conjunctival dryness (i.e., sicca syndrome) associated with autoimmune disease affecting various organs. The disease is discussed in detail in Chapter 14.

Renal changes consist of interstitial inflammation with mononuclear cells including histiocytes, plasma cells, and lymphocytes. Plasma cells may occasionally be abundant (see Fig. 25.3). Several cases have been reported in which immunofluorescence and electron microscopy revealed immune deposits along the TBM. However, in our experience, and based on literature review, it appears that most cases do not have obvious tubulointerstitial immune complex deposits detectable...
by immunofluorescence and/or electron microscopy. Patients with Sjögren syndrome are prone to develop lymphoma, in particular, marginal zone lymphoma (mucosa-associated lymphoid tissue [MALT] lymphoma). The lymphoma primarily involves the salivary glands and head and neck lymph nodes. Involvement of the kidney by lymphoma in Sjögren syndrome is exceptional (371). For more details, see Chapter 14.

**Membranoproliferative Glomerulonephritis/Dense Deposit Disease**

Membranoproliferative glomerulonephritis occasionally may manifest with granular deposits of immunoglobulins or complement in TBM. In dense deposit disease (a form of C3 glomerulopathy), the characteristic very electron-dense ribbon-like deposits may occasionally be seen along the TBM as well.

**Mixed Cryoglobulinemia**

Mixed cryoglobulinemia usually manifests with proliferative glomerulonephritis, and some patients can present with focal interstitial inflammation, including mononuclear cells, edema, and tubular cell injury associated with granular IgG and C3 deposits in the TBM (285). In our experience, TBM deposits in cryoglobulinemic glomerulonephritis are rare.

**Membranous Glomerulonephritis**

A few patients with membranous glomerulonephritis have tubulointerstitial inflammation with monocytes, plasma cells and eosinophils, and granular deposits of immunoglobulins and complement in the TBM. As mentioned above, many of these patients probably have IgG4-related disease or other autoimmune disease–associated interstitial nephritis and membranous glomerulonephritis.

**HypoComplementemic Urticarial Vasculitis Syndrome**

HUVS is an uncommon autoimmune disease resembling SLE. The disease is characterized by recurrent urticarial lesions, complement activation with marked decrease in C1q, anti–Clq antibodies, arthritis, and frequently glomerulonephritis, obstructive lung disease, and other symptoms (372,373). Renal involvement is usually immune complex glomerulonephritis, resembling membranoproliferative glomerulonephritis; sometimes, crescents may also be found. Interstitial nephritis may also occur but usually accompanying the immune complex glomerulonephritis (374,375). A recent publication from Japan describes prominently elevated serum IgG4 level in a patient with HUVS, raising the possibility of an overlap between IgG4-related disease and HUVS (376).

**Familial Immune Complex Tubulointerstitial Nephritis**

Familial immune complex TIN is a syndrome characterized by familial occurrence of tubulointerstitial immune complex disease, often with membranous glomerulonephritis. Patients present with diarrhea, dermatitis, proteinuria or the nephrotic syndrome, and renal insufficiency (323). TIN is characterized by a mononuclear cell infiltrate, variable tubular atrophy, and interstitial fibrosis. By immunofluorescence, granular deposits of immunoglobulin and complement are found in the TBM. Chronic tubulointerstitial disease and villous atrophy of the small intestine were found in two first cousins (323). Both had proximal tubule dysfunction and malabsorption syndrome with granular deposits of IgG and C3 in intestinal epithelial cells, and their sera (IgG) were reactive with intestinal epithelial antigen. Membranous glomerulonephritis was detected in only one of these patients; the other had normal glomeruli.

**Giant Cell Tubulitis With Tubular Basement Membrane Immune Complex Deposits**

Recently, several cases of giant cell tubulitis with TBM immune complex deposits were described (84,377–379). Morphologically, this entity is characterized by acute TIN with numerous giant cells, associated with tubules and TBM immune complex deposits. The TBM deposits contain IgG and C3. Interestingly, all patients had cardiac surgery (aortic valve replacements with mechanical valves, (377); mitral valve replacement with a mechanical valve (378); nonspeciﬁed mitral valve repair, (379); multiple cardiac surgeries, (84)) preceding the onset of TIN. The majority of reported patients are adults, but one 15-year-old young patient has been described as well (84). The pathogenesis of this disease is unclear. Hypocomplementemia is common, similar to IgG4-related interstitial nephritis, but no case was worked up for IgG subclass deposition in the TBM, serum IgG4 levels, or other stigmata of IgG4-related disease.

**Other Miscellaneous Diseases**

Rarely, patients with various types of crescentic glomerulonephritis (295,298), graft versus host disease (380), postinfectious glomerulonephritis, shunt nephritis, hepatitis B, syphilis (298), or fibrillary glomerulonephritis (381) may show TIN with deposits of immunoglobulins or complement in the interstitium, the TBM, or both.

**Pathology of Tubulointerstitial Nephritis With Immune Complexes**

The kidney size varies and may be normal, enlarged, or reduced, depending on whether TIN is acute or chronic. The interstitial infiltrate is multifocal or diffuse and is composed predominantly of lymphocytes, monocytes, and plasma cells (see Fig. 25.23A) (298). Neutrophils may be present. By immunofluorescence, granular deposits of immunoglobulins, often with complement, are seen in the TBM, the interstitium, or both (see Fig. 25.23B) (112,298). By electron microscopy, dense deposits are usually present in the same location (see Fig. 25.23C). Overall, dense deposits are more frequently seen in biopsies of patients with SLE. The pathology of IgG4-related interstitial nephritis has been detailed previously in this chapter. We would like to reiterate that one has to be careful evaluating the immunofluorescence and electron microscopy findings for TBM deposits because C3 deposits are commonly seen along the TBM, particularly in biopsies with chronic injury and tubular atrophy. Also, granular cell debris in the TBM may mimic electron-dense immune-type deposits on electron microscopy if the TBM is examined only under low magnification (see Fig. 25.11).

Tubular atrophy and interstitial fibrosis are usually absent from early lesions, but are present in patients with chronic renal insufficiency. In primary TIN, glomeruli are normal or show nonspecific changes. In secondary TIN, glomeruli may show crescentic, membranous, proliferative, exudative, or segmental changes according to the primary disease. Arteries and arterioles are normal or show hypertensive or age-related changes.
Pathogenesis of Tubulointerstitial Nephritis With Immune Complexes

To establish that TIN is mediated by immune complexes, the same basic requirements delineated for anti-TBM nephritis apply, except that deposits of antibody, usually IgG, and complement have a granular configuration and localize in the TBM and interstitium, and antigen targets differ and are usually unknown. Because only some of the requirements can be satisfied, the diagnosis of human TIN with immune complexes is also inferential and based on data derived from experimental models.

In an experimental model developed by Hoyer (382), the putative antigen is Tamm-Horsfall glycoprotein, synthesized and secreted by epithelial cells of the thick ascending limb of Henle. Rats and mice immunized with Tamm-Horsfall glycoprotein develop granular TBM deposits of immunoglobulins and complement, electron-dense deposits along the base of tubular cells of thick ascending limb of loops of Henle, and tubulointerstitial mononuclear cell infiltration (382–384). The distribution of THP varies with species, and in mice, immune deposits also are formed in the TBM of distal convoluted tubules (383). Deposits are formed in situ by interaction of circulating antibodies with antigen present on the abluminal side of the tubular cells. Ureteral obstruction in mice promotes the localization of such deposits in extratubular sites and apparently contributes to interstitial inflammation and scarring (385). Tamm-Horsfall glycoprotein does elicit weak antibody response in humans (386), and a component of interstitial inflammation may be related to extravasation of this glycoprotein into the interstitium. Antibodies to *E. coli* that are cross-reactive with Tamm-Horsfall glycoprotein (387) and some anti-DNA antibodies cross-reactive with heparan sulfate (388) provide examples in which autoimmunity may contribute to TIN mediated by immune complexes. However, the exact role of Tamm-Horsfall glycoprotein in humans is still unclear, and whether Hoyer’s animal model has a human counterpart is unknown (389,390).

