whereby signs and symptoms of the underlying malignancy are evident within months of the detection of hypercalcemia. Although clinical considerations are helpful in arriving at the correct diagnosis of the cause of hypercalcemia, appropriate laboratory testing is essential for definitive diagnosis. The immunoassay for PTH usually separates hyperparathyroidism from all other causes of hypercalcemia (exceptions are very rare reports of ectopic production of excess PTH by nonparathyroid tumors). Patients with hyperparathyroidism have elevated PTH levels despite hypercalcemia, whereas patients with malignancy and the other causes of hypercalcemia (except for disorders mediated by PTH such as lithium-induced hypercalcemia) have levels of hormone below normal or undetectable levels. Assays based on the double-antibody method for PTH exhibit very high sensitivity (especially if serum calcium is simultaneously evaluated) and specificity for the diagnosis of primary hyperparathyroidism (Fig. 424-4).

In summary, PTH values are elevated in >90% of parathyroid-related causes of hypercalcemia, undetectable or low in malignancy-related hypercalcemia, and undetectable or normal in vitamin D–related and high-bone-turnover causes of hypercalcemia. In view of the specificity of the PTH immunoassay and the high frequency of hyperparathyroidism in hypercalcemic patients, it is cost-effective to measure the PTH level in all hypercalcemic patients unless malignancy or a specific nonparathyroid disease is obvious. False-positive PTH assay results are rare. Immunoassays for PTHrP are helpful in diagnosing certain types of malignancy-associated hypercalcemia. Although FHH is parathyroid-related, the disease should be managed distinctively from hyperparathyroidism. Clinical features and the low urinary calcium excretion can help make the distinction. Because the incidence of malignancy and hyperparathyroidism both increase with age, they can coexist as two independent causes of hypercalcemia.

$1,25(OH)_2D$ levels are elevated in many (but not all) patients with primary hyperparathyroidism. In other disorders associated with hypercalcemia, concentrations of $1,25(OH)_2D$ are low or, at the most, normal. However, this test is of low specificity and is not cost-effective, as not all patients with hyperparathyroidism have elevated $1,25(OH)_2D$ levels and not all nonparathyroid hypercalcemic patients have suppressed $1,25(OH)_2D$. Measurement of $1,25(OH)_2D$ is, however, critically valuable in establishing the cause of hypercalcemia in sarcoidosis and certain lymphomas.

A useful general approach is outlined in Fig. 424-6. If the patient is *asymptomatic* and there is evidence of *chronicity* to the hypercalcemia, hyperparathyroidism is almost certainly the cause. If PTH levels (usually measured at least twice) are elevated, the clinical impression is confirmed and little additional evaluation is necessary. If there is only a short history or no data as to the duration of the hypercalcemia, *occult malignancy* must be considered; if the PTH levels are not elevated, then a thorough workup must be undertaken for malignancy, including chest x-ray, CT of chest and abdomen, and bone scan. Immunoassays for PTHrP may be especially useful in such situations. Attention should also be paid to clues for underlying hematologic disorders such as anemia, increased plasma globulin, and abnormal serum immunoelectrophoresis; bone scans can be negative in some patients with metastases such as in multiple myeloma. Finally, if a patient with chronic hypercalcemia is asymptomatic and malignancy therefore seems unlikely on clinical grounds, but PTH values are not elevated, it is useful to search for other chronic causes of hypercalcemia such as occult sarcoidosis. A careful history of dietary supplements and drug use may suggest intoxication with vitamin D or vitamin A or the use of thiazides.

TREATMENT HYPERCALCEMIC STATES

The approach to medical treatment of hypercalcemia varies with its severity (Table 424-4). Mild hypercalcemia, <3 mmol/L (12 mg/dL), can be managed by hydration. More severe hypercalcemia (levels of 3.2–3.7 mmol/L [13–15 mg/dL]) must be managed aggressively; above that level, hypercalcemia can be life-threatening and requires emergency measures. By using a combination of approaches in severe hypercalcemia, the serum calcium concentration can be decreased by 0.7–2.2 mmol/L (3–9 mg/dL) within 24–48 h in most patients, enough to relieve acute symptoms, prevent death from hypercalcemic crisis, and permit diagnostic evaluation. Therapy can then be directed at the underlying disorder—the second priority.

Hypercalcemia develops because of excessive skeletal calcium release, increased intestinal calcium absorption, or inadequate renal calcium excretion. Understanding the particular pathogenesis helps guide therapy. For example, hypercalcemia in patients with malignancy is primarily due to excessive skeletal calcium release and is, therefore, minimally improved by restriction of dietary calcium. On the other hand, patients with vitamin D hypersensitivity or vitamin D intoxication have excessive intestinal calcium absorption, and

TABLE 424-4 THERAPIES FOR SEVERE HYPERCALCEMIA

Treatment	Onset of Action	Duration of Action	Advantages	Disadvantages
Most Useful Therapies				
Hydration with saline	Hours	During infusion	Rehydration invariably needed	Volume overload
Forced diuresis; saline plus loop diuretic	Hours	During treatment	Rapid action	Volume overload, cardiac decompensation, intensive monitoring, electrolyte disturbance, inconvenience
Pamidronate	1–2 days	10–14 days to weeks	High potency; intermediate onset of action	Fever in 20%, hypophosphatemia, hypocalcemia, hypomagnesemia, rarely jaw necrosis
Zoledronate	1–2 days	>3 weeks	Same as for pamidronate (may last longer)	Same as pamidronate above
Calcitonin	Hours	1–2 days	Rapid onset of action; useful as adjunct in severe hypercalcemia	Rapid tachyphylaxis
Special Use Therapies				
Phosphate oral	24 h	During use	Chronic management (with hypophosphatemia); low toxicity if phosphate <4 mg/dL	Limited use except as adjuvant or chronic therapy
Glucocorticoids	Days	Days, weeks	Oral therapy, antitumor agent	Active only in certain malignancies, vitamin D excess and sarcoidosis; glucocorticoid side effects
Dialysis	Hours	During use and 24–48 h afterward	Useful in renal failure; onset of effect in hours; can immediately reverse life-threatening hypercalcemia	Complex procedure, reserved for extreme or special circumstances