Tertiary HPT refers to HPT associated with hypercalcemia that occurs in the setting of prolonged stimulation of the parathyroid glands, such as chronic renal failure with hypocalcemia or chronic vitamin D deficiency resulting from malabsorption. Chronic parathyroid stimulation leads to parathyroid hyperplasia and sometimes adenomas, and these conditions may fail to suppress normally and cause hypercalcemia. The classic example is development of PTH-dependent hypercalcemia after successful renal transplantation.

Familial Hypocalciuric Hypercalcemia

Familial hypocalciuric hypercalcemia, also called *familial benign hypercalcemia*, is an autosomal dominant inherited disorder that results from heterozygous inactivating mutations in the calcium receptor. Parathyroid glands that bear such a defective receptor on their surface inappropriately perceive circulating calcium concentrations to be low. They therefore behave as though the patient is hypocalcemic and appropriately secrete additional PTH. This action causes the serum calcium concentration to rise, and the PTH equilibrates at a high-normal to elevated level. The hypercalcemia is usually mild, in the 11- to 12-mg/dL range, but it may be higher. Because the partially inactivated calcium receptors are expressed in the kidney, the kidney inappropriately conserves calcium, leading to hypocalciuria and contributing to hypercalcemia. Because these same calcium receptors are also expressed in the central nervous system, the hypercalcemia is not perceived, and affected individuals are therefore asymptomatic. The two names of this syndrome describe it accurately.

With the exception of the hypocalciuria and the autosomal dominant pattern of inheritance, these individuals are similar biochemically to patients with primary HPT. Because affected individuals are asymptomatic and do not develop adverse sequelae from the syndrome, its primary importance is that affected individuals be properly identified and protected from unnecessary and ineffective parathyroidectomy. Homozygous individuals, usually infants, develop severe hypercalcemia requiring urgent total parathyroidectomy.

Granulomatous Disorders

Most granulomatous disorders can lead to hypercalcemia (see Table 73-1). The prototypes are sarcoidosis, tuberculosis, and the fungal diseases listed. As with the kidney, granulomas have the ability to convert inactive 25-hydroxyvitamin D to the active metabolite, $1,25(OH)_2D$. When exposed to sunlight, ultraviolet radiation, or relatively trivial quantities of dietary vitamin D, individuals with these disorders may develop mild to severe hypercalcemia.

Hypercalcemia results from intestinal calcium hyperabsorption and $1,25(OH)_2D$-induced bone resorption; the former is the important component in most cases. Because of the hypercalcemia, PTH is suppressed, and the serum phosphorus level is elevated. The combination of hypercalcemia and hyperphosphatemia may lead to nephrocalcinosis and renal failure. Treatment focuses on correcting the underlying disorder. Measures include a low dietary calcium intake, a low vitamin D intake, limiting sun exposure, and hydration. Loop diuretics are administered to accelerate calcium clearance, and if the hypercalcemia is severe, glucocorticoids are used.

Endocrine Disorders Other Than Hyperparathyroidism

In addition to HPT, four other endocrine disorders have been associated with the development of hypercalcemia. As many as 50% of people with *hyperthyroidism* have at least mild hypercalcemia. The hypercalcemia is rarely greater than 11 mg/dL. The mechanism is thought to be an increase in osteoclast activation by thyroid hormone.

A second disorder is *pheochromocytoma.* Some of these individuals are hypercalcemic as a result of primary HPT occurring in the MEN 2 syndrome, but others become hypercalcemic as a result of PTHrP secretion by a pheochromocytoma. Hypercalcemia has also been reported in patients with hypoadrenalism and those with islet cell tumors called VIPomas.

Medications

Drugs that may cause hypercalcemia include thiazide diuretics, lithium, aminophylline, theophylline, vitamins D and A, foscarnet, and estrogens and tamoxifen in the setting of breast cancer with extensive skeletal metastases.

Milk-Alkali Syndrome

The normal intake of calcium is in the range of 600 to 1200 mg/day for most people. As reviewed in Chapter 72, absorption of calcium from the diet is tightly controlled. However, ingestion of very large quantities of calcium may overwhelm this system and lead to hypercalcemia. This condition was originally described in the 1940s in patients ingesting enormous quantities of milk, cream, and antacids. It is still encountered with some regularity in patients ingesting large quantities of calcium carbonate or other calcium-containing antacids for peptic ulcer disease. For hypercalcemia to occur, calcium intake must exceed 4 g/day, and it is often in the 10- to 20-g/day range. Severe hypercalcemia is common and may lead to renal failure.

Immobilization

Hypercalcemia due to immobilization requires two conditions: *complete immobilization* (e.g., quadriplegia) for a period of weeks, occurring on a background of *high bone turnover*, as occurs in young adults or children, HPT, Paget's disease, and malignant skeletal disease such as breast cancer with bone metastases or multiple myeloma. Immobilization activates osteoclastic bone resorption and inhibits osteoblastic activity, producing a severe uncoupling of bone resorption from formation, with rapid and enormous net losses of calcium from the skeleton into the ECF. Left untreated, the condition results in severe demineralization. The syndrome is associated with hypercalciuria, which with chronic urinary catheterization leads to urinary tract infection and severe calcium nephrolithiasis.

The most effective treatment for hypercalcemia is active weight bearing. Hydration and antiresorptive drugs such as the bisphosphonates may be used.

Chronic and Acute Renal Failure

Chronic and acute renal failure has been associated with hypercalcemia. The more common initial abnormality is hypocalcemia induced by a reduction in kidney-derived $1,25(OH)_2D$ and an