In human TIN with immune complexes, antigens involved, with few possible exceptions (391,392), are unknown. Antibodies are usually of the IgG class and, less frequently, of other classes (285). As discussed above, in IgG4-related interstitial nephritis, a specific subclass of IgG (IgG4) appears pathogenic. Immune deposits may result from immune complexes formed in the circulation, or they may result from local interaction between free antibody and antigen in tissues. Both mechanisms may be operational in SLE, in which immune complexes activate complement, as judged by the presence of C3 and terminal components of complement in electron-dense deposits (369). Complement also can be activated by mechanisms other than those involving immune complexes. For example, ammonia can trigger the alternative pathway of complement activation and cause tubulointerstitial inflammation and injury (393). Based on experimental models, some forms of TIN may require complement activation by antibody, release of chemoattractants, activation of leukocytes, and release of proteases and toxic oxygen radicals (282). Whether such mechanisms play a pathogenic role in human TIN with immune deposits awaits demonstration, particularly because the degree of interstitial inflammation does not always correlate well with the degree of tubulointerstitial immune complex deposition (23).

Tubulointerstitial Nephritis With Cellular (Mainly T-Cell) Mechanisms

TIN in which T-cell mechanisms have been implicated are probably more common than appreciated and include drug reactions; reactions to allograft antigens; systemic disease with renal involvement; reactions to renal localization of various microorganisms, foreign bodies, and crystals; renal involvement in sarcoidosis; and most forms of progressive renal disease.

Primary Tubulointerstitial Nephritis With Cellular (T-Cell) Mechanisms

Allograft Rejection

Most allograft rejections represent a form of TIN that results from disparity of the major histocompatibility complex (MHC) antigens between the recipient and the donor. Allograft rejection is covered in Chapter 29.

Tubulointerstitial Nephritis With Uveitis

The syndrome of tubulointerstitial nephritis with uveitis (TINU) was described in 1975 by Dobrin et al. (394). The two patients reported presented with acute renal failure owing to TIN, with predominance of eosinophils in the infiltrate associated with anterior uveitis and granulomas in bone marrow and lymph nodes. These patients were Caucasian females, 14 and 17 years of age. Both recovered renal function, but one required treatment with corticosteroids for about 1 year. The syndrome has been reported mainly in children (395–397), rarely in adults (398–400). It may occur in siblings with identical haplotypes (401) and monozygotic twins (395). Males are affected more often than females (396).

Patients may present with one or more of the following features: proximal tubule dysfunction, including Fancconi syndrome, renal insufficiency and proteinuria, renal failure, and ocular symptoms (402,403). Urinary beta-2 immunoglobulin levels are frequently very high (396). Uveitis may precede or follow renal dysfunction or acute renal failure. Elevated serum levels of autoantibodies against modified C reactive protein may be useful in the diagnosis (403a).

The kidney shows inflammatory infiltrates comprising mononuclear cells, including many lymphocytes and fewer plasma cells and macrophages (Fig. 25.28). Eosinophils, prominent in the initial cases presented by Dobrin (394), are less commonly seen by others. By immunofluorescence, immunoreactants usually are not found in the TBM, and repeat or late biopsies may show variable amounts of interstitial fibrosis and fewer inflammatory cells. Inflammatory cells are mostly T cells, but the predominance of a CD4+ or CD8+ phenotype varies (404,405). The proximal tubules show the greatest degree of alterations, with circular arrays of infiltrating mononuclear cells. Acute tubular epithelial injury and flattening of the tubular epithelium often occur. Noncaseating granulomas may be found in bone marrow, lymph nodes, and the kidneys (394). We have seen a similar case with giant cells in the kidney biopsy; in such patients, an underlying sarcoidosis should always be considered. Serial kidney biopsies from three pediatric patients showed that acute inflammation diminishes after treatment with prednisone, but the chronic kidney injury increases (406). Morino et al. (401) reported two sisters with TIN and chronic sialadenitis, one of them with recurrent uveitis; this patient also had an immune complex–mediated glomerulonephritis, which is not a component of the syndrome.
Sarcoidosis is a chronic disorder, involving multiple systems and characterized by accumulation of lymphocytes and other mononuclear cells forming noncaseating epithelioid granulomas. Most patients present with enlarged lymph nodes, cough, weight loss, fever, dyspnea, polyuria, increased serum calcium concentrations, and occasionally with proteinuria and microscopic hematuria (26,419). Sarcoidosis is more common in males and in blacks, and the peak incidence occurs in the second and third decades of life (26,419). Serum levels of angiotensin-converting enzyme (ACE) are frequently high. Renal involvement, manifested by renal dysfunction, is rare and occurs in only 1% to 2% of all patients with sarcoidosis. For example, of 75 cases of sarcoidosis reviewed by Richmond et al. (420), only 1 patient had TIN (1.3%). However, this low incidence of clinically manifest renal disease is misleading, because in autopsy series, an incidence of 9% to 25% has been reported (419,421,422). A more recent publication from Heidelberg, Germany, describes 46 patients with sarcoidosis and 48% of them had renal abnormalities (422). The patients underwent renal biopsies—one of these 10 patients had nephrocalcinosis, and only 3 patients had interstitial nephritis; 1 patient had IgA nephropathy. Five of the six patients with nephrocalcinosis had hypercalcemia. These authors found a positive correlation between serum ACE levels and granuloma formation in the renal tissue (422). The most common renal complication in patients with sarcoidosis is related to disturbance in calcium metabolism. Hypercalcuria is present in 50% to 60% of patients with sarcoidosis, and 10% to 20% of them also have hypercalcemia (172,423). Sometimes, AKI may be the first clinical symptom in sarcoidosis interstitial nephritis (424,425), including cases of familial sarcoidosis (426).

In renal sarcoidosis, granulomas are abundant and usually sharply delineated with many epithelioid cells and giant cells (see Fig. 25.4B). The granulomas are associated with an inflammatory infiltrate of mononuclear cells, including many plasma cells and lymphocytes (172,423). Differentiation of sarcoid granulomas from other granulomas causing granulomatous interstitial nephritis, such as drug-induced granulomas, can be difficult; however, drug-induced granulomas may be less distinct (see Fig. 25.4A). Calcifications may occur in and around the interstitial granulomas (Fig. 25.29). Changes of renal sarcoidosis can be focal in nature, and characteristic lesions can be missed in a small-needle core biopsy. Inconclusive renal biopsies...
with only nonspecific findings are frequent in patients with sarcoidosis and AKI. The presence of granulomatous interstitial nephritis in renal biopsy, although classic, is uncommon (427). ACE levels are often high in many patients' sera (428), and they can also be detected in the giant cells and epithelioid cells in the granulomas. Unfortunately, this methodology is not commonly used by renal pathologists to differentiate granulomas in sarcoidosis; we could find only one case report describing ACE-positive epithelioid granulomas in a renal biopsy from a patient with sarcoidosis (429). For the same reason, the specificity of this methodology in renal biopsies cannot be assessed. Renal function may improve after early corticosteroid therapy; however, Scr rarely returns to normal, and long-term follow-up has shown that some patients develop permanent renal dysfunction (430) or chronic renal failure (172,423,431). Current views on the pathogenesis of sarcoidosis implicate an immune mechanism whereby T cells and macrophages are involved (423). Sarcoidosis may recur in renal transplants (432,433).

