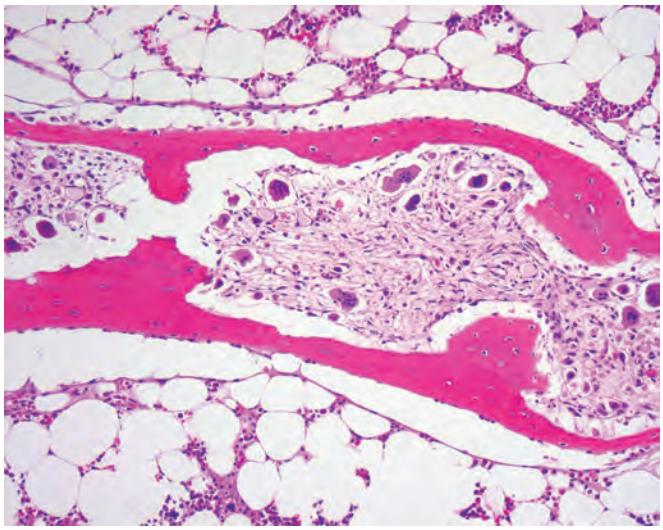

Figure 24-26 Hyperparathyroidism with osteoclasts boring into the center of the trabeculum (dissecting osteitis). (Photomicrograph reproduced from Horvai A: Bone and Soft Tissue Pathology: A Volume in the High Yield Pathology Series, Elsevier, Philadelphia, 2012.)

calcification secondary to hypercalcemia may also be seen in other sites, including the stomach, lungs, myocardium, and blood vessels.

Clinical Course. Primary hyperparathyroidism may be (1) asymptomatic and identified on routine blood chemistry profile, or (2) associated with the classic clinical manifestations of primary hyperparathyroidism.

Asymptomatic Hyperparathyroidism. Because serum calcium levels are routinely assessed, most patients with primary hyperparathyroidism are diagnosed incidentally, on the basis of clinically silent hypercalcemia. In fact, primary hyperparathyroidism is the most common cause of *asymptomatic* hypercalcemia. Hence, many of the classic manifestations, particularly those referable to bone and renal disease, are now seen infrequently in clinical practice. Among other causes of hypercalcemia (Table 24-5), *malignancy* stands out as the most frequent cause of *symptomatic* hypercalcemia in adults, and must be excluded by appropriate clinical and laboratory investigations. As discussed in Chapter 7, hypercalcemia can occur both with solid tumors, such as lung, breast, head and neck, and renal cancers, and with hematologic malignancies, notably multiple myeloma. The most common mechanism (in ~80% of cases) through which osteolytic tumors induce hypercalcemia is by secretion of PTH-related peptide (PTHrP), whose functions are similar to PTH in inducing osteoclastic bone resorption and hypercalcemia; the remaining 20% induce hypercalcemia through metastases to the bone and subsequent cytokine-induced bone resorption. In individuals with primary hyperparathyroidism, serum PTH levels are inappropriately elevated for the level of serum calcium, whereas PTH levels are low to undetectable in hypercalcemia caused by of nonparathyroid diseases (Table 24-5). Radioimmunoassays specific for PTH and PTHrP are available and can be useful in distinguishing primary hyperparathyroidism and malignancy-associated hypercalcemia. Other laboratory alterations referable to PTH excess include hypophosphatemia and increased urinary excretion of both calcium and phosphate. Secondary renal disease may lead to phosphate retention with normalization of serum phosphate levels.

Table 24-5 Causes of Hypercalcemia

Raised [PTH]	Decreased [PTH]
Hyperparathyroidism	Hypercalcemia of malignancy*
Primary (adenoma > hyperplasia)*	Vitamin D toxicity
Secondary†	Immobilization
Tertiary†	Thiazide diuretics
Familial hypocalciuric hypercalcemia	Granulomatous disease (sarcoidosis)

[PTH], Parathyroid hormone concentration.
*Primary hyperparathyroidism is the most common cause of hypercalcemia overall. Malignancy is the most common cause of *symptomatic* hypercalcemia. Primary hyperparathyroidism and malignancy account for nearly 90% of cases of hypercalcemia.
†Secondary and tertiary hyperparathyroidism are most commonly associated with progressive renal failure.

Symptomatic Primary Hyperparathyroidism. The signs and symptoms of hyperparathyroidism reflect the combined effects of increased PTH secretion and hypercalcemia. Primary hyperparathyroidism is associated with "painful bones, renal stones, abdominal groans, and psychic moans." The constellation of symptoms includes:

- *Bone disease* and bone pain secondary to fractures of bones weakened by osteoporosis or osteitis fibrosa cystica.
- *Nephrolithiasis* (renal stones) in 20% of newly diagnosed patients, with attendant pain and obstructive uropathy. Chronic renal insufficiency and abnormalities in renal function lead to polyuria and secondary polydipsia.
- Gastrointestinal disturbances, including constipation, nausea, peptic ulcers, pancreatitis, and gallstones.
- Central nervous system alterations, including depression, lethargy, and eventually seizures.
- Neuromuscular abnormalities, including weakness and fatigue.
- Cardiac manifestations, including aortic or mitral valve calcifications (or both).

The abnormalities most directly related to hyperparathyroidism are nephrolithiasis and bone disease, whereas those attributable to hypercalcemia include fatigue, weakness, pancreatitis, metastatic calcifications, and constipation.

Secondary Hyperparathyroidism

Secondary hyperparathyroidism is caused by any condition that gives rise to chronic hypocalcemia, which in turn leads to compensatory overactivity of the parathyroid glands. Renal failure is by far the most common cause of secondary hyperparathyroidism, although several other diseases, including inadequate dietary intake of calcium, steatorrhea, and vitamin D deficiency, may also cause this disorder. The mechanisms by which chronic renal failure induces secondary hyperparathyroidism are complex and not fully understood. Chronic renal insufficiency is associated with decreased phosphate excretion, which in turn results in hyperphosphatemia. The elevated serum phosphate levels directly depress serum calcium levels and