TABLE 423-1 CAUSES OF HYPOPHOSPHATEMIA

- I. Reduced renal tubular phosphate reabsorption
  - A. PTH/PTHrP-dependent
    - 1. Primary hyperparathyroidism
    - 2. Secondary hyperparathyroidism
      - a. Vitamin D deficiency/resistance
      - b. Calcium starvation/malabsorption
      - c. Bartter's syndrome
      - d. Autosomal recessive renal hypercalciuria with hypomagnesemia
    - 3. PTHrP-dependent hypercalcemia of malignancy
    - 4. Familial hypocalciuric hypercalcemia
  - B. PTH/PTHrP-independent
    - 1. Excess FGF23 or other "phosphatonins"
      - a. X-linked hypophosphatemic rickets (XLH)
      - b. Autosomal recessive hypophosphatemia (ARHP)
      - c. Autosomal dominant hypophosphatemic rickets (ADHR) (DMP1, ENPP1 deficiency)
      - d. Tumor-induced osteomalacia syndrome (TIO)
      - e. McCune-Albright syndrome (fibrous dysplasia)
      - f. Epidermal nevus syndrome
    - 2. Intrinsic renal disease
      - a. Fanconi's syndrome(s)
      - b. Cystinosis
      - c. Wilson's disease
      - d. NaPi-2a or NaPi-2c mutations
    - 3. Other systemic disorders
      - a. Poorly controlled diabetes mellitus
      - b. Alcoholism
      - c. Hyperaldosteronism
      - d. Hypomagnesemia
      - e. Amyloidosis
      - f. Hemolytic-uremic syndrome
      - g. Renal transplantation or partial liver resection
      - h. Rewarming or induced hyperthermia
    - 4. Drugs or toxins
      - a. Ethanol
      - b. Acetazolamide, other diuretics
      - c. High-dose estrogens or glucocorticoids
      - d. Heavy metals (lead, cadmium, saccharated ferric oxide)
      - e. Toluene, *N*-methyl formamide
      - f. Cisplatin, ifosfamide, foscarnet, rapamycin
- II. Impaired intestinal phosphate absorption
  - A. Aluminum-containing antacids
  - B. Sevelamer
- III. Shifts of extracellular phosphate into cells
  - A. Intravenous glucose
  - B. Insulin therapy for prolonged hyperglycemia or diabetic ketoacidosis
  - C. Catecholamines (epinephrine, dopamine, albuterol)
  - D. Acute respiratory alkalosis
  - E. Gram-negative sepsis, toxic shock syndrome
  - F. Recovery from starvation or acidosis
  - G. Rapid cellular proliferation
    - 1. Leukemic blast crisis
    - 2. Intensive erythropoietin, other growth factor therapy
- IV. Accelerated net bone formation
  - A. After parathyroidectomy
  - B. Treatment of vitamin D deficiency, Paget's disease
  - C. Osteoblastic metastases

Abbreviations: PTH, parathyroid hormone; PTHrP, parathyroid hormone–related peptide.

of *PHEX* leads to increased levels of FGF23 has not been determined. Two rare autosomal recessive hypophosphatemic syndromes associated with elevated FGF23 are due to inactivating mutations of dentin matrix protein-1 (*DMP1*) and ectonucleotide pyrophosphatase/phosphodiesterase 1 (*ENPP1*), both of which normally are highly expressed in bone and regulate FGF23 production. An unusual hypophosphatemic disorder, tumor-induced osteomalacia (TIO), is an acquired disorder in which tumors, usually of mesenchymal origin and generally histologically benign, secrete FGF23 and/or other molecules that induce renal phosphate wasting. The hypophosphatemic syndrome resolves completely within hours to days after successful resection of the responsible tumor. Such tumors typically express large amounts of FGF23 mRNA, and patients with TIO usually exhibit elevations of FGF23 in their blood.

Dent's disease is an X-linked recessive disorder caused by inactivating mutations in *CLCN5*, a chloride transporter expressed in endosomes of the proximal tubule; features include hypercalciuria, hypophosphatemia, and recurrent kidney stones. Renal phosphate wasting is common among poorly controlled diabetic patients and alcoholics, who therefore are at risk for iatrogenic hypophosphatemia when treated with insulin or IV glucose, respectively. Diuretics and certain other drugs and toxins can cause defective renal tubular phosphate reabsorption (Table 423-1).

In hospitalized patients, hypophosphatemia is often attributable to massive redistribution of phosphate from the ECF into cells. Insulin therapy for diabetic ketoacidosis is a paradigm for this phenomenon, in which the severity of the hypophosphatemia is related to the extent of antecedent depletion of phosphate and other electrolytes (Chap. 417). The hypophosphatemia is usually greatest at a point many hours after initiation of insulin therapy and is difficult to predict from baseline measurements of serum phosphate at the time of presentation, when prerenal azotemia can obscure significant phosphate depletion. Other factors that may contribute to such acute redistributive hypophosphatemia include antecedent starvation or malnutrition, administration of IV glucose without other nutrients, elevated blood catecholamines (endogenous or exogenous), respiratory alkalosis, and recovery from metabolic acidosis.

Hypophosphatemia also can occur transiently (over weeks to months) during the phase of accelerated net bone formation that follows parathyroidectomy for severe primary hyperparathyroidism or during treatment of vitamin D deficiency or lytic Paget's disease. This is usually most prominent in patients who preoperatively have evidence of high bone turnover (e.g., high serum levels of alkaline phosphatase). Osteoblastic metastases can also lead to this syndrome.

Clinical and Laboratory Findings The clinical manifestations of severe hypophosphatemia reflect a generalized defect in cellular energy metabolism because of ATP depletion, a shift from oxidative phosphorylation toward glycolysis, and associated tissue or organ dysfunction. Acute, severe hypophosphatemia occurs mainly or exclusively in hospitalized patients with underlying serious medical or surgical illness and preexisting phosphate depletion due to excessive urinary losses, severe malabsorption, or malnutrition. Chronic hypophosphatemia tends to be less severe, with a clinical presentation dominated by musculoskeletal complaints such as bone pain, osteomalacia, pseudofractures, and proximal muscle weakness or, in children, rickets and short stature.

Neuromuscular manifestations of severe hypophosphatemia are variable but may include muscle weakness, lethargy, confusion, disorientation, hallucinations, dysarthria, dysphagia, oculomotor palsies, anisocoria, nystagmus, ataxia, cerebellar tremor, ballismus, hyporeflexia, impaired sphincter control, distal sensory deficits, paresthesia, hyperesthesia, generalized or Guillain-Barré–like ascending paralysis, seizures, coma, and even death. Serious sequelae such as paralysis, confusion, and seizures are likely only at phosphate concentrations <0.25 mmol/L (<0.8 mg/dL). Rhabdomyolysis may develop during rapidly progressive hypophosphatemia. The diagnosis of hypophosphatemia-induced rhabdomyolysis may be overlooked, as up to 30% of patients with acute hypophosphatemia (<0.7 m*M*) have creatine phosphokinase