TABLE 73-1 DISORDERS ASSOCIATED WITH HYPERCALCEMIA

- Malignancy-associated hypercalcemia
  - Humoral hypercalcemia of malignancy
  - Hypercalcemia caused by 1,25-dihydroxyvitamin D_3 ($1,25[OH]_2D_3$)–secreting lymphomas
  - Hypercalcemia caused by direct skeletal invasion
  - True ectopic hyperparathyroidism
- Primary and tertiary hyperparathyroidism
- Familial hypocalciuric hypercalcemia or familial benign hypercalcemia
- Granulomatous disorders
  - Sarcoid
  - Berylliosis
  - Foreign body
  - Tuberculosis
  - Coccidioidomycosis
  - Blastomycosis
  - Histoplasmosis
  - Granulomatous leprosy
  - Eosinophilic granuloma
  - Histiocytosis
  - Inflammatory bowel disease
- Endocrine disorders other than hyperparathyroidism
  - Hyperthyroidism
  - Pheochromocytoma
  - Addisonian crisis
  - Vasoactive intestinal peptide–producing tumor (VIPoma); watery diarrhea, hypokalemia, and achlorhydria (WDHA) syndrome
- Medications
  - Thiazides
  - Aminophylline
  - Lithium
  - Estrogen/antiestrogen in breast cancer with bone metastases (estrogen flare)
  - Vitamin D and derivatives (calcitriol, dihydrotachysterol)
  - Vitamin A (including retinoic acid derivatives)
  - Foscarnet
- Milk-alkali syndrome
- Immobilization plus high bone turnover
  - Juvenile skeleton
  - Paget's disease
  - Myeloma and breast cancer with bone metastases
  - Prehumoral hypercalcemia of malignancy
  - Mild primary hyperparathyroidism
  - Secondary hyperparathyroidism (e.g., from continuous ambulatory peritoneal dialysis)
- Chronic and acute renal failure
  - Recovery phase of rhabdomyolysis-induced acute renal failure
  - Chronic hemodialysis
  - Calcitriol
  - Immobilization
  - Decreased calcium clearance
  - Calcium carbonate
- Total parenteral nutrition (TPN)
  - Calcium-containing TPN in patients with decreased glomerular filtration rate
  - Chronic TPN in patients with short bowel syndrome
- Hyperproteinemia
  - Volume contraction with hyperalbuminemia
  - Myeloma with calcium-binding immunoglobulin
- End-stage liver disease
- Manganese intoxication

and on the skeleton to activate osteoclasts and induce bone resorption. PTHrP is the product of many normal cell types and, in health, is typically produced at low levels.

Tumors classically associated with the HHM mechanism are squamous carcinomas of any site (i.e., larynx, lung, cervix, and esophagus), renal carcinomas, ovarian carcinomas, and breast cancer. Hypercalcemia in HHM occurs in the absence of skeletal metastases or in the setting of a few skeletal metastases. If tumor resection or ablation is possible, hypercalcemia reverses. In addition to hypercalcemia, these patients have elevations in PTHrP concentrations and reductions in the levels of PTH, 1,25-dihydroxyvitamin D_3 ($1,25[OH]_2D$), and serum phosphorus and the tubular maximum for phosphorus (TmP) (see Chapter 72).

A second form of MAHC is caused by local tumor invasion of the skeleton, a process called *local osteolytic hypercalcemia* (LOH). LOH accounts for about 20% of patients with MAHC. In these patients, unlike those with HHM, the skeletal metastatic or primary tumor burden is large, and the offending tumor is most often a breast cancer or a hematologic neoplasm such as multiple myeloma, leukemia, or lymphoma. Local factors are secreted by tumors in the bone marrow that induce osteoclastic bone resorption. They include PTHrP, macrophage inflammatory protein 1α (MIP-1α), receptor-activating nuclear factor-κB ligand (RANKL), interleukin-6, and interleukin-1. These patients have reductions in PTH, PTHrP, and $1,25(OH)_2D$ levels, and have normal to elevated serum phosphorus values.

A third form of MAHC is secretion of $1,25(OH)_2D$ by lymphomas and dysgerminomas. This form is unusual, and the mechanism is interesting. Although direct bone involvement may occur and may contribute to hypercalcemia, the increase in $1,25(OH)_2D$ leads to intestinal calcium hyperabsorption and to systemically driven bone resorption. This condition is essentially a malignant version of the hypercalcemia that occurs in sarcoidosis (see Granulomatous Disorders).

Primary and Tertiary Hyperparathyroidism

Although MAHC is the most common cause of hypercalcemia among inpatients, primary HPT is by far the most common cause among healthy outpatients. Together, MAHC and HPT account for about 90% of cases of hypercalcemia. Most often, the hypercalcemia of HPT is mild, with serum calcium values in the range of 10.6 to 11.5 mg/dL. However, HPT occasionally produces spectacular hypercalcemia in the 20-mg/dL range. In about 85% of patients, hypercalcemia results from a single parathyroid adenoma that overproduces PTH, and in about 15% of patients, it results from multiple-gland hyperplasia. In less than 1% of patients, HPT may result from parathyroid carcinoma. For all these etiologies, the diagnosis is made by the discovery of an elevated serum PTH level in a patient with hypercalcemia. Hypophosphatemia, a reduction in the TmP, increased plasma $1,25(OH)_2D$ and serum chloride levels, and a reduction in the serum bicarbonate concentration are typical features.

Primary HPT often is asymptomatic. However, some patients develop hypercalciuria and calcium nephrolithiasis, most often as a result of calcium oxalate and, less commonly, calcium phosphate stones. Some patients with HPT, especially those with a more severe form, have a reduction in bone mineral density characterized histologically as hyperparathyroid bone disease, also called *osteitis fibrosa cystica* (see Chapter 74). Other patients may develop mild to severe renal failure as a result of the mechanisms described earlier. Each of the previously described conditions—significant osteopenia, kidney stones, reduced renal function, and a serum calcium concentration greater than 1 mg/dL above normal—is an indication for parathyroidectomy. Other patients may be monitored conservatively. In patients who refuse or are unable to undergo surgery, medical management of hypercalcemia may be attempted using bisphosphonates or the calcium receptor mimetic cinacalcet.

HPT can occur as part of one of the multiple endocrine neoplasia (MEN) syndromes. It is associated with pituitary and islet tumors (MEN 1) and with pheochromocytomas and medullary carcinoma of the thyroid (MEN 2).

Secondary HPT is an appropriate increase in circulating PTH associated with eucalcemia or hypocalcemia. It occurs in an attempt to correct hypocalcemia resulting, for example, from vitamin D deficiency or chronic renal failure