Granulomatous Tubulointerstitial Nephritis

A list of agents and conditions that can be associated with granulomatous interstitial nephritis is given in Table 25.2. This list is always incomplete because additional causes of granulomatous interstitial nephritis are constantly reported. All these causes should be carefully considered in the differential diagnosis, but one has to remember that, occasionally, granuloma formation can be associated with any etiologic agent causing interstitial nephritis.

The most common cause of granulomatous TIN is exposure to drugs. This was discussed previously in this chapter. For example, in the report by Mignon et al. (434) of 32 patients studied, 28% were owing to drugs, 16% to granulomatosis with polyangiitis (Wegener granulomatosis), and 9% each to tuberculosis and sarcoidosis. Most infectious granulomatous tubulointerstitial nephritides other than tuberculous are caused by infection with bacteria, fungi, or parasites (discussed in Chapter 24). These data may vary in different regions. Joss et al. (26) reported that in Glasgow, the majority of biopsy-proven granulomatous interstitial nephritides (50%) were idiopathic, whereas drug-induced represented only 6% of the cases. Bijol et al. (24) from the Brigham and Women's Hospital in Boston reported that 44.7% of their granulomatous interstitial nephritis cases were drug associated. Sarcoidosis-related granulomas were seen in 28.9% of cases, and 10.5% of the biopsies were diagnosed as idiopathic granulomatous interstitial nephritis (24).

Oxalosis or hyperoxaluria after small intestine bypass is associated with granulomatous reaction to deposited oxalate crystals. In general, the inflammatory reaction is discrete, and granulomas are few and are of the giant cell foreign body type. Other particles or crystals, as may occur in intravenous drug abuse and gout, also can result in granulomatous TIN. Interstitial granulomas may occur in ANCA-associated vasculitis, including granulomatosis with polyangiitis (Wegener granulomatosis). The number of granulomas varies, but in general, few are found in kidney biopsies (435). The granulomas in granulomatous vasculitis are usually localized around glomerular crescents and/or involve arteries.

Several cases of the so-called idiopathic granulomatous interstitial nephritis have been reported (24–26,436). Some authors consider granulomatous idiopathic interstitial nephritis with sarcoid features as cases of isolated renal sarcoidosis (25). They base their assumption on elevated ACE levels in some patients and a positive response to steroids. However, steroid treatment is not always successful in idiopathic granulomatous interstitial nephritis (25). Interestingly, a case of a good response and recovery of renal function following treatment with an antibody to tumor necrosis factor alpha (infliximab) was described (436).

Secondary Tubulointerstitial Nephritis With Cellular (Mainly T-Cell) Mechanisms

Tubulointerstitial Nephritis Associated With Progressive Nephropathies

Chronic interstitial disease is present in almost all forms of progressive glomerular and vascular disease of the kidney. This subject has been reviewed by several groups, including Pichler et al. (437), Strutz and Neilson (438), and Dodd (439), and is considered here because cell-mediated immunity appears to play a major role in its pathogenesis. Chronic progressive TIN has a diverse etiology, ranging from infection and drugs to immune-mediated, hematologic, metabolic, and hereditary disorders and even chronic ischemia. In other words, several different diseases may result in a common pathologic pathway of progressive interstitial fibrosis and tubular atrophy. Experimental studies revealed several common factors and mechanisms responsible for chronic tubulointerstitial injury, such as activation of peritubular fibroblasts, leukocyte infiltration, release of inflammatory cytokines and growth factors at affected regions, epithelial-mesenchymal transition of tubular epithelium, and apoptosis. The execution of each is mediated by a number of local stimuli, such as filtered albumin, chronic hypoxia, and oxidative stress, in addition to cytokines and growth factors (reviewed 440). Epithelial to mesenchymal transition of tubular epithelial cells may be mediated by hypoxia-inducible factor (HIF) signaling, including HIF-1 and HIF-2 (441). However, as pointed out earlier, the true existence and role of epithelial-mesenchymal transition in kidney fibrosis have been recently questioned (51,52).

Tubulointerstitial inflammation plays a significant role in the pathogenesis of chronic kidney injury (31,442). During the inflammatory phase, inflammatory cells accumulate in the interstitium in response to deposition or local formation of immune complexes or in response to cytokines and other mediators released from injured glomeruli into the filtrate and subsequently to the tubules. Cytokines may also exit the glomeruli through the Bowman capsule, the vascular pole, and the efferent arteriole (437). In response to cytokines and other mediators, adhesion molecules (443) and growth factors (444) are expressed or overexpressed, and inflammatory cells, mostly lymphocytes and macrophages, accumulate in the interstitium. In patients with proteinuria, proximal tubular cells, when exposed to high concentration of proteins, may produce proinflammatory and profibrotic factors. The activation of nuclear factor kB results in the up-regulation of a variety of cytokines and chemokines, overexpression of adhesion molecules, and interstitial infiltration of inflammatory cells. In many cases, fibrosis is promoted by release of transforming growth factor–β, which induces myofibroblast formation and collagen deposition (442).

Pathology of Tubulointerstitial Nephritis With Cellular (Mainly T-Cell) Mechanisms

The kidneys are usually enlarged and show variable edema, and the inflammatory infiltrate consists of lymphocytes, plasma cells, and few eosinophils. Lymphocytes account for more than
50% of the infiltrating cells, and monocytes/macrophages and plasma cells account for most of the remainder (445). Neutrophils may be seen, but they are infrequently present in large numbers. Granulomas may be found (see above). Tubulitis, tubular cell injury, regenerative epithelial changes, and variable numbers of casts are seen. Tubular atrophy and interstitial fibrosis are variable and more likely to be present in patients who have biopsies late in the course of their disease or in chronic forms. By immunofluorescence, deposits of immune complexes are absent from glomeruli or tubules. Vessels are normal or show hypertension and age-related changes. In secondary TIN with T-cell mechanisms, the glomeruli or vessels may show active, healing, or healed lesions characteristic of the underlying glomerulonephritis and vasculitis.

**Pathogenesis of Tubulointerstitial Nephritis With Cellular (Mainly T-Cell) Mechanisms**

The mechanism by which inflammatory cells induce fibrosis has been reviewed (45,46,438) and will be discussed here briefly. To establish that TIN is mediated by cellular mechanisms, it is necessary to demonstrate that the transfer of T cells, but not of serum, from a donor with TIN to a normal syngeneic recipient results in TIN in the recipient of T cells or that neonatal thymectomy obviates the expression of TIN (446). Because studies of this type cannot be performed with humans, the diagnosis of cell-mediated TIN is inferential and based on animal models in which T cells have been demonstrated to have a pathogenic role.

