glands is controlled by the level of free (ionized) calcium in the bloodstream. Normally, decreased levels of free calcium stimulate the synthesis and secretion of PTH. The metabolic functions of PTH that regulate serum calcium levels are several. Specifically, PTH:

- Increases the renal tubular reabsorption of calcium, thereby conserving free calcium
- Increases the conversion of vitamin D to its active dihydroxy form in the kidneys
- Increases urinary phosphate excretion, thereby lowering serum phosphate levels
- Augments gastrointestinal calcium absorption

The net result of these activities is to elevate the level of free calcium, which, in turn, inhibits further PTH secretion in a classic feedback loop. Similar to the other endocrine organs, abnormalities of the parathyroid glands include both hyperfunction and hypofunction. Tumors of the parathyroid glands, in contrast to thyroid tumors, usually come to attention because of excessive secretion of PTH rather than mass effects.

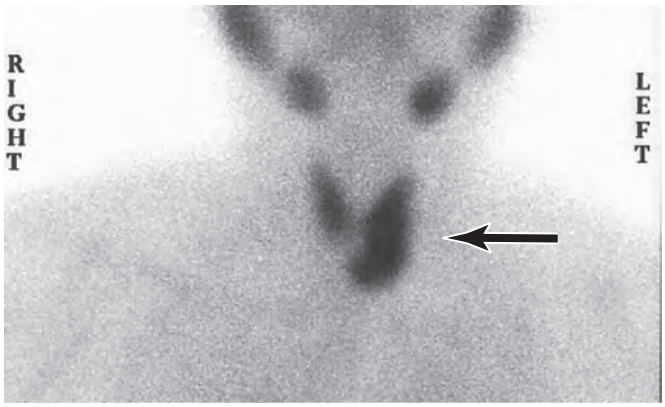

Figure 24-24 Parathyroid adenoma imaging. Technetium-^{99}m-sestamibi radionuclide scan demonstrates an area of increased uptake corresponding to the left inferior parathyroid gland *(arrow)*, which contained a parathyroid adenoma. Preoperative scintigraphy is useful in localizing and distinguishing adenomas from parathyroid hyperplasia, where more than one gland would demonstrate increased uptake.

Hyperparathyroidism

Hyperparathyroidism is caused by elevated parathyroid hormone and is classified into primary, secondary, and least commonly, tertiary types.

- *Primary hyperparathyroidism*: an autonomous overproduction of parathyroid hormone (PTH), usually resulting from an adenoma or hyperplasia of parathyroid tissue
- *Secondary hyperparathyroidism*: compensatory hypersecretion of PTH in response to prolonged hypocalcemia, most commonly from chronic renal failure
- *Tertiary hyperparathyroidism*: persistent hypersecretion of PTH even after the cause of prolonged hypocalcemia is corrected, for example after renal transplant

Primary Hyperparathyroidism

Primary hyperparathyroidism is one of the most common endocrine disorders, and it is an important cause of hypercalcemia. The frequency of the various parathyroid lesions underlying the hyperfunction is as follows:

- Adenoma: 85% to 95%
- Primary hyperplasia (diffuse or nodular): 5% to 10%
- Parathyroid carcinoma: ~1%

Primary hyperparathyroidism is usually a disease of adults and is more common in women than in men by a ratio of nearly 4:1. The annual incidence is now estimated to be about 25 cases per 100,000 in the United States and Europe; as many as 80% of patients with this condition are identified in the outpatient setting, when hypercalcemia is discovered incidentally on a serum electrolyte panel. Most cases occur in the 50s or later in life.

The most common cause of primary hyperparathyroidism is a solitary parathyroid adenoma arising sporadically (Fig. 24-24). Most, if not all, sporadic parathyroid adenomas are monoclonal, consistent with their being neoplasms. As with nodules in goitrous thyroids, sporadic parathyroid "hyperplasia" is also monoclonal in many instances, particularly when associated with a persistent stimulus for parathyroid growth (refractory secondary or tertiary parathyroidism; see later), suggesting that these lesions lie in the gray zone between reactive hyperplasias and neoplasia. There are two molecular defects that have an established role in the development of sporadic adenomas:

- *Cyclin D1 gene inversions leading to overexpression of cyclin D1,* a major regulator of the cell cycle. A pericentromeric inversion on chromosome 11 results in relocation of the *cyclin D1* gene (normally on 11q), so that it is positioned adjacent to the 5′-flanking region of the *PTH* gene (on 11p). As a consequence of these changes, a regulatory element from the *PTH* gene 5′-flanking sequence directs overexpression of cyclin D1 protein, causing the cells to proliferate. Between 10% and 20% of adenomas have this clonal rearrangement. In addition, cyclin D1 is overexpressed in approximately 40% of parathyroid adenomas, suggesting that mechanisms other than *cyclin D1* gene inversion can lead to its overexpression.
- *MEN1 mutations:* Approximately 20% to 30% of sporadic parathyroid tumors have mutations in both copies of the *MEN1* gene, a tumor suppressor gene on chromosome 11q13. Germline mutations of *MEN1* are also found in patients with familial parathyroid adenomas (see later). The spectrum of *MEN1* mutations in sporadic tumors is virtually identical to that in familial parathyroid adenomas.

Familial syndromes are a distant second to sporadic adenomas as causes of primary hyperparathyroidism. The genetic syndromes associated with *familial parathyroid adenomas* include Multiple Endocrine Neoplasia, types 1 and 2, caused by germline mutations of *MEN1* and *RET*, respectively (both are discussed in further detail later), and familial hypocalciuric hypercalcemia, a rare autosomal-dominant disorder caused by loss-of-function mutations in