renal disease in such patients is often irreversible and can slowly progress to ESRD. The most prudent approach is to monitor lithium levels frequently and adjust dosing to avoid toxic levels (preferably <1 meq/L). This is especially important because lithium is cleared less effectively as renal function declines. In patients who develop significant proteinuria, ACEI or ARB treatment should be initiated.

CALCINEURIN-INHIBITOR NEPHROTOXICITY

The calcineurin inhibitor (CNI) immunosuppressive agents cyclosporine and tacrolimus can cause both acute and chronic renal injury. Acute forms can result from vascular causes such as vasoconstriction or the development of thrombotic microangiopathy, or can be due to a toxic tubulopathy. Chronic CNI-induced renal injury is typically seen in solid organ (including heart-lung and liver) transplant recipients and manifests with a slow but irreversible reduction of glomerular filtration rate, with mild proteinuria and arterial hypertension. Hyperkalemia is a relatively common complication and is caused, in part, by tubular resistance to aldosterone. The histologic changes in renal tissue include patchy interstitial fibrosis and tubular atrophy, often in a "striped" pattern. In addition, the intrarenal vasculature often demonstrates hyalinosis, and focal glomerulosclerosis can be present as well. Similar changes may occur in patients receiving CNIs for autoimmune diseases, although the doses are generally lower than those used for organ transplantation. Dose reduction or CNI avoidance appears to mitigate the chronic tubulointerstitial changes, but may increase the risk of rejection and graft loss.

HEAVY METAL (LEAD) NEPHROPATHY

Heavy metals, such as lead or cadmium, can lead to a chronic tubulointerstitial process after prolonged exposure. The disease entity is no longer commonly diagnosed, because such heavy metal exposure has been greatly reduced due to the known health risks from lead and the consequent removal of lead from most commercial products and fuels. Nonetheless, occupational exposure is possible in workers involved in the manufacture or destruction of batteries, removal of lead paint, or manufacture of alloys and electrical equipment (cadmium) in countries where industrial regulation is less stringent. In addition, ingestion of moonshine whiskey distilled in lead-tainted containers has been one of the more frequent sources of lead exposure.

Early signs of chronic lead intoxication are attributable to proximal tubule dysfunction, particularly hyperuricemia as a result of diminished urate secretion. The triad of "saturnine gout," hypertension, and renal insufficiency should prompt a practitioner to ask specifically about lead exposure. Unfortunately, evaluating lead burden is not as straightforward as ordering a blood test; the preferred methods involve measuring urinary lead after infusion of a chelating agent or by radiographic fluoroscopy of bone. Several recent studies have shown an association between chronic low-level lead exposure and decreased renal function, although either of these two factors may have been the primary event. In those patients who have CIN of unclear origin and an elevated total body lead burden, repeated treatments of lead chelation therapy have been shown to slow the decline in renal function.

METABOLIC DISORDERS

Disorders leading to excessively high or low levels of certain electrolytes and products of metabolism can also lead to chronic kidney disease if untreated.

CHRONIC URIC ACID NEPHROPATHY

The constellation of pathologic findings that represent *gouty nephropathy* are very uncommon nowadays and are more of historical interest than clinical importance, as gout is typically well managed with allopurinol and other agents. However, there is emerging evidence that hyperuricemia is an independent risk factor for the development of chronic kidney disease, perhaps through endothelial damage. The complex interactions of hyperuricemia, hypertension, and renal failure are still incompletely understood.

Presently, gouty nephropathy is most likely to be encountered in patients with severe tophaceous gout and prolonged hyperuricemia from a hereditary disorder of purine metabolism (Chap. 431e). This should be distinguished from juvenile hyperuricemic nephropathy, a form of medullary cystic kidney disease caused by mutations in uromodulin (UMOD) (Chap. 339). Histologically, the distinctive feature of gouty nephropathy is the presence of crystalline deposits of uric acid and monosodium urate salts in the kidney parenchyma. These deposits not only cause intrarenal obstruction but also incite an inflammatory response, leading to lymphocytic infiltration, foreign-body giant cell reaction, and eventual fibrosis, especially in the medullary and papillary regions of the kidney. Since patients with gout frequently suffer from hypertension and hyperlipidemia, degenerative changes of the renal arterioles may constitute a striking feature of the histologic abnormality, out of proportion to the other morphologic defects. Clinically, gouty nephropathy is an insidious cause of chronic kidney disease. Early in its course, glomerular filtration rate may be near normal, often despite morphologic changes in medullary and cortical interstitium, proteinuria, and diminished urinary concentrating ability. Treatment with allopurinol and urine alkalinization is generally effective in preventing uric acid nephrolithiasis and the consequences of recurrent kidney stones; however, gouty nephropathy may be intractable to such measures. Furthermore, the use of allopurinol in asymptomatic hyperuricemia has not been consistently shown to improve renal function.

HYPERCALCEMIC NEPHROPATHY

(See also Chap. 424) Chronic hypercalcemia, as occurs in primary hyperparathyroidism, sarcoidosis, multiple myeloma, vitamin D intoxication, or metastatic bone disease, can cause tubulointerstitial disease and progressive renal failure. The earliest lesion is a focal degenerative change in renal epithelia, primarily in collecting ducts, distal tubules, and loops of Henle. Tubular cell necrosis leads to nephron obstruction and stasis of intrarenal urine, favoring local precipitation of calcium salts and infection. Dilation and atrophy of tubules eventually occur, as do interstitial fibrosis, mononuclear leukocyte infiltration, and interstitial calcium deposition (nephrocalcinosis). Calcium deposition may also occur in glomeruli and the walls of renal arterioles.

Clinically, the most striking defect is an inability to maximally concentrate the urine, due to reduced collecting duct responsiveness to arginine vasopressin and defective transport of sodium and chloride in the loop of Henle. Reductions in both glomerular filtration rate and renal blood flow can occur, both in acute and in prolonged hypercalcemia. Eventually, uncontrolled hypercalcemia leads to severe tubulointerstitial damage and overt renal failure. Abdominal x-rays may demonstrate nephrocalcinosis as well as nephrolithiasis, the latter due to the hypercalciuria that often accompanies hypercalcemia.

Treatment consists of reducing the serum calcium concentration toward normal and correcting the primary abnormality of calcium metabolism (Chap. 424). Renal dysfunction of acute hypercalcemia may be completely reversible. Gradual progressive renal insufficiency related to chronic hypercalcemia, however, may not improve even with correction of the calcium disorder.

HYPOKALEMIC NEPHROPATHY

Patients with prolonged and severe hypokalemia from chronic laxative or diuretic abuse, surreptitious vomiting, or primary aldosteronism may develop a reversible tubular lesion characterized by vacuolar degeneration of proximal and distal tubular cells. Eventually, tubular atrophy and cystic dilation accompanied by interstitial fibrosis may ensue, leading to irreversible chronic kidney disease. Timely correction of the hypokalemia will prevent further progression, but persistent hypokalemia can cause ESRD.

GLOBAL PERSPECTIVE

The causes of acute and chronic interstitial nephritis vary widely across the globe. Analgesic nephropathy continues to be seen in countries where phenacetin-containing compound analgesic preparations are readily available. Adulterants in unregulated herbal and traditional medicaments pose a threat of toxic interstitial nephritis, as