Mononuclear cells can mediate TIN by two types of reactions (447). The first, delayed-type hypersensitivity, involves prior exposure and sensitization of the host and is caused by CD4+ T cells and macrophages, resulting in production of various lymphokines and a granulomatous reaction. Interstitial lymphocytes interact with monocytes/macrophages, with endothelial cells, and possibly with tubular epithelial cells (448) in antigen presentation, resulting in a delayed-type cell-mediated reaction. IFN-γ augments but is not a necessary requirement for up-regulation of class I and class II molecule expression in renal tubules (449). Some drug reactions and sarcoidosis appear to result from this mechanism. The second, cytotoxic T-cell injury, requires no prior sensitization and involves CD4+ T cells and CD8+ T cells. Whether a diffuse cellular infiltrate or a granulomatous inflammation develops is also determined by the interplay of cytokines brought into the interstitial microenvironment by T cells (446).

The mechanism of interstitial inflammation involves several biologic events, as discussed previously. Briefly, CD4+ T cells become activated by cells expressing class II MHC antigens (450), including tubular epithelial cells (451). Activated T cells, monocytes/macrophages, and renal tubular epithelial cells release chemokines and cytokines (e.g., macrophage colony-stimulating factor [M-CSF], platelet-derived growth factor [PDGF], and TGF-β) that induce chemotaxis of cells to inflammatory sites (315,326,444) and various enzymes that degrade collagens and facilitate fibroblast motility (452). It is now evident that renal tubular epithelial cells are a major site of M-CSF production. Therefore, activated/injured tubular epithelial cells in interstitial nephritis, in turn, may further attract macrophages into the kidney and interstitium, aggravating the disease process (35,36). TGF-β and PDGF activate fibroblasts (453), enhance collagen deposition, and promote fibrogenesis (45–47). TGF-β was thought to have an important role in the induction of tubular epithelial cell/mesenchymal transdifferentiation, but the pathogenetic significance of this in vivo is still debated (51). Other cytokines (IL-1, TNF-α, IFN-γ) modulate inflammation and fibrogenesis (454).

**TUBULOINTERSTITIAL NEPHROPATHY ASSOCIATED WITH METABOLIC DISORDERS OR MONOCLONAL GAMMOPATHIES**

Tubulointerstitial nephropathy associated with metabolic disorders is reviewed in Chapter 27. Tubulointerstitial nephropathy associated with monoclonal gammopathies is reviewed in Chapter 22.

**TUBULOINTERSTITIAL NEPHROPATHY ASSOCIATED WITH HEAVY METAL EXPOSURE**

Exposure to heavy metals results in tubular dysfunction and acute or chronic renal disease. The nephropathies caused by chronic exposure to the most abundant toxic metals—lead, cadmium, and mercury—are considered here in some detail; other nephropathies associated with heavy metal exposure are mentioned briefly. Diagnosing chronic heavy metal exposure–associated nephropathy is quite difficult, and the condition is probably frequently overlooked. Contaminating food supply (such as seafood) and possibly also drinking water (possible well water contamination in areas of fracking [hydraulic fracturing during natural gas/petroleum exploration]) is a growing concern and can potentially be the source of low-level chronic heavy metal exposure to certain populations (455). Acute tubular toxicity of heavy metals is discussed in Chapter 26.

**Lead Nephropathy**

Lead exposure in the form of inhaled fumes and dust is an occupational illness for industrial workers (i.e., painters, printers, welders, foundry workers, and electric storage battery makers). In the form of dust and contaminating fluids and surfaces, it is still of some risk to the general population, in spite of banning lead as an additive in gasoline (456). Soil and paints containing lead are sources of lead exposure, particularly for children (457). Absorbed lead is widely distributed, but the principal sites of long-term storage are the bones, in which 94% of the lead in the body is found. This storage site constitutes a slow-exchange pool, and the biologic half-life of lead in bone is about 16 years (458). Another 4% is present in the blood, tissue fluids, and soft tissues, and these constitute a rapid-exchange pool. The remaining 2% is distributed between actively exchanging parts of the skeleton and soft tissues. Chronic lead intoxication has been widespread, and its history and effects on health are appreciated and well documented as a result of contamination of foods and as an occupational hazard of mining and smelting operation as early as 2500 BCE (459,460). An epidemic of childhood lead poisoning in Queensland, Australia, established lead nephropathy as a recognized clinical and pathologic entity (460,461).
Clinical Presentation

The clinical diagnosis of lead nephropathy is based on history of exposure, evidence of renal dysfunction, and a positive calcium disodium edetate (ethylenediaminetetraacetic acid [EDTA]) mobilization test. The test measures urinary excretion of lead after two 1-g doses of EDTA 12 hours apart (462). The test suggests lead nephropathy if excretion of lead is greater than 650 mg in 24 hours. Because the half-life of circulating lead is about 1 month, the test reflects only recent exposure (457), and the result can be normal for patients with chronic lead toxicity (457,462). The lead concentration can also be measured in tissues (primarily bone) by x-ray fluorescence and neutron activation analyses (458). In addition to its use as a diagnostic test, EDTA has also been advocated as a therapeutic agent (457,462). EDTA causes disruption of the lead inclusions and may contribute to their removal from tissues.

Many studies have confirmed a relationship between lead exposure and chronic renal disease (462–464). However, a well-controlled, prospective study comparing two groups of patients, one with high (more than 100 mg/dL) and the other with low (less than 40 mg/dL) lead concentrations in the blood, failed to show significant differences in blood pressure and in various tests of renal function between these two groups 17 to 23 years after chelation therapy (465). On the other hand, a study from Taiwan recently examined the effect of environmental lead exposure on the progression of chronic renal disease and found that even low-level environmental lead exposure is associated with progressive renal insufficiency (463). One hundred and twenty-one patients were included in the study with a baseline creatinine level between 1.5 and 3.9 mg/dL. Seventeen patients doubled their baseline Scr volume within the follow-up period of 48 months. Blood lead levels and body lead burden at baseline were the most important risk factors to predict progression of renal insufficiency. None of the patients had a history of lead exposure, and all of them had blood lead levels and body lead burden above acceptable levels (463).

Lin et al. (455) demonstrated that even low-level environmental lead exposure accelerates progressive diabetic nephropathy in patients with diabetes mellitus type 2. Thus, thirty patients with type 2 diabetes and diabetic nephropathy (Scr of 1.5 to 3.9 mg/dL) and high-normal body lead burdens (80 to 600 μg) were randomly divided into two groups and received either lead chelation therapy with calcium disodium EDTA weekly until body lead burden fell to less than 60 μg or placebo. The rate of decline in GFR in the chelation group was significantly lower as compared to the control group during a 12-month observation period, suggesting that lead chelation therapy can decrease the rate of diabetic nephropathy progression in patients with lead exposure (455).

Staessen et al. (466) investigated the effects of lead exposure in the general population and found that patients with decreased renal function had increased lead content in the blood and that the decrease in renal function was proportionate to increased lead concentration in the blood. Because of the nature of their study, they could not conclude whether lead exposure resulted in impaired renal function or whether impaired renal function caused increased concentration of lead in the blood. Chronic lead intoxication is manifested by proximal tubular defects, and decreased glucose reabsorptive capacity is an early indicator of tubular cell injury (467). Most patients have recurrent gout, hyperuricemia, and hypertension (468). Whether hypertension and hyperuricemia are caused by lead exposure, however, is controversial (457,459). Both increased uric acid levels and hypertension are more common in patients with renal insufficiency; therefore, it is difficult to decide whether these are secondary to the lead exposure itself or rather to the subsequent chronic renal injury. However, several studies support the fact that lead can cause decreased renal uric acid excretion and uric acid deposition in the kidney, which may be one important factor in the development of chronic lead nephropathy (468). Also, long-term accumulation of lead in the body is probably an independent risk factor for the development of hypertension (468).

