TABLE 424-1 CLASSIFICATION OF CAUSES OF HYPERCALCEMIA

- **I. Parathyroid-Related**
  - A. Primary hyperparathyroidism
    - 1. Adenoma(s)
    - 2. Multiple endocrine neoplasia
    - 3. Carcinoma
  - B. Lithium therapy
  - C. Familial hypocalciuric hypercalcemia
- **II. Malignancy-Related**
  - A. Solid tumor with metastases (breast)
  - B. Solid tumor with humoral mediation of hypercalcemia (lung, kidney)
  - C. Hematologic malignancies (multiple myeloma, lymphoma, leukemia)
- **III. Vitamin D–Related**
  - A. Vitamin D intoxication
  - B. ↑ $1,25(OH)_2D$; sarcoidosis and other granulomatous diseases
  - C. ↑ $1,25(OH)_2D$; impaired $1,25(OH)_2D$ metabolism due to 24-hydroxylase deficiency
- **IV. Associated with High Bone Turnover**
  - A. Hyperthyroidism
  - B. Immobilization
  - C. Thiazides
  - D. Vitamin A intoxication
  - E. Fat necrosis
- **V. Associated with Renal Failure**
  - A. Severe secondary hyperparathyroidism
  - B. Aluminum intoxication
  - C. Milk-alkali syndrome

is the cause. Nevertheless, differentiating primary hyperparathyroidism from occult malignancy can occasionally be difficult, and careful evaluation is required, particularly when the duration of the hypercalcemia is unknown. Hypercalcemia not due to hyperparathyroidism or malignancy can result from excessive vitamin D action, impaired metabolism of $1,25(OH)_2D$, high bone turnover from any of several causes, or renal failure (Table 424-1). Dietary history and a history of ingestion of vitamins or drugs are often helpful in diagnosing some of the less frequent causes. Immunometric PTH assays serve as the principal laboratory test in establishing the diagnosis.

Hypercalcemia from any cause can result in fatigue, depression, mental confusion, anorexia, nausea, vomiting, constipation, reversible renal tubular defects, increased urine output, a short QT interval in the electrocardiogram, and, in some patients, cardiac arrhythmias. There is a variable relation from one patient to the next between the severity of hypercalcemia and the symptoms. Generally, symptoms are more common at calcium levels >2.9–3.0 mmol/L (11.6–12.0 mg/dL), but some patients, even at this level, are asymptomatic. When the calcium level is >3.2 mmol/L (12.8 mg/dL), calcification in kidneys, skin, vessels, lungs, heart, and stomach occurs and renal insufficiency may develop, particularly if blood phosphate levels are normal or elevated due to impaired renal excretion. Severe hypercalcemia, usually defined as ≥3.7–4.5 mmol/L (14.8–18.0 mg/dL), can be a medical emergency; coma and cardiac arrest can occur.

Acute management of the hypercalcemia is usually successful. The type of treatment is based on the severity of the hypercalcemia and the nature of associated symptoms, as outlined below.

PRIMARY HYPERPARATHYROIDISM

Natural History and Incidence Primary hyperparathyroidism is a generalized disorder of calcium, phosphate, and bone metabolism due to an increased secretion of PTH. The elevation of circulating hormone usually leads to hypercalcemia and hypophosphatemia. There is great variation in the manifestations. Patients may present with multiple signs and symptoms, including recurrent nephrolithiasis, peptic ulcers, mental changes, and, less frequently, extensive bone resorption. However, with greater awareness of the disease and wider use of multiphasic screening tests, including measurements of blood calcium, the diagnosis is frequently made in patients who have no symptoms and minimal, if any, signs of the disease other than hypercalcemia and elevated levels of PTH. The manifestations may be subtle, and the disease may have a benign course for many years or a lifetime. This milder form of the disease is usually termed *asymptomatic hyperparathyroidism*. Rarely, hyperparathyroidism develops or worsens abruptly and causes severe complications such as marked dehydration and coma, so-called hypercalcemic parathyroid crisis.

The annual incidence of the disease is calculated to be as high as 0.2% in patients >60, with an estimated prevalence, including undiscovered asymptomatic patients, of ≥1%; some reports suggest the incidence may be declining. If confirmed, these changing estimates may reflect less frequent routine testing of serum calcium in recent years, earlier overestimates in incidence, or unknown factors. The disease has a peak incidence between the third and fifth decades but occurs in young children and in the elderly.

Etiology Parathyroid tumors are most often encountered as isolated adenomas without other endocrinopathy. They may also arise in hereditary syndromes such as MEN syndromes. Parathyroid tumors may also arise as secondary to underlying disease (excessive stimulation in secondary hyperparathyroidism, especially chronic renal failure) or after other forms of excessive stimulation such as lithium therapy. These etiologies are discussed below.

SOLITARY ADENOMAS A single abnormal gland is the cause in ~80% of patients; the abnormality in the gland is usually a benign neoplasm or adenoma and rarely a parathyroid carcinoma. Some surgeons and pathologists report that the enlargement of multiple glands is common; double adenomas are reported. In ~15% of patients, all glands are hyperfunctioning; *chief cell parathyroid hyperplasia* is usually hereditary and frequently associated with other endocrine abnormalities.

HEREDITARY SYNDROMES AND MULTIPLE PARATHYROID TUMORS Hereditary hyperparathyroidism can occur without other endocrine abnormalities but is usually part of a *multiple endocrine neoplasia* (MEN) syndrome (Chap. 408). MEN 1 (Wermer's syndrome) consists of hyperparathyroidism and tumors of the pituitary and pancreas, often associated with gastric hypersecretion and peptic ulcer disease (Zollinger-Ellison syndrome). MEN 2A is characterized by pheochromocytoma and medullary carcinoma of the thyroid, as well as hyperparathyroidism; MEN 2B has additional associated features such as multiple neuromas but usually lacks hyperparathyroidism. Each of these MEN syndromes is transmitted in an apparent autosomal dominant manner, although, as noted below, the genetic basis of MEN 1 involves biallelic loss of a tumor suppressor.

The *hyperparathyroidism jaw tumor* (HPT-JT) syndrome occurs in families with parathyroid tumors (sometimes carcinomas) in association with benign jaw tumors. This disorder is caused by mutations in *CDC73* (*HRPT2*), and mutations in this gene are also observed in parathyroid cancers. Some kindreds exhibit hereditary hyperparathyroidism without other endocrinopathies. This disorder is often termed *nonsyndromic familial isolated hyperparathyroidism* (FIHP). There is speculation that these families may be examples of variable expression of the other syndromes such as MEN 1, MEN 2, or the HPT-JT syndrome, but they may also have distinctive, still unidentified genetic causes.

Pathology Adenomas are most often located in the inferior parathyroid glands, but in 6–10% of patients, parathyroid adenomas may be located in the thymus, the thyroid, the pericardium, or behind the esophagus. Adenomas are usually 0.5–5 g in size but may be as large as 10–20 g (normal glands weigh 25 mg on average). Chief cells are predominant in both hyperplasia and adenoma. With chief cell hyperplasia, the enlargement may be so asymmetric that some involved glands appear grossly normal. If generalized hyperplasia is present, however, histologic examination reveals a uniform pattern of chief cells and disappearance of fat even in the absence of an increase in gland weight. Thus, microscopic examination of biopsy specimens of several glands is essential to interpret findings at surgery.