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relatively inaccessible, since osteoclasts cannot resorb unmineralized osteoid, and frank hypocalcemia ensues. Since PTH is a major stimulus for the renal 25(OH)D 1α-hydroxylase, there is increased synthesis of the active hormone, 1,25(OH)2D. Paradoxically, levels of this hormone are often normal in severe vitamin D deficiency. Therefore, measure ments of 1,25(OH)2D are not accurate reflections of vitamin D stores and should not be used to diagnose vitamin D deficiency in patients with normal renal function. Radiologic features of vitamin D deficiency in children include a widened, expanded growth plate that is characteristic of rickets. These findings not only are apparent in the long bones but also are present at the costochondral junction, where the expansion of the growth plate leads to swellings known as the “rachitic rosary.” Impairment of intramembranous bone mineralization leads to delayed fusion of the calvarial sutures and a decrease in the radiopacity of cortical bone in the long bones. If vitamin D deficiency occurs after epiphyseal fusion, the main radiologic finding is a decrease in cortical thickness and relative radiolucency of the skeleton. A specific radiologic feature of osteomalacia, whether associated with phosphate wasting or vitamin D deficiency, is pseudofractures, or Looser’s zones. These are radiolucent lines that occur where large arteries are in contact with the underlying skeletal elements; it is thought that the arterial pulsations lead to the radiolucencies. As a result, these pseudofractures are usually a few mil limeters wide, are several centimeters long, and are seen particularly in the scapula, the pelvis, and the femoral neck. TREATMENT Vitamin D Deficiency Based on the National Academy of Medicine 2010 report, the rec ommended daily intake of vitamin D is 600 IU from 1 to 70 years of age, and 800 IU for those >70. Based on the observation that 800 IU of vitamin D, with calcium supplementation, decreases the risk of hip fractures in elderly women, this higher dose is thought to be an appropriate daily intake for prevention of vitamin D defi ciency in adults. Multiple clinical trials, including the Vitamin D and Omega-3 Trial (VITAL), revealed that supplementation of vitamin D in older community-dwelling adults (>50 years of age) with adequate vitamin D levels, at doses at or above the recom mended daily intake, does not further improve bone mineral density. The VITAL trial further showed that supraphysiologic doses of vitamin D in adults with normal vitamin D levels do not improve skeletal microarchitecture and

do not prevent falls. Fur thermore, treating older adults with daily small doses of vitamin D3, such as 400 IU, can prevent fractures and falls, as compared with large intermittent bolus doses of vitamin D3, which can result in increased incidence of fractures and falls. The safety margin for vitamin D is large, and vitamin D toxicity usually is observed only in patients taking doses in the range of 40,000 IU daily. Treatment of vitamin D deficiency should be directed at the underlying dis order, if possible, and also should be tailored to the severity of the condition. Vitamin D should always be repleted in conjunction with calcium supplementation since most of the consequences of vitamin D deficiency are a result of impaired mineral ion homeostasis. In patients in whom 1α-hydroxylation is impaired, metabolites that do not require this activation step are the treatment of choice. They include 1,25(OH)2D3 (calcitriol [Rocaltrol], 0.25– 0.5 μg/d) and 1α-hydroxyvitamin D2 (doxercalciferol [Hectorol], 2.5–5 μg/d). Outside the United States, 1α-hydroxyvitamin D3 (alfacalcidol [One-Alpha], 0.25–1.0 μg/d) is also used. If the path way required for activation of vitamin D is intact, severe vitamin D deficiency can be treated with pharmacologic repletion initially (50,000 IU weekly for 3–12 weeks), followed by maintenance therapy (800 IU daily). Pharmacologic doses may be required for maintenance therapy in patients who are taking medications such as barbiturates or phenytoin that accelerate metabolism of or cause resistance to 1,25(OH)2D. Polymorphisms in the 25-hydroxylase and the 24-hydroxylase genes can also lead to different responses

to the normal recommended daily intake of vitamin D. The hepatic enzyme cytochrome P450 3A4 (CYP3A4) is a strong inducer of the catabolism of vitamin D metabolites. Polymorphisms of the CYP3A4 gene and certain drugs, such as phenytoin and rifampin, lead to strong induction of this enzyme; thus, those affected may also require higher doses of vitamin D supplementation. Calcium supplementation should include 1.5–2 g/d of elemental calcium. Normocalcemia is usually observed within 1 week of the institution of therapy, although increases in PTH and alkaline phosphatase levels may persist for 3–6 months. The most efficacious methods to monitor treatment and resolution of vitamin D deficiency are serum and urinary calcium measurements. In patients who are vitamin D replete and are taking adequate calcium supplementa tion, the 24-h urinary calcium excretion should be in the range of 100–250 mg/24 h. Lower levels suggest problems with adherence to the treatment regimen or with absorption of calcium or vitamin D supplements. Levels >250 mg/24 h predispose to nephrolithiasis and should lead to a reduction in vitamin D dosage and/or calcium supplementation.

