western coast of Central America. This Mesoamerican nephropathy is particularly common in Nicaragua and El Salvador. Mesoamerican nephropathy patients do not have significant proteinuria, suggesting that this is a disease of the kidney tubules and interstitium. The cause is unknown, but some have suggested that a combination of toxic environmental factors and heat stress underlies the development of this kidney disease, which has a striking male predominance. However, the fact that, in many families, a large fraction of the men are affected with kidney disease has suggested that a strong genetic component may be involved as well.

340 Tubulointerstitial Diseases of the Kidney

Laurence H. Beck, David J. Salant

Inflammation or fibrosis of the renal interstitium and atrophy of the tubular compartment are common consequences of diseases that target the glomeruli or vasculature. Distinct from these secondary phenomena, however, are a group of disorders that primarily affect the tubules and interstitium, with relative sparing of the glomeruli and renal vessels. Such disorders are conveniently divided into acute and chronic tubulointerstitial nephritis (TIN) (Table 340-1).

Acute TIN most often presents with acute renal failure (Chap. 334). The acute nature of this group of disorders may be caused by aggressive inflammatory infiltrates that lead to tissue edema, tubular cell injury, and compromised tubular flow, or by frank obstruction of the tubules with casts, cellular debris, or crystals. There is sometimes flank pain due to distention of the renal capsule. Urinary sediment is often active with leukocytes and cellular casts, but depends on the exact nature of the disorder in question.

The clinical features of chronic TIN are more indolent and may manifest with disorders of tubular function, including polyuria from impaired concentrating ability (nephrogenic diabetes insipidus), defective proximal tubular reabsorption leading to features of Fanconi's syndrome (glycosuria, phosphaturia, aminoaciduria, hypokalemia, and type II renal tubular acidosis [RTA] from bicarbonaturia), or non-anion-gap metabolic acidosis and hyperkalemia (type IV RTA) due to impaired ammoniagenesis, as well as progressive azotemia (rising creatinine and blood urea nitrogen [BUN]). There is often modest proteinuria (rarely >2 g/d) attributable to decreased tubular reabsorption of filtered proteins; however, nephrotic-range albuminuria may occur in some conditions due to the development of secondary focal segmental glomerulosclerosis (FSGS). Renal ultrasonography may reveal changes of "medical renal disease," such as increased echogenicity of the renal parenchyma with loss of corticomedullary differentiation, prominence of the renal pyramids, and cortical scarring in some conditions. The predominant pathology in chronic TIN is interstitial fibrosis with patchy mononuclear cell infiltration and widespread tubular atrophy, luminal dilation, and thickening of tubular basement membranes. Because of the nonspecific nature of the histopathology, biopsy specimens rarely provide a specific diagnosis. Thus, diagnosis relies on careful analysis of history, drug or toxin exposure, associated symptoms, and imaging studies.

TABLE 340-1 CLASSIFICATION OF THE CAUSES OF TUBULOINTERSTITIAL DISEASES OF THE KIDNEY

Acute Tubulointerstitial Disorders
Acute Interstitial Nephritis
Therapeutic agents
• Antibiotics (β-lactams, sulfonamides, quinolones, vancomycin, erythromycin, linezolid, minocycline, rifampin, ethambutol, acyclovir)
• Nonsteroidal anti-inflammatory drugs, COX-2 inhibitors
• Diuretics (rarely thiazides, loop diuretics, triamterene)
• Anticonvulsants (phenytoin, valproate, carbamazepine, phenobarbital)
• Miscellaneous (proton pump inhibitors, H_2 blockers, captopril, mesalazine, indinavir, allopurinol, lenalidomide)
Infection
• Bacteria (*Streptococcus, Staphylococcus, Legionella, Salmonella, Brucella, Yersinia, Corynebacterium diphtheriae*)
• Viruses (EBV, CMV, hantavirus, polyomavirus, HIV)
• Miscellaneous (*Leptospira, Rickettsia, Mycoplasma, Histoplasma*)
Autoimmune
• Tubulointerstitial nephritis with uveitis (TINU)
• Sjögren's syndrome
• Systemic lupus erythematosus
• Granulomatous interstitial nephritis
• IgG4-related systemic disease
• Idiopathic autoimmune interstitial nephritis
Acute obstructive disorders
• Light chain cast nephropathy ("myeloma kidney")
• Acute phosphate nephropathy
• Acute urate nephropathy
Chronic Tubulointerstitial Disorders
• Vesicoureteral reflux/reflux nephropathy
• Sickle cell disease
• Chronic exposure to toxins or therapeutic agents
• Analgesics, especially those containing phenacetin
• Lithium
• Heavy metals (lead, cadmium)
• Aristolochic acid (Chinese herbal and Balkan endemic nephropathies)
• Calcineurin inhibitors (cyclosporine, tacrolimus)
Metabolic Disturbances
• Hypercalcemia and/or nephrocalcinosis
• Hyperuricemia
• Prolonged hypokalemia
• Hyperoxaluria
• Cystinosis (see Chap. 339)
Cystic and Hereditary Disorders (see Chap. 339)
• Polycystic kidney disease
• Nephronophthisis
• Adult medullary cystic disease
• Medullary sponge kidney
Miscellaneous
• Aging
• Chronic glomerulonephritis
• Chronic urinary tract obstruction
• Ischemia and vascular disease
• Radiation nephritis (rare)

Abbreviations: CMV, cytomegalovirus; COX, cyclooxygenase; EBV, Epstein-Barr virus.

ACUTE INTERSTITIAL NEPHRITIS

In 1897, Councilman reported on eight cases of acute interstitial nephritis (AIN) in the Medical and Surgical Reports of the Boston City Hospital; three as a postinfectious complication of scarlet fever and two from diphtheria. Later, he described the lesion as "an acute inflammation of the kidney characterized by cellular and fluid exudation in the interstitial tissue, accompanied by, but not dependant on, degeneration of the epithelium; the exudation is not purulent in character, and the lesions may be both diffuse and focal." Today AIN is far more often encountered as an allergic reaction to a drug (Table 340-1). Immune-mediated AIN may also occur as part of a known autoimmune syndrome, but in some cases there is no identifiable cause despite features suggestive of an immunologic etiology (Table 340-1).