Pathologic Findings

The kidneys are reduced in size, show a finely granular surface with reduction of the cortex, and may weigh one third of normal (461). There is variable multifocal tubular atrophy, tubular loss, and interstitial fibrosis (461,469). Nuclear inclusions seen in acute lead nephropathy (see Chapter 26) are not a common feature. Glomeruli are normal (469), and arteries and arterioles demonstrate medial thickening and luminal narrowing, probably related to hypertension. Urate, in the form of microtophi, may be seen in the medulla (461). Immunofluorescence studies are noncontributory or show only nonspecific findings. The glomeruli and vessels may be spared, except in patients with ESRD, whose kidneys may show features of nephrosclerosis because of the frequently severe hypertension in these patients.

Etiology and Pathogenesis

The pathogenesis of lead nephropathy is not completely understood. Lead in fluids is bound to lead-binding proteins and is taken up by epithelial cells by membrane binding and possibly by passive transport; absorbed lead accumulates preferentially in proximal tubular cells (469,470). A cleavage product of α₂-microglobulin is the principal component of complexed lead that makes Pb₂⁺ available to enzymes (Δ-aminolevulinic acid dehydrase) and mediates intranuclear transport and chromatin binding, resulting in changes in gene expression. Lead interacts with renal membranes and enzymes; disrupts energy production, calcium metabolism, and glucose homeostasis; and interferes with ion transport. Oxidative stress most likely plays a significant role in the pathogenesis because serum levels of oxidative stress markers show a close correlation with lead exposure levels (470). It appears that urine level of alphaglutathione S-transferase, a marker of proximal tubular injury, may be an early marker of lead nephrotoxicity (470). The clinical usefulness of this marker needs further confirmation.

Cadmium Nephropathy

Cadmium exposure from inhalation of cadmium oxide dust or cadmium fumes is an occupational illness (456) that occurs in the manufacture of pigments, plastics, electric storage batteries, and metal alloys. In the general population, exposure occurs by the oral route through contaminated water or food or inhalation of indoor dust contaminated with cadmium (471). Cigarette smoking is another potential source of exposure, because cadmium aerosol, produced during smoking, facilitates absorption of the metal. The kidney content of cadmium is greater in smokers than in nonsmokers (472). Once absorbed, cadmium binds avidly to metallothionein. Cadmium is stored mainly in
Clinical Presentation
Cadmium toxicity is manifested by increased excretion of high and low molecular weight proteins, such as β2-microglobulin (475), kidney-derived antigens, enzymes, prostanoids, glycosaminoglycans, sialic acid, glucose, and amino acids or the full complement of substances seen in the Fanconi syndrome (476). Subclinical changes in tubular function also occur in the general population above a threshold excretion of urinary cadmium of 2 mg in 24 hours (476). Once manifested, renal injury tends to be progressive, even if exposure is discontinued (477,478). In addition to irreversible dysfunction of proximal tubules, excess cadmium exposure is also known to cause hypercalcuria, nephrolithiasis, and osteomalacia. It has been demonstrated that for each doubling of urinary cadmium concentration, the relative risk for mortality increases by 17% (473). Nogawa (479) reported low-level prolonged environmental exposure to cadmium through contaminated water in the Kakehashi River basin in Japan. Patients in this area suffered from Itai-Itai disease (i.e., ouch-ouch disease), with bone pain from osteomalacia. Hypertension is present in patients with cadmium toxicity (480), but whether cadmium causes hypertension is controversial (472). A study from Sweden examined the effects of occupational and non-occupational exposure to cadmium on the development of ESRD in a population working in and/or living near a cadmium battery factory (475). They found a 2.3-fold increase in the ratio of ESRD in the population with occupational exposure and a 1.4-fold increase in the patients with low exposure living between 2 and 10 km from the cadmium battery factory. A cross-sectional analysis of 14,778 adults in the United States showed that subjects in the highest quartile of blood cadmium (greater than 0.6 µg/L) were almost two times more likely to exhibit albuminuria (greater than 30 mg/g creatinine) and 32% more likely to have reduced GFR (less than 60 mL/min/1.73 m²) (481). Epidemiologic evidence suggests higher susceptibility for persons with diabetes mellitus to develop cadmium-induced kidney injury. A study of 122 adults between 18 and 85 years of age in Australia, who were exposed to cadmium by consuming seafood, found a statistically significant correlation between urinary cadmium levels and albuminuria in individuals with type 2 diabetes, but not in nondiabetic individuals (482). A similar trend was observed in 820 Swedish women, without evidence of environmental cadmium exposure, between the ages of 53 and 64 (483). Increased urinary or blood cadmium levels potentiated diabetes-induced effects on kidney. Even in nondiabetic women, cadmium caused increased urinary acetyl-beta-D-glucosaminidase excretion, at lower cadmium levels than previously documented (483). Cadmium exposure has also been associated with a greater risk of kidney stone formation not only in occupational exposure studies but in the general population as well (484).

Pathologic Findings
Very little is known about the pathologic findings in chronic cadmium nephrotoxicity. Yasuda et al. (485) reported 15 cases of Itai-Itai disease. The kidneys were red-brown, had a granular surface described as sandpaper-like, were decreased in size, had a hard consistency, and weighed about 60 g each. Microscopically, there were extensive tubular atrophy and interstitial fibrosis involving preferentially the outer cortex. Inflammatory cells were present in small numbers. Some degree of glomerular sclerosis was present. However, five patients in the autopsy series of Smith et al. (486) and three patients in the series of Kazantzis et al. (487), including one autopsy case, showed no significant renal pathology. As judged by excessive mortality from chronic renal failure in areas of environmental cadmium pollution, tissue changes may be proportionate to the quantity of cadmium detected in the tissue (488).

Etiology and Pathogenesis
The pathogenesis of chronic cadmium nephrotoxicity is under investigation. Once absorbed, cadmium is initially deposited in the liver, where it is bound to metallothionein-forming complexes that are released in the circulation and are widely distributed. Filtered by the glomeruli, cadmium-metallothionein complexes are absorbed by proximal tubular epithelial cells and are degraded in lysosomes with release of Cd²⁺ to the cytosol, where it is bound to metallothionein and to non–metallothionein-binding proteins. Cadmium complexed with non–metallothionein-binding proteins probably interferes with biogenesis of lysosomes, because it is this fraction that is temporally associated with cell injury and tubular dysfunction, as denoted by increased numbers of electron-dense lysosomes, decreased lysosomal protease activity, appearance of cellular vesiculation, increased excretion of low molecular weight protein, calcium, and enzymuria (489). Cadmium may impair reabsorption of proteins by proximal tubular epithelial cells via down-regulation of megalin and chloride channel 5, two key players in albumin receptor-mediated endocytosis (490). Renal excretion of cadmium occurs only after a threshold is exceeded (489). A pathogenetic role for heat shock protein (491,492) and oxidative stress has been raised (470,493,494). The role of kidney injury molecule-1 in the pathogenesis of cadmium toxicity has emerged. Kidney injury molecule-1 is a transmembrane glycoprotein not normally detected in the kidney that is up-regulated and shed into the urine following nephrotoxic injury. Significant elevation of kidney injury molecule-1 in the urine and proximal tubular epithelial cells was detected in Sprague Dawley rats treated with cadmium (495). Urinary excretion of kidney injury molecule 1 levels is correlated with urinary cadmium concentration in an elderly population after long-term, low-dose exposure to cadmium (496).