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CHAPTER 422 Acknowledgment The authors acknowledge Marie Demay (also a former author of this chapter) and Michael Mannstadt for their valuable input into this chapter. ■ ■FURTHER READING Bikle D et al: Vitamin D metabolites in captivity? Should we measure free or total 25(OH)D to assess vitamin D status? J Steroid Biochem Mol Biol 173:105, 2017. Bouillon R et al: Health effects of vitamin D supplementation: Lessons learned from randomized controlled trials and mendelian randomization studies. J Bone Miner Res 38:1391, 2023. Carpenter TO et al: Burosumab therapy in children with X-linked hypophosphatemia. N Engl J Med 378:1987, 2018. Christakos S et al: Vitamin D: Metabolism, molecular mechanism of action, and pleiotropic effects. Physiol Rev 96:365, 2016. De Baaij JH et al: Magnesium in man: Implications for health and disease. Physiol Rev 95:1, 2015. Kim JM et al: Osteoblast-osteoclast communication and bone homeo stasis. Cells 10:2073, 2020. Kovacs CS et al: The role of biomineralization in disorders of skeletal development and tooth formation. Nat Rev Endocrinol 17:336, 2021. Robling AG, Bonewald LF: The

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Disorders of the

Parathyroid Gland and

Calcium Homeostasis Four parathyroid glands are located posterior to the thyroid gland. They produce parathyroid hormone (PTH), which is the primary regulator of calcium homeostasis. PTH acts directly on bone, where it induces calcium (and phosphate) release, and on the kidney, where it enhances calcium reabsorption in the distal tubules. In the proximal renal tubules, PTH increases excretion of phosphate and the synthesis of 1,25-dihydroxyvitamin D (1,25(OH)2D), a hormone that increases

gastrointestinal calcium absorption. Serum PTH levels are tightly regulated by a negative feedback loop. Calcium, acting through the calcium-sensing receptor, and vitamin D, acting through its nuclear receptor, reduce PTH release and synthesis. Additional evidence indicates that fibroblast growth factor 23 (FGF23), a phosphaturic hormone, can suppress PTH secretion. Understanding the hormonal pathways that regulate calcium and phosphate levels as well as bone metabolism is essential for effective diagnosis and management of a wide array of hyper- and hypocalcemic disorders.

Primary hyperparathyroidism, characterized by excess production of PTH, is a common cause of hypercalcemia and is usually the result of autonomously functioning adenomas or hyperplasia. Surgery for this disorder is highly effective and has been shown to reverse some of the deleterious effects of long-standing PTH excess on bone density. Humoral hypercalcemia of malignancy (HHM) is also a common cause of hypercalcemia, which is usually due to the overproduction of parathyroid hormone–related peptide (PTHrP) by cancer cells. The similarities in the biochemical characteristics of hyperparathyroidism and HHM, first noted by Albright in 1941, are now known to reflect the actions of PTH and PTHrP through the same G protein–coupled PTH/PTHrP receptor (PH1R). The converse, namely hypocalcemia, can be caused by the lack of functional PTH, i.e., hypoparathyroidism, or by reduced PTH responsiveness of the proximal renal tubules, i.e., pseudohypoparathyroidism (PHP). PART 12 Endocrinology and Metabolism The genetic basis of numerous calcium and phosphate disorders, and the molecular characterization of parathyroid cell biology, have provided new insights into the regulation of calcium and phosphate homeostasis. In addition, PTH(1-34) and possibly some of its ana logues are promising agents for the treatment of postmenopausal osteoporosis and as replacement therapy for hypoparathyroidism. Cal cimimetic agents, which activate the calcium-sensing receptor (CaSR), have provided new approaches for PTH suppression, and calcilytics, which are negative allosteric modulators of the CaSR, show promis ing results in early clinical trials of patients with autosomal dominant hypocalcemia type 1, a rare dominant disease that is caused by activat ing CaSR mutations. ■ ■PTH Structure and Physiology PTH is an 84-amino-acid single-chain peptide. The amino-terminal portion, PTH(1–34), is highly conserved and is critical for the biologic actions of the molecule. Modified syn thetic fragments of the amino-terminal sequence as small as PTH(1–11) are sufficient to activate the

