TABLE 73-2 DIFFERENTIAL DIAGNOSIS OF HYPOCALCEMIA

- Hypoparathyroidism
  - Surgical
  - Idiopathic and autoimmune
  - Infiltrative diseases
    - Wilson's disease (copper)
    - Hemochromatosis
    - Sarcoidosis
    - Metastatic (breast) cancer
  - Congenital
    - Isolated, sporadic
    - DiGeorge syndrome
    - Infant of mother with hyperparathyroidism
  - Hereditary
    - X-linked
    - Parathyroid gland calcium receptor (Gα11 subunit)–activating mutations
    - Parathyroid hormone (PTH) signal peptide mutation
    - *GCM2* (formerly *GCMB*) mutation
- Pseudohypoparathyroidism
  - Type Ia: multiple hormone resistance, Albright's hereditary osteodystrophy
  - Type Ib: PTH resistance without other abnormalities
  - Type Ic: specific PTH resistance, resulting from defect in catalytic subunit of PTH-receptor complex
  - Type II: specific PTH resistance, postreceptor defect of adenylyl cyclase, undefined
- Vitamin D disorders
  - Absent ultraviolet exposure
  - Vitamin D deficiency
  - Fat malabsorption
  - Vitamin D–dependent rickets, renal 1α-hydroxylase deficiency, 1,25-dihydroxyvitamin D–receptor defects
  - Chronic renal failure
  - Hepatic failure
- Hypoalbuminemia
- Sepsis
- Hypermagnesemia and hypomagnesemia
- Rapid bone formation
  - Hungry bone syndrome after parathyroidectomy or thyroidectomy
  - Osteoblastic metastases
  - Vitamin D therapy of osteomalacia, rickets
- Hyperphosphatemia
  - Crush injury, rhabdomyolysis
  - Renal failure
  - Tumor lysis
  - Excessive phosphate (PO_4) administration (PO, IV, PR)
- Medications
  - Mithramycin, plicamycin
  - Bisphosphonates
  - Calcitonin
  - Fluoride
  - Ethylenediaminetetraacetic acid (EDTA)
  - Citrate
  - Intravenous contrast
  - Foscarnet
- Pancreatitis
  - Hypoalbuminemia
  - Hypomagnesemia
  - Calcium soap formation

tissue infiltrative diseases such as breast cancer, hemochromatosis (i.e., iron deposition), or sarcoidosis may destroy or replace normal parathyroid tissue.

The diagnosis is made by finding a low serum ionized calcium level in a patient with an inappropriately reduced serum PTH concentration. The phosphorus concentration usually is high normal or frankly elevated, and plasma $1,25(OH)_2D$ concentrations are reduced (see Chapter 72).

Treatment is normally directed at increasing intestinal calcium absorption through the use of large doses of calcium (up to 6-8 g of elemental calcium per day) and, when necessary, the addition of the active form of vitamin D ($1,25[OH]_2D$), in replacement amounts of 0.25 to 1.0 µg/day. The goal is to induce sufficient intestinal calcium hyperabsorption to overwhelm the ability of the kidney to excrete it. It carries the risk of inducing significant hypercalciuria and therefore nephrocalcinosis and nephrolithiasis. Accordingly, 24-hour urinary calcium levels must be measured regularly to identify dangerously high hypercalciuria. The serum calcium concentration is maintained in the low-normal range, about 8.5 to 9.0 mg/dL. In some instances, addition of a thiazide diuretic such as hydrochlorothiazide, which stimulates renal calcium reabsorption, may be effective in preventing hypercalciuria while raising the serum calcium level.

Pseudohypoparathyroidism

Pseudohypoparathyroidism refers to a group of disorders that have in common resistance to the actions of PTH. In most cases, resistance results from different inactivating mutations in the signal-transducing protein $G_{s\alpha}$. The most common form of the syndrome, type Ia, is associated with multiple hormone resistance and a phenotype referred to as *Albright's hereditary osteodystrophy*, which includes short stature, shortened fourth and fifth metacarpals and metatarsals, obesity, mental retardation, subcutaneous calcifications, and cafe au lait spots.

Patients resemble those with hypoparathyroidism; they are hypocalcemic and have hyperphosphatemia. The diagnosis is made by the finding of an elevated circulating PTH level in a patient with hypocalcemia and hyperphosphatemia for whom other causes of hypocalcemia and secondary hypoparathyroidism have been excluded. The treatment is similar to that of hypoparathyroidism.

Vitamin D Disorders

Active vitamin D, $1,25(OH)_2D$, is required to absorb calcium from the intestine. Activation of vitamin D requires adequate amounts of vitamin D from the diet or sunlight exposure, an intact intestine through which to absorb calcium and vitamin D, an intact liver with which to convert vitamin D to 25-hydroxyvitamin D, and an intact kidney to convert 25-hydroxyvitamin D to $1,25(OH)_2D$ (see Chapter 72).

Developing hypocalcemia and osteomalacia or rickets (see Chapter 74) in settings in which one or more of the conversion steps is disrupted is common. Malabsorption syndromes, such as short-bowel syndrome and celiac sprue, lead to hypocalcemia as a result of calcium and vitamin D malabsorption. Chronic liver diseases, particularly primary biliary cirrhosis, lead to hypocalcemia and osteomalacia. Chronic renal insufficiency leads to failure to produce $1,25(OH)_2D$, with reductions in serum calcium levels and inefficient absorption of intestinal calcium.

Although Western diets are supplemented with vitamin D in milk and multivitamins, diets composed of no milk, human milk, or unsupplemented bovine milk are vitamin D deficient. Relatively trivial exposure to sunlight can provide ample vitamin D and replace dietary needs for vitamin D. However, vitamin D deficiency can occur in settings in which both sun exposure and dietary intake of vitamin D are poor (i.e., cloudy climates, excessive clothing or body covering, prolonged nursing by infants, and the standard tea and toast diet of older adults), vitamin D deficiency is the rule rather than the exception.

Certain genetic syndromes affecting vitamin D conversion can result in severe hypocalcemia. Long-term, high-dose treatment with anticonvulsants such as phenytoin or phenobarbital or their derivatives may lead to hypocalcemia and osteomalacia.

Hypoalbuminemia

Reductions in serum albumin, as occur in burn patients, the nephrotic syndrome, malnutrition, and cirrhosis, lead to reductions in serum total calcium without a reduction in the ionized total serum calcium level. Several formulas exist for correcting total serum calcium for albumin, but none is entirely accurate.