vomiting, and headaches. Its breakdown product (cyanate) can result in carbamylation of lipoproteins and peptides, leading to multiple organ dysfunctions. Guanidines, byproducts of protein metabolism, are increased and can inhibit α_1-hydroxylase activity within the kidney, leading to secondary hyperparathyroidism. β_2-Microglobulin accumulation in patients with ESRD has been associated with neuropathy, carpal tunnel syndrome, and amyloid infiltration of the joints. Specific roles for other accumulated metabolites are under investigation. The major manifestations of uremia are summarized in Figure 32-3.

Cardiovascular

In addition to hypertension, cardiovascular disorders are common in patients with CKD. More than 60% of patients with ESRD who start dialysis have echocardiographic manifestations of left ventricular hypertrophy, dilation, and systolic or diastolic dysfunction. Metabolic consequences of CKD, including accelerated atherogenesis, contribute to metastatic calcification in the myocardium, cardiac valves, and arteries. Arrhythmias, including those resulting in sudden death, may be caused by electrolyte abnormalities, cardiac structural changes, or ischemic cardiovascular disease. Pericarditis can occur in patients with uremia before they start dialysis or in ESRD patients receiving inadequate dialysis.

Gastrointestinal

Gastrointestinal disturbances are among the earliest and most common signs of the uremic syndrome. Patients describe a metallic taste and loss of appetite. Later, they experience nausea, vomiting, and weight loss, and those with severe uremia may also experience stomatitis and enteritis. Gastrointestinal bleeding caused by gastritis, peptic ulceration, and arterial venous malformations in the setting of platelet dysfunction may be present.

Neurologic

Central nervous system manifestations are frequent in advanced CKD and are characterized predominantly by changes in cognitive function and sleep disturbances. Lethargy, irritability, asterixis, seizures, and frank encephalopathy with coma are late manifestations of uremia and are usually avoided by timely initiation of renal replacement therapy (RRT). Peripheral neurologic manifestations appear as a progressive, symmetrical sensory neuropathy in a glove-and-stocking distribution. Patients have decreased distal tendon reflexes and loss of vibratory perception. Peripheral motor impairment can result in restless legs, footdrop, or wristdrop. Most of these neurologic manifestations reverse with adequate dialysis or kidney transplantation.

Musculoskeletal

Alterations in calcium and phosphate homeostasis, with hyperparathyroidism and disturbance of vitamin D metabolism, also are common. Hypocalcemia and secondary hyperparathyroidism are the result of phosphate retention and lack of α_1-hydroxylase activity in the failing kidney, with consequent deficiency of the most active form of vitamin D. Over time, maladaptive parathyroid hypertrophy leads to bone disease and tissue calcification.

Hematologic and Immunologic

Erythropoietin (EPO), a hormone produced by the kidney that regulates erythrocyte production, becomes progressively

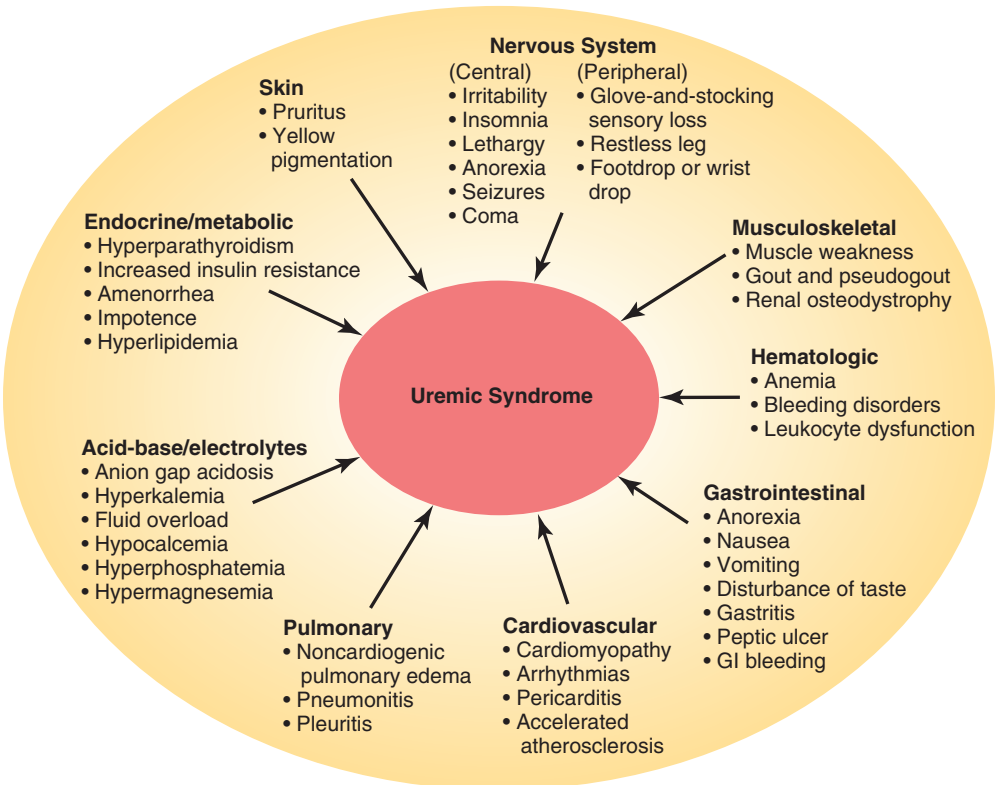

FIGURE 32-3 Diagrammatic summary of the major manifestations of the uremic syndrome. GI, Gastrointestinal.