PTH/PTHrP receptor, if provided at high enough concentrations (see below). C-terminal portions of full-length PTH(1–84) were shown to bind to a separate binding protein/receptor; however, the properties and biologic role(s), if any, of this presumed receptor for C-terminal PTH remain undefined. The primary function of PTH is to maintain ionized calcium con centration in the extracellular fluid (ECF) within a narrow normal range. The hormone acts directly on bone and kidney and indirectly on the intestine through its effects on synthesis of 1,25(OH)2D to increase serum calcium concentrations; in turn, PTH production is closely regulated by the concentration of serum ionized calcium. This feedback system is the critical homeostatic mechanism for mainte nance of ECF calcium. Any tendency toward hypocalcemia, as might be induced by calcium- or vitamin D–deficient diets, is counteracted by increased PTH secretion. This in turn (1) increases bone turnover, thereby increasing the flow of calcium (and phosphate) from bone into blood; (2) increases calcium reabsorption in the distal tubules; and (3) indirectly increases the efficiency of calcium absorption in the intes tine by stimulating the renal production of 1,25(OH)2D. Immediate control of blood calcium is due to PTH effects on bone and, to a lesser extent, on renal calcium clearance. Maintenance of calcium balance over a longer timescale, on the other hand, probably results from the effects of 1,25(OH)2D on intestinal calcium absorption (Chap. 421). The renal actions of PTH are exerted at multiple sites; in the proximal tubules, it increases urinary phosphate excretion, it augments calcium reabsorption in the distal tubules, and it enhances in the proximal

tubules expression of CYP27B1, the enzyme that encodes the 25(OH) D-1α-hydroxylase. Every day, up to 12 mmol (500 mg) of calcium is transferred between the ECF and bone, which is a significant amount in relation to the total ECF calcium pool, and PTH plays a crucial role in regulating this transfer. PTH has multiple actions on bone and integrates its calcemic actions (bone resorption to protect against hypocalcemia) with stimu lation of bone formation. PTH-mediated changes in bone calcium release can be seen within minutes. The chronic effects of PTH are to increase the number of bone cells, both osteoblasts and osteoclasts, and to increase the remodeling of bone; these effects are apparent within hours after the hormone is given and persist for hours after PTH is withdrawn. Continuous exposure to elevated PTH (as in primary hyperparathyroidism or long-term PTH infusions in animals) leads to increased osteoclast-mediated bone resorption. However, the intermit tent administration of relatively small amounts of PTH that elevate hormone levels minimally for 1–2 h each day lead to a net increase of bone mass rather than bone loss. Striking increases, especially in trabecular bone in the spine and hip, have been reported with the intermittent use of PTH for osteoporosis, and large clinical trials with PTH(1–34) as monotherapy revealed a highly significant increase in bone density and reduction in fracture incidence. Osteoblasts (or their stromal cell precursors), which have PTH/ PTHrP receptors, are crucial to this bone-forming effect of PTH. When PTH activates PTH/PTHrP receptors on osteocytes, release of calcium from the matrix surrounding these cells is enhanced; osteoclasts, which mediate bone breakdown, lack such receptors. PTH-mediated stimula tion of osteoclasts is indirect, acting in part through RANKL released from osteoblasts to activate RANK on osteoclasts; in experimental studies of bone resorption in vitro, osteoblasts must be present for PTH to activate osteoclasts to resorb bone (Chap. 421). Synthesis, Secretion, and Metabolism • SYNTHESIS Para thyroid cells have multiple methods of adapting to increased needs for PTH production. Most rapid (within minutes) is secretion of pre formed hormone in response to hypocalcemia. Second, within hours, PTH mRNA expression is induced by sustained hypocalcemia. Finally, protracted challenge leads within days to cellular replication to increase parathyroid gland mass. PTH is initially synthesized as a larger molecule (preproPTH, consisting of 115 amino acids). After a first cleavage step to remove the

