TABLE 340-3 MAJOR CAUSES OF PAPILLARY NECROSIS

Analgesic nephropathy
Sickle cell nephropathy
Diabetes with urinary tract infection
Prolonged NSAID use (rare)

Abbreviation: NSAID, nonsteroidal anti-inflammatory drug.

consequence of prolonged glomerular dysfunction. Potential mechanisms by which glomerular disease might cause tubulointerstitial injury include proteinuria-mediated damage to the epithelial cells, activation of tubular cells by cytokines and complement, or reduced peritubular blood flow leading to downstream tubulointerstitial ischemia, especially in the case of glomeruli that are globally obsolescent due to severe glomerulonephritis. It is often difficult to discern the initial cause of injury by renal biopsy in a patient who presents with advanced renal disease in this setting.

ANALGESIC NEPHROPATHY

Analgesic nephropathy results from the long-term use of compound analgesic preparations containing phenacetin (banned in the United States since 1983), aspirin, and caffeine. In its classic form, analgesic nephropathy is characterized by renal insufficiency, papillary necrosis (Table 340-3) attributable to the presumed concentration of the drug to toxic levels in the inner medulla, and a radiographic constellation of small, scarred kidneys with papillary calcifications best appreciated by computed tomography (Fig. 340-5). Patients may also have polyuria due to impaired concentrating ability and non-anion-gap metabolic acidosis from tubular damage. Shedding of a sloughed necrotic papilla can cause gross hematuria and ureteric colic due to ureteral obstruction. Individuals with ESRD as a result of analgesic nephropathy are at increased risk of a urothelial malignancy compared to patients with other causes of renal failure. Recent cohort studies in individuals with normal baseline renal function suggest that the moderate chronic use of current analgesic preparations available in the United States, including acetaminophen and NSAIDs, does not seem to cause the constellation of findings known as analgesic nephropathy, although volume-depleted individuals and those with chronic kidney disease are at higher risk of NSAID-related renal toxicity. Nonetheless, it is recommended that heavy users of acetaminophen and NSAIDs be screened for evidence of renal disease.

ARISTOLOCHIC ACID NEPHROPATHY

Two seemingly unrelated forms of CIN, Chinese herbal nephropathy and Balkan endemic nephropathy, have recently been linked by the underlying etiologic agent aristolochic acid and are now collectively termed aristolochic acid nephropathy (AAN). In Chinese herbal nephropathy, first described in the early 1990s in young women taking traditional Chinese herbal preparations as part of a weight-loss regimen, one of the offending agents has been identified as aristolochic acid, a known carcinogen from the plant *Aristolochia*. Multiple *Aristolochia* species have been used in traditional herbal remedies for centuries and continue to be available despite official bans on their use in many countries. Molecular evidence has also implicated aristolochic acid in Balkan endemic nephropathy, a chronic tubulointerstitial nephritis found primarily in towns along the tributaries of the Danube River and first described in the 1950s. Although the exact route of exposure is not known with certainty, contamination of local grain preparations with the seeds of *Aristolochia* species seems most likely. Aristolochic acid, after prolonged exposure, produces renal interstitial fibrosis with a relative paucity of cellular infiltrates. The urine sediment is bland, with rare leukocytes and only mild proteinuria. Anemia may be disproportionately severe relative to the level of renal dysfunction. Definitive diagnosis of AAN requires two of the following three features: characteristic histology on kidney biopsy; confirmation of aristolochic acid ingestion; and detection of aristolactam-DNA adducts in kidney or urinary tract tissue. These latter lesions represent a molecular signature of aristolochic acid–derived DNA damage and often consist of characteristic A:T-to-T:A transversions. Due to this mutagenic activity, AAN is associated with a very high incidence of upper urinary tract urothelial cancers, with risk related to cumulative dose. Surveillance with computed tomography, ureteroscopy, and urine cytology is warranted, and consideration should be given to bilateral nephroureterectomy once a patient has reached ESRD.

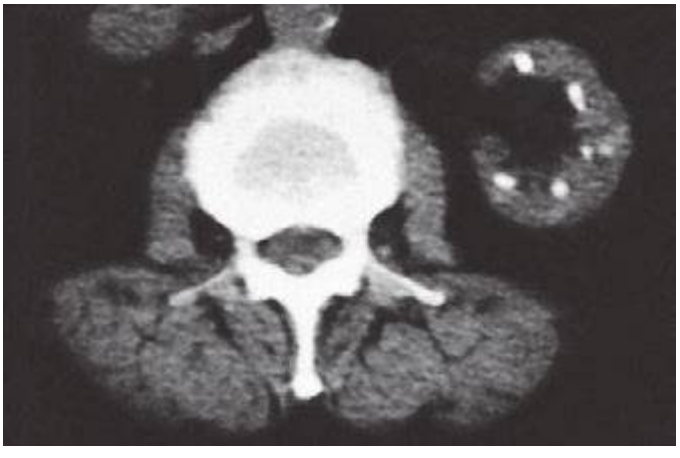

FIGURE 340-5 Radiologic appearance of analgesic nephropathy. A noncontrast computed tomography scan shows an atrophic left kidney with papillary calcifications in a garland pattern. *(Reprinted by permission from Macmillan Publishers, Ltd., MM Elseviers et al: Kidney International 48:1316, 1995.)*

KARYOMEGALIC INTERSTITIAL NEPHRITIS

Karyomegalic interstitial nephritis is an unusual form of slowly progressive chronic kidney disease with mild proteinuria, interstitial fibrosis, tubular atrophy, and oddly enlarged nuclei of proximal tubular epithelial cells. It has been linked to mutations in *FAN1*, a nuclease involved in DNA repair, which may render carriers of the mutation susceptible to environmental DNA-damaging agents.

LITHIUM-ASSOCIATED NEPHROPATHY

The use of lithium salts for the treatment of manic-depressive illness may have several renal sequelae, the most common of which is nephrogenic diabetes insipidus manifesting as polyuria and polydipsia. Lithium accumulates in principal cells of the collecting duct by entering through the epithelial sodium channel (ENaC), where it inhibits glycogen synthase kinase 3β and downregulates vasopressin-regulated aquaporin water channels. Less frequently, chronic tubulointerstitial nephritis develops after prolonged (>10–20 years) lithium use and is most likely to occur in patients who have experienced repeated episodes of toxic lithium levels. Findings on renal biopsy include interstitial fibrosis and tubular atrophy that are out of proportion to the degree of glomerulosclerosis or vascular disease, a sparse lymphocytic infiltrate, and small cysts or dilation of the distal tubule and collecting duct that are highly characteristic of this disorder. The degree of interstitial fibrosis correlates with both duration and cumulative dose of lithium. Individuals with lithium-associated nephropathy are typically asymptomatic, with minimal proteinuria, few urinary leukocytes, and normal blood pressure. Some patients develop more severe proteinuria due to secondary FSGS, which may contribute to further loss of renal function.

TREATMENT LITHIUM-ASSOCIATED NEPHROPATHY

Renal function should be followed regularly in patients taking lithium, and caution should be exercised in patients with underlying renal disease. The use of amiloride to inhibit lithium entry via ENaC has been effective to prevent and treat lithium-induced nephrogenic diabetes insipidus, but it is not clear if it will prevent lithium-induced CIN. Once lithium-associated nephropathy is detected, the discontinuation of lithium in attempt to forestall further renal deterioration can be problematic, as lithium is an effective mood stabilizer that is often incompletely substituted by other agents. Furthermore, despite discontinuation of lithium, chronic