Eosinophils and neutrophils may be present (Fig. 20-33), often in clusters and large numbers, and smaller numbers of plasma cells and mast cells are sometimes also present. Inflammation may be more prominent in the medulla where the inciting agent is often concentrated. With some drugs (e.g., methicillin, thiazides), interstitial nonnecrotizing granulomas may be seen. Tubulitis, the infiltration of tubules by lymphocytes, is common. Variable degrees of tubular necrosis and regeneration are present. The glomeruli are normal except in some cases caused by NSAIDs, when minimal-change disease and the nephrotic syndrome develop concurrently (see below). In analgesic nephropathy, papillae can show various stages of necrosis, calcification, fragmentation, and sloughing.

Clinical Features. It is important to recognize drug-induced acute interstitial nephritis because withdrawal of the offending drug is followed by recovery, although it may take several months, and irreversible damage can occur. It is also important to remember that while drugs are the leading identifiable cause of acute interstitial nephritis, in many affected patients (approximately 30% to 40%) an offending drug or mechanism cannot be identified.

On occasion, necrotic papillae are excreted, and may cause gross hematuria or renal colic due to ureteric obstruction. Papillary necrosis is not specific for analgesic nephropathy, and is also seen in diabetes mellitus, as well as in urinary tract obstruction, sickle cell disease or trait (described later), and focally in renal tuberculosis. In all cases it is caused by ischemia resulting from compression or obstruction of small blood vessels in the medulla. Such compression may be caused by interstitial edema (as in inflammatory reactions and urinary tract obstruction) or microvascular disease (as in diabetes). Table 20-9 lists the main features of papillary necrosis in these conditions. A small percentage of patients with analgesic nephropathy develop *urothelial carcinoma of the renal pelvis.*

Nephropathy Associated with NSAIDs

NSAIDs, one of the most commonly used classes of drugs, produce several forms of renal injury. Although these complications are uncommon, they should be kept in mind since NSAIDs are frequently administered to patients with other potential causes of renal disease. Many NSAIDs are nonselective cyclooxygenase inhibitors, and their adverse renal effects are related to their ability to inhibit cyclooxygenase-dependent prostaglandin synthesis. The selective COX-2 inhibitors, while sparing the gastrointestinal tract, do affect the kidneys because COX-2 is expressed in human kidneys. NSAID-associated renal syndromes include

- *Acute kidney injury*, due to the decreased synthesis of vasodilatory prostaglandins and resultant ischemia. This is particularly likely to occur in the setting of other renal diseases or conditions causing volume depletion.
- *Acute hypersensitivity interstitial nephritis,* resulting in renal failure, as described earlier.
- *Acute interstitial nephritis and minimal-change disease.* This curious association of two diverse renal conditions, one leading to renal failure and the other to nephrotic syndrome, suggests a hypersensitivity reaction affecting the interstitium and possibly the glomeruli, but also is consistent with injury to podocytes mediated by cytokines released as part of the inflammatory process.
- *Membranous nephropathy,* with the nephrotic syndrome, is a recently appreciated association, also of unclear pathogenesis.

KEY CONCEPTS

Tubulointerstitial Nephritis Induced by Drugs and Toxins

- Drug-induced tubulointerstitial nephritis is the second most common cause of acute kidney injury.
- Prominent interstitial inflammation with associated tubular injury, which may or may not be accompanied by eosinophils or granulomatous inflammation, can be induced by almost any pharmacologic agent.
- NSAIDs can cause tubulointerstitial nephritis and/or glomerular injury, such as minimal change disease or membranous nephropathy.

Other Tubulointerstitial Diseases

Urate Nephropathy

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

- *Acute uric acid nephropathy* is caused by the precipitation of uric acid crystals in the renal tubules, principally in collecting ducts, leading to obstruction of nephrons and the development of acute renal failure. This is particularly likely to occur in individuals with leukemias or lymphomas who are undergoing chemotherapy (tumor lysis syndrome); the drugs kill tumor cells, and uric acid is produced as released nucleic acids are broken down. Precipitation of uric acid is favored by the acidic pH in collecting tubules.
- *Chronic urate nephropathy*, or gouty nephropathy, occurs in a subset of patients with protracted forms of

Table 20-9 Causes of Papillary Necrosis

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

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