“pre” sequence of 25 amino acid residues, a second cleavage step removes the “pro” sequence of 6 amino acid residues before secretion of the mature peptide comprising 84 residues. Homozygous or heterozy gous mutations in the prepro-region can cause hypoparathyroidism by interfering with hormone synthesis, transport, or secretion. Thus far, only three homozygous mutations have been identified in the secreted PTH(1–84) that reduce its biological activity and are detected in some, but not all, PTH assays (see below). Transcriptional suppression of the PTH gene by calcium is nearly maximal at physiologic calcium concentrations. Hypocalcemia increases transcriptional activity within hours. 1,25(OH)2D also strongly sup presses PTH gene transcription. In patients with chronic kidney dis ease (CKD), administration of supraphysiologic doses of 1,25(OH)2D or analogues of this active metabolite can dramatically suppress PTH overproduction and is thus used clinically to control severe secondary hyperparathyroidism. Regulation of proteolytic destruction of pre formed PTH (posttranslational regulation of hormone production) is an important mechanism for mediating rapid (within minutes) changes in hormone availability. High calcium increases and low calcium inhib its the proteolytic destruction of stored hormone. REGULATION OF PTH SECRETION PTH secretion increases steeply to a maximum value of about five times the basal rate of secretion as the cal cium concentration falls from normal to 1.9–2.0 mmol/L (7.6–8.0 mg/dL; measured as total calcium). Severe intracellular magnesium deficiency impairs PTH secretion (see below). ECF calcium controls PTH secretion by interaction with a CaSR, a G protein–coupled receptor (GPCR) for which Ca2+ ions act as the primary ligand (see below). This receptor, which also has phosphate

binding sites, is a member of the class C GPCR superfamily and func tions as an obligate homodimer. Characterized by a large extracellular domain that effectively clamps the small-molecule ligand, the CaSR is expressed in many tissues and cell types. The CaSR can couple to all four classes of G proteins in a cell-dependent context. In the parathy roids, the CaSR mediates its actions by coupling to two closely related G protein alpha-subunits, namely Gαq and Gα11, as well as Gαi. Acti vation of the CaSR by high calcium levels negatively regulates PTH secretion in the parathyroids and reduces calcium reabsorption in the distal renal tubules. Genetic evidence further reinforced the essential role for the CaSR in maintaining calcium balance. Heterozygous loss-of-function CaSR mutations cause familial hypocalciuric hypercalcemia (FHH) type 1, a benign disease in which the blood calcium abnormality resembles that observed in hyperparathyroidism but with hypocalciuria; other more recently defined variants of FHH, namely FHH2 and FHH3, are caused either by heterozygous loss-of-function mutations in Gα11, the alphasubunit of one of the signaling proteins downstream of the CaSR, or by heterozygous mutations in the adaptor protein AP2S1, which is key in the intracellular trafficking of the CaSR. Homozygous loss-of-function mutations in the CaSR are the cause of severe neonatal hyperparathy roidism, a disorder that is typically lethal if not treated within the first days of life. On the other hand, heterozygous gain-of-function mutations cause a form of hypocalcemia resembling hypoparathyroidism (see below). METABOLISM PTH undergoes intraglandular proteolysis, which is regulated by extracellular calcium, and further degradation occurs after secretion into the circulation, mainly by liver and kidney. Removal of the critically important amino-terminus (as little as the first amino acid) produces biologically inactive PTH fragments, such as PTH(7–84), which can be detected equally well as PTH(1–84) by several commonly used immunometric PTH assays that employ two antibodies directed against portions of the N- and C-terminus, respectively. Earlier assays, now used only infrequently, measure pre dominantly middle and carboxyl-terminal fragments that have no or incompletely defined biological activity and are cleared more slowly from blood than the secreted PTH(1–84). Although the

problems inherent in PTH measurements have been largely circumvented by use of double-antibody immunometric assays, some evidence suggests that the PTH(7–84) (and probably related amino-terminally truncated fragments) can act, through yet unde fined mechanisms, as an inhibitor of PTH action and may therefore be of clinical significance, particularly in patients with CKD. In this group of patients, efforts to prevent secondary hyperparathyroidism by a variety of measures (vitamin D analogues, higher calcium intake, higher dialysate calcium, phosphate-lowering strategies, and calcimi metic drugs) can lead to oversuppression of the parathyroid glands since some amino-terminally truncated PTH fragments can react in some immunometric PTH assays, thus overestimating the levels of bio logically active PTH(1–84). Excessive parathyroid gland suppression in CKD can lead to adynamic bone disease (see below), which has been associated in children with further impaired growth and increased bone fracture rates in adults and can furthermore lead to significant

hPTH SER VAL SER GLU ILE GLN LEU MET HIS ASN LEU GLY LYS HIS LEU ASN SER MET GLU ARG VAL GLU TRP LEU ARG LYS LYS LEU GLN ASP hPTHrp ALA – – – HIS – – LEU – ASP LYS – – SER ILE GLN ASP LEU ARG – ARG PHE PHE – HIS HIS LEU ILE ALA GLU hPTH hPTHrP