Cadmium may induce injury in the proximal tubular epithelial cells by accumulation of p53 secondary to down-regulation of the Ube2d4 gene (a member of the ubiquitin-conjugating enzyme Ube2d family), resulting in apoptosis of tubular epithelial cells both in vitro and in vivo (497).

Mercury Nephropathy
Mercury exposure results from accidental or suicidal ingestion of inorganic mercurial compounds (e.g., mercuric chloride), from occupational activity (462) owing to inhalation of mercury vapors in the manufacture of scientific instruments and amalgam handling for dental fillings, from use of various products (e.g., topical ointments, cathartics, cosmetics, paints, pesticides), and from consumption of contaminated food. Mercury salts are methylated by bacteria in the environment, and the product, methyl mercury, finds its way into the food chain...
Chapter 25 | Acute and Chronic Tubulointerstitial Nephritis

Miscellaneous Heavy Metal Nephropathy

Organic compounds containing gold were used in the treatment of rheumatoid arthritis. Gold salts cause various autoimmune diseases in humans (499). Patients chronically exposed to gold compounds develop proteinuria or the nephrotic syndrome (secondary to membranous glomerulonephritis), microscopic hematuria, tubular injury, and chronic TIN with lymphocytic inflammatory infiltrate (506). Gold inclusions are often found in the cytoplasm of epithelial cells and free in the interstitium (506). The pathogenesis of gold nephropathy is unknown. Patients with HLA-DQA haplotype are more susceptible to develop gold nephropathy (see Chapter 7).

Exposure to copper and iron results in deposits of these metals in tubular cells. Iron may induce tubular cell necrosis and acute renal failure when ingested in large doses as sulfate salts (6). Copper also may cause TIN. In the case reported by Hocher et al. (507), TIN, with diffuse inflammatory infiltration by lymphocytes and eosinophils and renal failure requiring dialysis, was induced by a copper-containing intrauterine device. Removal of the device was followed by near normalization of renal function.

Cis-platinum is a chemotherapeutic agent whose major toxicity is renal (508). Cis-platinum administration results in variable renal dysfunction and tubular cell injury, including flattening of epithelial cells, dilation of tubules, necrosis and desquamation of epithelial cells, and focal edema and interstitial fibrosis. Acute cis-platinum nephrotoxicity is discussed in Chapter 26. Cis-platinum has been associated with contracted kidneys (508). Studies in which platinum analogs were administered to rats suggest that nephrotoxicity is characterized by early inhibition of protein synthesis and late mitochondrial dysfunction (509).

Intoxication with arsenic is uncommon. Arsenic exposure can result in chronic renal injury (510) in the form of TIN with interstitial fibrosis manifesting with the Fanconi syndrome and renal insufficiency (510). The source of arsenic was tentatively traced to consumption of “organic health foods” (511). Diagnosis rests on heavy metal screening. Chronic administration of arsenic impaired renal function in diabetic rats (512). Chromium copper arsenate (CCA) was used for the protection of wood building materials until 2002, before it was banned by the EPA. Studies in animals demonstrated that this triple-metal compound has more prominent nephrotic effect than its component single metals, suggesting a synergistic effect (513).

The nephrotoxicity of uranium in humans has been reported (514). The toxicity of the metal depends on several factors, such as sex, age, body mass index (515), and species. Of all the mammals, humans seem to be the least sensitive to uranium (516). People may be exposed to uranium, both acutely and chronically, as a consequence of contamination (e.g., nuclear accidents, war, human dumping), the usual sources of normal exposure with high amounts of uranium arising from the anisotropy of the distribution of the metal in the earth’s crust, or from increased contact with the metal, such as in the military and aeronautics or in the fields of mining and industry. Uranium levels in urine are strongly correlated to levels in drinking water from drilled wells in people who used drinking water from private drilled wells located in uranium-rich bedrock, but no significant signs of nephrotoxicity were found (515,517). Nephrotoxicity has been reported in uranium mill workers (518). There is now renewed interest in the toxicity of depleted uranium in soldiers exposed on battlefields. So far, there is no evidence that depleted uranium is associated with nephrotoxicity in human (519).

In 1992, approximately 152 kg of depleted uranium were missing after a cargo aircraft crash near Amsterdam (the Netherlands). It has been suspected that this missed uranium could have been completely oxidized at high temperatures (in the range 600° to 1200°C) that occurred during the fire, resulting in the poorly soluble uranium oxides UO₂ and U₃O₈. A large study was performed on the health effects of the disaster on professional assistance workers. Data of a historically defined cohort of 2499 (exposed and nonexposed) firefighters, police officers, and hangar workers were collected 8.5 years after the disaster. Albumin-to-creatinine ratio and the fractional excretion of β₂-microglobulin were calculated in the urine and simultaneous blood samples. Exposed assistance workers were compared with their nonexposed colleagues, and associations between uranium and kidney function data were investigated. No statistically significant differences between exposed and nonexposed workers were found in the uranium concentrations and kidney function (520). Several studies describing uranium nephrotoxicity are experimental (521). Thus, uranium may induce apoptosis in rat kidney proximal cells (522). Uranium affects the expression of vitamin D receptor and X receptor in the rat kidneys after chronic exposure (523). Interestingly, chronic exposure to uranium may lead to accumulation of iron in the kidney (524).
TUBULOINTERSTITIAL NEPHROPATHY ASSOCIATED WITH HEREDITARY DISEASES

The pathology of Alport syndrome is discussed in Chapter 13. Tubulointerstitial diseases in renal developmental defects and cystic diseases, as well as familial metabolic renal diseases, are discussed in Chapters 4 and 27, respectively. In this section, only two somewhat controversial entities will be addressed: familial TIN with hypokalemia and familial TIN secondary to mitochondrial DNA abnormalities.

Familial Tubulointerstitial Nephritis With Hypokalemia

Patients with chronic TIN and hypokalemia have been reported in several families (525,526). The interstitial inflammatory cells are predominantly lymphocytes, and there are associated interstitial fibrosis and variable tubular atrophy. In the report of Gullner et al. (525) of three siblings, a characteristic tubular lesion was described wherein proximal tubular cells stained very darkly with methylene-basic fuchsin stain; TBMs were thickened; and the mitochondria showed dense, flocculent material and appeared enlarged. We have seen a kidney biopsy from a 16-year-old male with familial hyperkalemia who had mild interstitial nephritis and ultrastructural findings similar to those described by Gullner et al. (525) (Fig. 25.30).

Familial TIN with hypokalemia has an autosomal recessive mode of inheritance that is MHC linked, and one or more genes that control potassium reabsorption, present in the short arm of chromosome 6, appear to be involved (526). The pathogenesis is unknown. Although acquired hypokalemia owing to malnutrition or abuse of laxatives has been reported to result in chronic TIN and chronic renal failure (527), this hypothesis is debated (528). Familial chronic TIN with hypokalemia must be differentiated from nonfamilial chronic TIN with secondary hypokalemia. This latter condition is possibly immune mediated, and the loss of potassium may be hormonally driven (529). Most affected patients are postpubertal females with systemic features of autoimmune disease (529). In one of the three families reported initially, renal failure developed in three siblings (526).