Amino acid residues FIGURE 422-1 Schematic diagram to illustrate similarities and differences in structure of human parathyroid hormone (hPTH) and human PTH-related peptide (hPTHrP). Close structural (and functional) homology exists between the first 30 amino acids of hPTH and hPTHrP. The PTHrP sequence may be ≥139 amino acid residues in length. PTH is only 84 residues long; after residue 30, there is little structural homology between the two. Dashed lines in the PTHrP sequence indicate identity; underlined residues, although different from those of PTH, still represent conservative changes (charge or polarity preserved). Ten amino acids are identical, and a total of 20 of 30 are homologues.

hypercalcemia. The measurement of PTH with newer third-generation immunometric assays, which use detection antibodies directed against extreme amino-terminal PTH epitopes and thus detect only full-length PTH(1–84), has not yet clearly shown to be advantageous in the clini cal setting.

■ ■PTHRP Structure and Physiology PTHrP is responsible for most instances of HHM (Chap. 98), a syndrome that resembles primary hyperparathyroidism but without elevated PTH levels. Most cell types normally produce PTHrP, including brain, pancreas, heart, lung, mam mary tissue, placenta, endothelial cells, and smooth muscle. In fetal animals, PTHrP directs transplacental calcium transfer, and high con centrations of PTHrP are produced in mammary tissue and secreted into milk, but the biologic significance of this peptide in breast milk is unknown. PTHrP has paracrine and autocrine functions and it plays an essential role in diverse functions such as endochondral bone forma tion, branching morphogenesis of the breast, and possibly in uterine contraction.
 PTH and PTHrP, although products of different genes, exhibit con siderable functional and structural homology (Fig. 422-1) and have evolved from a shared ancestral gene. The structure of the gene encod ing human PTHrP, however, is more complex than that of PTH, con taining multiple additional exons, which can undergo alternate splicing patterns during formation of the mature mRNA. Protein products of 139, 141, and 173 amino acids are produced, and other molecular forms may result from tissue-specific degradation at accessible internal cleavage sites. The biologic roles of these various molecular species and the nature of the circulating forms of

PTHrP are unclear. In fact, it is uncertain whether PTHrP circulates at any significant level in healthy children and adults. As a paracrine factor, PTHrP may be produced, act, and be destroyed locally within tissues. In adults, PTHrP appears to have little influence on calcium homeostasis, except in disease states, when large tumors, especially of the squamous cell type as well as renal cell carcinomas, lead to massive overproduction of the hormone and hypercalcemia. Both PTH and PTHrP bind to and activate the PTH/PTHrP recep tor. The PTH/PTHrP receptor (also known as the PTH-1 receptor [PTH1R]) belongs to the class B GPCRs that includes the receptors for calcitonin, glucagon, secretin, vasoactive intestinal peptide, and a few other peptides. Although both ligands activate the PTH1R, the two peptides induce distinct responses by the receptor, which explains how a single receptor without isoforms can serve different biologic roles. The extracellular regions of the receptor are involved in hormone binding, and the intracellular domains, after hormone activation, bind G protein subunits to transduce hormone signaling into cellular responses through the stimulation of second messenger formation.

A second receptor that binds PTH, originally termed the PTH-2 receptor (PTH2R), is primarily expressed in brain, pancreas, and tes tis. Different mammalian PTH1Rs respond equivalently to PTH and PTHrP, at least when tested with traditional assays, whereas the human PTH2R responds efficiently only to PTH, but not to PTHrP. PTH2Rs from other species show little or no stimulation of second-messenger

Amino acid residues

formation in response to PTH or PTHrP. In fact, the endogenous ligand of the PTH2R was shown to be a hypothalamic peptide referred to as tubular infundibular peptide of 39 residues, TIP39, that is only distantly related to PTH and PTHrP. The PTH1R and the PTH2R can be traced backward in evolutionary time to fish, which express also a third receptor, the PTH3R, that is more closely related to the fish PTH1R than to the fish PTH2R. The evolutionary conservation of structure and function suggests important biologic roles for these receptors, even in fish, which lack discrete parathyroid glands but pro duce two molecules that are closely related to mammalian PTH.

Studies using the cloned PTH1R confirm that it can be coupled to more than one G protein and second-messenger pathway, thus contrib uting to the multiplicity of pathways stimulated by PTH. Activation of protein kinases (A and C) and calcium transport channels is associated with a variety of hormone-specific tissue responses. These responses include inhibition of phosphate and bicarbonate transport, stimulation of calcium transport, and activation of renal 1α-hydroxylase in the kidney. The responses in bone include effects on collagen synthesis, alkaline phosphatase, ornithine decarboxylase, citrate decarboxyl ase, and glucose-6-phosphate dehydrogenase activities; phospholipid synthesis; and calcium and phosphate transport. Ultimately, these biochemical events lead to an integrated hormonal response in bone turnover and calcium homeostasis. PTH also activates Na+/Ca2+ exchangers at renal distal tubular sites and stimulates translocation of preformed calcium transport channels, moving them from the interior to the apical surface to increase tubular uptake of calcium. PTHdependent stimulation of phosphate excretion involves reduced expres sion of two sodium-dependent phosphate co-transporters, NPT2a and NPT2c, at the apical membrane, thereby reducing phosphate reab sorption in the proximal renal tubules. Similar mechanisms may be involved in other renal tubular transporters that are influenced by PTH. PART 12 Endocrinology and Metabolism PTHrP exerts important developmental

influences on fetal bone development and in adult physiology. Homozygous ablation of the gene encoding PTHrP (or disruption of the PTH1R gene) in mice causes a lethal phenotype in which animals are born with pronounced acceleration of chondrocyte maturation that resembles a human dis ease, Blomstrand lethal chondrodysplasia (BLC), that is caused by homozygous or compound heterozygous, inactivating PTH1R muta tions (Fig. 422-2). Heterozygous inactivating PTH1R mutations in humans furthermore can be a cause of delayed tooth eruption, while heterozygous inactivating PTHrP mutations lead to premature growth plate closure and reduced adult heights. Besides the lethal, biallelic PTH1R mutations that cause BLC, several homozygous mutations in this gene have now been identified in a rare recessive disease referred to as Eiken syndrome. Affected patients typically have normal min eral ion regulation, yet delayed growth plate maturation resulting in Many organs Parathyroids PTHrP PTH Ca2+ Growth Plate Breast Kidney Brain Smooth muscle Skin Bone Calcium Homeostasis Paracrine Actions FIGURE 422-2 Dual role for the actions of the PTH/PTHrP receptor (PTH1R). Parathyroid hormone (PTH; endocrine-calcium homeostasis) and PTH-related peptide (PTHrP; paracrine–multiple tissue actions including growth plate cartilage in developing bone) use the single receptor for their disparate functions mediated by the amino-terminal 34 residues of either peptide. Other regions of both ligands interact with other receptors (not shown).

some bone deformities, reduced growth, and delayed tooth eruption; recently, a few cases were described with symptomatic hypocalcemia and considerably elevated PTH levels. ■ ■CALCITONIN (See also Chap. 400) Calcitonin is a peptide hormone with hypocal cemic properties that in several mammalian species acts as an indirect antagonist to the calcemic actions of PTH. Calcitonin seems to be of limited physiologic significance in humans, at least with regard to calcium homeostasis. It is of medical significance because of its role as a tumor marker in sporadic and hereditary cases of medullary thyroid carcinoma and its medical use as an adjunctive treatment in severe hypercalcemia and in Paget’s disease of bone at pharmacologic doses. Levels can also be elevated in patients with pseudohypoparathyroidism (PHP); the significance of this observation is unclear. The hypocalcemic activity of calcitonin is accounted for primarily by inhibition of osteoclast-mediated bone resorption and secondarily by stimulation of renal calcium clearance. These effects are mediated by receptors on osteoclasts and renal tubular cells. Calcitonin exerts additional effects through receptors present in the brain, the gastro intestinal tract, and the immune system. The hormone, for example, exerts analgesic effects directly on cells in the hypothalamus and related structures, possibly by interacting with receptors for related peptide hormones such as calcitonin gene–related peptide (CGRP) or amylin. Both of these ligands have specific high-affinity receptors that share considerable structural similarity with the PH1R and can also bind to and activate calcitonin receptors. The calcitonin receptor shares considerable structural similarity with the PTH1R. The naturally occurring calcitonins consist of a peptide chain of 32 amino acids. There is considerable sequence variability among species. Calcitonin from salmon, which is used therapeutically, is 10–100 times more potent than mammalian forms in lowering serum calcium. The circulating level of calcitonin in humans is lower than that in many other species. In humans, even extreme variations in calcito nin production do not change calcium and phosphate metabolism; no definite effects are attributable to calcitonin deficiency (totally thyroidectomized patients receiving only replacement thyroxine) or excess (patients with medullary carcinoma of the thyroid, a calcitoninsecreting tumor) (Chap. 400). Calcitonin has been a useful pharmaco logic agent to suppress bone resorption in Paget’s disease (Chap. 424) and osteoporosis (Chap. 423) and in the treatment of hypercalcemia of malignancy (see below). However, bisphosphates are usually