Chronic Tubulointerstitial Nephritis Secondary to Mitochondrial Abnormalities

In 1994, Szabolcs et al. (529) from Columbia University reported on an 8-year-old girl who had megaloblastic anemia, growth retardation, and progressive renal insufficiency. Renal biopsy revealed chronic tubulointerstitial disease with tubular atrophy and interstitial fibrosis. Ultrastructural examination showed extremely dysmorphic, bizarre mitochondria. Molecular analysis of the mitochondrial DNA detected a 2.7-kb mitochondrial DNA deletion. A year later, a group from France reported a young patient with progressive TIN and leukodystrophy who had a 2.6-kb mitochondrial DNA deletion (530). Consequently, two groups described point mutations in mitochondrial DNA that was associated with progressive interstitial nephritis in three families (531,532). The patients of Zsurka et al. (531) had thoracolumbar scoliosis, muscle weakness, breathing difficulties, mitral prolapse, cardiac conduction defects, pigmented retinopathy, and psychiatric disorders. The patients of Tzen et al. (532) had myopathy and central nervous system abnormalities. Some patients also had Fanconi syndrome.

The morphologic findings in the kidney were dominated by chronic tubulointerstitial injury. The light microscopy and immunofluorescence did not provide a diagnostic clue. Recently, it has been reported that granular swollen epithelial cells among the distal tubules and collecting ducts may be a distinct morphologic feature suggesting mitochondrial nephropathy (533). Ultrastructurally, all patients had bizarre, sometimes curvilinear-appearing mitochondria (530,531,534). The mitochondria also had abnormal cristae and inclusions. One has to keep in mind that dysmorphic, bizarre mitochondria are not necessarily diagnostic of mitochondrial DNA abnormality-associated renal diseases because abnormal mitochondria can occasionally be seen in various conditions, including drug toxicity (e.g., cyclosporine) (Fig. 25.31). Mitochondrial DNA abnormalities are associated not only with chronic progressive tubulointerstitial injury in the kidney, as cases of focal segmental glomerulosclerosis secondary to mitochondrial DNA abnormalities have now been reported (see Chapter 6).

The exact pathogenesis of mitochondrial DNA abnormality-related renal disease is unclear, but it is most likely related to disturbances in the mitochondrial respiratory chain. Renal disease is usually part of a multiorgan disease in these patients, which frequently involves the musculoskeletal system and the central nervous system. Interestingly, it appears that mutation of genes encoding mitochondrial proteins may also be associated with functional and morphologic mitochondrial abnormalities and renal disease, probably both in humans and in experimental animals (535). The kd/kd mouse has a mutant allele of a gene encoding a prenyltransferase-like mitochondrial protein (PLMP). The kd/kd mouse spontaneously develops severe and progressive nephritis leading to chronic renal failure (535). The mitochondrial defect in kd/kd mice primarily affects both the tubular and glomerular visceral epithelium. There is some evidence suggesting that the tubular epithelial defect triggers autoimmune interstitial nephritis, whereas a
defect in podocytes leads to proteinuria and glomerulosclerosis (536). Environmental factors play a significant role in the progression of kidney injury in these mice (537).

TUBULOINTERSTITIAL NEPHROPATHY ASSOCIATED WITH MISCELLANEOUS DISORDERS

Systemic Karyomegaly
Mihatsch et al. (538) in 1979 reported chronic TIN manifested by karyomegaly in three patients between 26 and 29 years of age whose TIN progressed to ESRD within 4 to 6 years. Spoendlin et al. (539) reported four additional patients whose presentation in the third decade of life was asymptomatic but later experienced progressive renal failure associated with infections of the upper respiratory tract. Several additional cases have been reported (540,541), some of them in siblings (542).

Renal changes include interstitial infiltration with mononuclear cells, tubular cell injury with focal loss of tubular cells, tubular atrophy, variable interstitial fibrosis, and nuclear changes in proximal and distal tubules. The nuclei are enlarged and measure up to 30 μm in diameter (Fig. 25.32). Enlarged nuclei are found in other cells such as those of bile duct, bronchi, smooth muscle, bowel, vessels, skeletal muscle, and connective tissue (538). The enlarged nuclei are polyploid. By immunofluorescence studies, no deposits of immunoreactants are found, and electron microscopy is not helpful. No convincing viral particles have been found.

The pathogenesis is unknown. Mihatsch et al. (538) reviewed the various causes of karyomegalic changes and suggested that chemical toxins or viral infections might be implicated. In a report by Hassen et al. (541), high concentrations of ochratoxin, a mycotoxin that interferes with mitotic activity, were found in the blood of affected siblings. Spoendlin et al. (539) studied Ki67 and proliferating cell nuclear antigen in tissues of four patients and concluded that there was inhibition of mitosis in karyomegalic cells. The hypothesis that the karyomegaly is secondary to a block in the G2 phase of the cell cycle has been proposed (539). MHC typing revealed the A9/B35 haplotype, which suggested a genetic defect in chromosome 6 that was linked to the MHC locus. However, the study of Bhandari et al. (543), based on their six patients, did not confirm clustering of A9 or B35.

Balkan Endemic Nephropathy
Balkan endemic nephropathy is found in Croatia, Bosnia, Serbia, Bulgaria, and Romania. In villages where the disease is endemic, the prevalence varies between 2% and 10%. The disease occurs in families but is not hereditary, and most affected persons are farmers (544). The condition is geographically localized and occurs along major tributaries of the Danube river basin. It does not affect children and rarely is seen in patients younger than 20 years of age. Individuals who have lived for a short time in the endemic area do not develop the condition, but individuals from nonendemic areas who spend several years in villages where the condition is endemic may become ill (545). Recent epidemiologic studies from the Kolubara region, the most affected region in Serbia, analyzed the incidence of the disease over a 33-year period from 1977 till 2009 (546). The age-adjusted incidence rates combined for males and females over the period of study fit a significant quadratic (U-shaped) trend ($y = 58.44 - 3.76 + 0.10x^2$, $P = 0.026$). Joinpoint regression analysis showed that the overall age-standardized incidence rates significantly decreased in the first decade of the observed period (1977–1989) by an
average of 10.0% annually, while a nonsignificant increase of 3.9% per year was recorded in the last 2 decades (1989–2009) (547). Some data indicate that in several regions, the incidence of Balkan endemic nephropathy is decreasing (548).

**Clinical Presentation**
Typical manifestations of the disease occur between 30 and 50 years of age, and the clinical presentation is insidious with weakness, anorexia, anemia, weight loss, copper-yellow skin, orange palms and soles, lumbar pain, mild proteinuria, and microscopic hematuria (544). Hypertension is relatively rare. Renal dysfunction, manifested by tubular proteinuria of usually less than 2 g per day with increased excretion of β2-microglobulin, is an early sign of the nephropathy. Proteomic data indicate that 6 proteins, including alpha-1-microglobulin, alpha-2-glycoprotein-1, beta-2-microglobulin, mannose-binding lectin-2, protection of telomeres protein-1, and superoxide dismutase, are found in patients with Balkan endemic nephropathy, but not in patients with AKI, patients with diabetic nephropathy, and healthy volunteers (548). Interestingly, there is a high incidence of upper urothelial carcinoma in patients with Balkan endemic nephropathy. Up to 50% of patients may develop urothelial carcinoma. Transitional cell carcinoma of the renal pelvis and the upper urinary tract can be up to 100 times more frequent in the endemic regions than in the nonendemic regions (549,550).