more effective, and the physiologic role, if any, of calcitonin in humans is uncertain. On the other hand, ablation of the calcitonin gene (com bined with ablation of the CGRP gene because both genes are in close proximity) in mice leads to reduced bone mineral density, suggesting that its biologic role in mammals is still not fully understood. ■ ■HYPERCALCEMIA Introduction (See also Chap. 57) Hypercalcemia can be a mani festation of a serious illness such as malignancy or can be detected coincidentally by laboratory testing in a patient with no obvious illness. The number of patients recognized with asymptomatic hypercalcemia, usually primary hyperparathyroidism, increased in the late twentieth century when wider testing became readily available. Whenever hypercalcemia is confirmed, a definitive diagnosis must be established. Although hyperparathyroidism, a frequent cause of asymptomatic hypercalcemia, is a chronic disorder in which manifes tations, if any, may be expressed only after months or years, hypercal cemia can also be the earliest manifestation of malignancy, the second most common cause of hypercalcemia in the adult. The causes of hypercalcemia are numerous (Table 422-1), but hyperparathyroidism and cancer account for 90% of all cases. Before initiating a diagnostic workup, confirm the presence of true hypercalcemia, not a false-positive laboratory test from factors like hemoconcentration during blood collection or elevation in serum proteins such as albumin. Since hypercalcemia is typically chronic, it is cost-effective to obtain several serum calcium and concomitant albumin measurements, which do not require fasting.

TABLE 422-1 Classification of Causes of Hypercalcemia I. Parathyroid-Related A. Primary hyperparathyroidism 1. Adenoma(s) 2. Multiple endocrine neoplasia 3. Parathyroid carcinoma 4. Ectopic production of parathyroid hormone (PTH) 5. Exogenous administration of PTH or analogues B. Lithium therapy C. Familial hypocalciuric hypercalcemia II. Malignancy-Related A. Tumors with osteolytic metastases (breast, multiple myeloma, lymphoma, etc.) B. Solid tumor with humoral mediation of hypercalcemia (squamous cell carcinoma of the lung, kidney, breast, and others) C. 1,25(OH)2D-mediated hypercalcemia of malignancies (lymphoma, ovarian dysgerminoma, etc.) III. Vitamin D–Related A. Vitamin D intoxication B. ↑ 1,25(OH)2D; sarcoidosis and other granulomatous diseases, lymphoma C. ↑ 1,25(OH)2D; impaired 1,25(OH)2D metabolism due to biallelic 24-hydroxylase mutations or increased 1,25(OH)2D synthesis due to inactivating biallelic mutations involving the renal sodium-dependent phosphate co-transporters 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. Tertiary hyperparathyroidism B. Aluminum intoxication and adynamic bone disease C. Milk-alkali syndrome Clinical features are helpful in differential diagnosis. Hypercal cemia in an adult who is asymptomatic is usually due to primary hyperparathyroidism. In malignancy-associated hypercalcemia, the disease is usually not occult; rather, symptoms of malignancy bring the patient to the physician, and hypercalcemia is discovered during the evaluation. If asymptomatic hypercalcemia can be documented for more than a year, malignancy is unlikely. Nevertheless, differentiating primary hyperparathyroidism from occult malignancy can occa sionally be difficult, and careful evaluation is required, particularly when the duration of the hypercalcemia is unknown. Other causes of hypercalcemia may include excessive intake of vitamin D or activated analogues, impaired metabolism of 1,25(OH)2D, high bone turnover from any of several causes, or renal failure (Table 422-1). Immuno metric 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, revers ible renal tubular defects, increased urine output, a short QT interval in the electrocardiogram, and, in some patients, cardiac arrhythmias. 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 excre tion. 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