**Pathologic Findings**
The kidneys are reduced in size and can weigh as little as 20 g each (551). The external surface is finely granular or smooth, and the cortex is thin (Fig. 25.33). The predominant microscopic changes are in the tubules and interstitium. There are abundant interstitial fibrosis and variable amounts of interstitial inflammatory cells. Nephrons in the superficial cortex are predominantly involved, and there is extensive solidification of glomeruli (552). Based on a study of 50 kidney biopsies, Ferluga et al. (553) described multifocal interstitial fibrosis spreading from the superficial to the deep cortex and tubular atrophy in most of their patients (Fig. 25.34). By immunofluorescence, Ferluga et al. (553) reported prominent glomerular capillary deposits of IgM in 16 of 50 patients. Papillary necrosis is uncommon, but benign and malignant tumors may be found in the pelvis and in the ureters (511,553). About 30% to 48% of Balkan nephropathy patients develop tumors of the upper urothelium, most frequently transitional cell carcinoma. These tumors can be bilateral. Tumors other than transitional cell carcinoma have been reported, including papillomas and squamous cell carcinomas (554).

**Pathogenesis**
The pathogenesis is unknown. It has been shown that Balkan endemic nephropathy may be associated with the GSTM-1 allele of the glutathione S-transferase (555). However, the absence of association with these and other examined alleles has been reported by others (556). Similarly, conflicting data have been published regarding viruses, including the possible role of coronavirus (557). Heavy metals (558), silica (559), low molecular weight proteins (560), and ochratoxin A (561) have been implicated but not substantiated. Pigs fed on barley contaminated with ochratoxin A, which is a fungal metabolite, develop tubular atrophy and interstitial fibrosis comparable to that seen in Balkan endemic nephropathy (562). The potential etiologic role of ochratoxin A or other mycotoxins as causative agents of Balkan endemic nephropathy is strengthened by the observation that 10% to 20% of cereals, pork meat, and bread from endemic regions are contaminated with ochratoxin A (563).

Another possibility, raised by the similarity of renal changes between Balkan endemic nephropathy and aristolochic acid nephropathy (AAN) (Chinese herb nephropathy), implicates aristolochic acid, a nephrotoxin and carcinogenic agent present in *Aristolochia*, one of the Chinese herbs containing herbal preparations taken for weight reduction (564–567). Apparently, *Aristolochia clematitis*, which contains aristolochic acid, is common in the endemic areas, and its seeds were found to be contaminants of wheat grains in endemic regions (566). Following metabolic activation, aristolochic acid reacts with genomic DNA to form aristolactam-DNA adducts. Jelakovic et al. (550) found such aristolactam-DNA adducts in 70% of 67 patients who underwent nephroureterectomy for carcinomas of the upper urinary tract in endemic regions for Balkan nephropathy. In contrast, none of the renal tissues from 10 patients from nonendemic regions with carcinomas of the upper urinary tract had such DNA adducts (550). These data suggest a pathogenetic role of aristolochic acid in both Balkan endemic nephropathy and Chinese herb nephropathy (see below). In fact, some investigators suggest...
that the names Chinese herb nephropathy and Balkan endemic nephropathy be abandoned and replaced by the term AAN for both diseases (567).

**Aristolochic Acid (Chinese Herb) Nephropathy**

During 1992 and 1993, an outbreak of rapidly progressive renal failure associated with a slimming regimen containing Chinese herbs occurred in Belgium (568). Withdrawal of the herbs did not prevent progression to chronic renal failure. A large body of subsequent literature appeared on herbal-induced nephropathies, initially mainly from Belgium (564,569,570). Subsequently, series of patients have been reported from Taiwan (571) and Japan (572). It became quickly evident that aristolochic acid (Chinese herb) nephropathy is very similar to Balkan endemic nephropathy (573). There is some controversy about the name of the disease. Some investigators suggested that the term “Chinese herb nephropathy” should be abandoned because most of the cases occurred in Belgium and the term is prejudicial (572). They recommended using the term “aristolochic acid–associated nephropathy.”

In a substantial proportion of patients, transitional cell carcinoma develops. The prevalence of carcinoma was 46% among patients with AAN who underwent nephrectomy (569,574). Because of this high prevalence rate in patients with ESRD secondary to AAN, bilateral nephrectomy may be an appropriate preventive measure.

**Clinical Presentation**

Most patients present with rapidly progressive renal failure leading to ESRD typically within months. Proteinuria is mild, and microscopic hematuria may be present. Hypokalemia or hyperkalemia may occur, and Fanconi syndrome is common in Japanese patients (572). Most patients in the Belgian studies are female, which may be related to gender differences in taking the diet aid. Males are frequently affected in far Eastern countries (572). Although many aspects of AAN are similar to Balkan endemic nephropathy, the clinical course is clearly different. Balkan endemic nephropathy leads to ESRD after many years (usually 20 years), whereas AAN is rapidly progressive.

Yang et al. (575) describe three clinical subtypes of patients with AAN:

1. AKI (acute AAN) in approximately 4% of the patients
2. Abrupt tubular dysfunction with normal Scr levels occurs in less than 2% of the patients.
3. Chronic tubulointerstitial nephropathy with slowly worsening renal function (in over 90% of cases)

The patients with AKI had the highest aristolochic acid intake per day, and they developed progressive kidney failure during the 1 to 7 years’ follow-up. The patients with isolated tubular dysfunction had the lowest cumulative aristolochic acid intake, and they maintained normal Scr levels during a 2- to 8-year follow-up. The patients with chronic tubulointerstitial nephropathy took the lowest aristolochic acid dose per day, but they used aristolochic acid for the longest period of time (575).

**Pathologic Findings**

Renal biopsy findings include extensive interstitial fibrosis with tubular atrophy and loss involving predominantly the outer cortex. Interlobular arteries frequently show fibromucoid intimal thickening. In the glomeruli, global sclerosis, collapse, and ischemic changes are common (570,575). The interstitial inflammatory cell infiltrate is usually sparse (hypocellular interstitial fibrosis) (Fig. 25.35). Immunofluorescence and ultrastructural studies are noncontributory. Scattered deposits of C3 may be present in the TBM and interstitium.

**Pathogenesis**

There is now widespread agreement that AAN is primarily caused by aristolochic acid, which is the constituent of the Chinese herb *Stephania tetrandra* (567,570). Aristolochic acid can form premutagenic aristolochic acid-DNA adducts in the kidney and urothelium and aristolochic acid-DNA adducts have been detected in a renal biopsy by Lo et al. (576). Interestingly, the patient developed transitional cell carcinoma 5 months later. It appears that the cumulative dose of aristolochic acid and the progression rate of renal failure show a
positive correlation (575). The nephrotoxicity of aristolochic acid was also proven in experimental animals (577). However, we would like to note that there are occasional case reports stating that Chinese herb nephropathy develops in the absence of aristolochic acid. In fact, we have encountered a case with typical history and morphology of AAN, but we were unable to prove that the herbal medications the patient was taking contained aristolochic acid.

**Idiopathic Tubulointerstitial Nephritis**

Idiopathic TIN encompasses a group of diverse conditions. This diagnosis is applied only after known causes or etiologic agents of TIN have been considered and excluded. To exclude every possibility, it is imperative to perform a full renal biopsy workup, including immunofluorescence and electron microscopy. Without immunofluorescence or electron microscopy, the possibility of underlying immune complex disease, anti-TBM disease, monoclonal immunoglobulin deposition disease, mitochondrial abnormalities, and other forms of underlying diseases cannot be excluded. It is also very important to review the clinical history in detail and consider all possible pathogenic factors to which the patient may have been exposed. The diagnosis of idiopathic TIN reflects only that we are unable to identify the etiologic factor(s).

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1155


Chapter 25 | Acute and Chronic Tubulointerstitial Nephritis


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