Pathophysiology • NATURAL HISTORY AND INCIDENCE Primary hyperparathyroidism, which is typically a disease of postmenopausal women, results from excessive secretion of PTH that is disproportion ate to serum calcium levels. This typically causes 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 fre quently, 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 dis ease other than hypercalcemia and elevated levels of PTH. The mani festations 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 and can present with or without end-organ involvement. 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 varies globally and has changed over the decades likely reflecting changes in the usage of laboratory screening panels that include serum calcium. The current incidence in the United States is calculated to be about 50 per 100,000 person-years. ETIOLOGY Parathyroid tumors are most often encountered as isolated monoclonal adenomas without other endocrinopathy. They may also arise in hereditary syndromes such as multiple endocrine neoplasia (MEN) syndromes. As many as 10% of patients with hyperparathyroid ism have a genetic basis for the disease (see below). Parathyroid tumors may also arise as secondary to underlying disease (excessive stimu lation 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 extremely rarely a parathyroid carcinoma. More than one adenoma has been reported, and genetic causes of the disease often underlies chief cell hyperplasia of all four glands. Hereditary Syndromes and Multiple Parathyroid Tumors Hereditary hyperpara thyroidism can occur without other endocrine abnormalities but is usually part of a MEN syndrome (Chap. 400). MEN 1 (Wermer’s syn drome) 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 fea tures such as multiple neuromas but usually lacks hyperparathyroid ism. MEN4, caused by mutations in the p27 cyclin-dependent kinase inhibitor (encoded for by CDKN1B), has similar clinical manifestations as MEN 1. Mutations in the

MAX gene are associated with familial forms of pheochromocytoma/paraganglioma, and a few family mem bers have also been reported to have primary hyperparathyroidism. Each of these MEN syndromes is transmitted in an apparent autosomal dominant manner. The hyperparathyroidism jaw tumor (HPT-JT) syndrome occurs in families with parathyroid tumors (sometimes carcinomas) in asso ciation with benign jaw tumors. This disorder is caused by mutations in CDC73 (HRPT2), and mutations in this gene are also observed in sporadic parathyroid cancers. Some kindreds exhibit hereditary hyperparathyroidism without other endocrinopathies, which has been referred to as nonsyndromic familial isolated hyperparathyroidism (FIHP). In some of these familial cases, the disease co-segregated with heterozygous mutations in GCM2. Inactivating or dominant-negative mutations in this parathyroid-specific transcription factor had initially been identified in familial forms of hypoparathyroidism. However, GCM2 variants that are predicted to cause a gain-of-function of GCM2 have been reported in a subset of patients with FIHP. Because the prevalence of these GCM2 variants is much higher than the prevalence

of primary hyperparathyroidism, they might be a risk factor for devel oping the disease. Furthermore, there is speculation that some FIHP cases 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.

Genetic Defects Associated with Hyperparathyroidism As in many other types of neoplasia, two fundamental types of genetic defects have been identified in parathyroid gland tumors: (1) overac tivity of protooncogenes and (2) loss of function of tumor-suppressor genes. The former, by definition, can lead to uncontrolled cellular growth and function by activation (gain-of-function mutation) of a single allele of the responsible gene, whereas the latter requires loss of function of both allelic copies. Biallelic loss of function of a tumorsuppressor gene is usually characterized by a germline defect (all cells) of one allele (autosomal-dominant mode of inheritance) and an additional somatic deletion/mutation in the second allele of the tumor (Fig. 422-3). PART 12 Endocrinology and Metabolism Mutations in the MEN1 gene, which encodes the tumor suppressor MENIN, on chromosome 11q13 are responsible for causing MEN 1. Inheritance of one mutated allele in this hereditary syndrome, followed by loss of the other allele via somatic cell mutation, leads to monoclo nal expansion and tumor development. Also, in ~15–20% of sporadic parathyroid adenomas, both alleles of the MEN1 locus on chromosome 11 are somatically deleted, implying that the same defect responsible for MEN 1 can also cause the sporadic disease (Fig. 422-3A). Con sistent with the Knudson hypothesis for two-step neoplasia in certain inherited cancer syndromes (Chap. 76), the earlier onset of hyperpara thyroidism in the hereditary syndromes reflects the need for only one mutational event to trigger the monoclonal outgrowth. In sporadic adenomas, typically occurring later in life, two different somatic events must occur before the MEN1 gene is silenced. MEN 2 is an example for a mutation in a protooncogene and is asso ciated with gain-of-function mutations in the Ret oncogene. Chromosome 11 Somatic deletion/mutation of remaining normal allele Normal copy Mutant copy Clonal progenitor cell lacks functional gene product Mutant copy of putative tumor suppressor gene on 11q13 is inherited in MEN1 and present in all parathyroid cells Mutation of one allele of same gene may occur somatically in other patients, present in specific parathyroid cell(s) Chromosome 1 Somatic deletion/mutation of remaining normal allele Normal copy Mutant copy Clonal progenitor cell lacks functional HRPT2 gene product Somatic mutation of one copy of the HRPT2 tumor suppressor gene on 1q21–31 no adverse consequences to parathyroid cell A B FIGURE 422-3 A. Schematic diagram indicating molecular events in tumor

susceptibility. The patient with the hereditary abnormality (multiple endocrine neoplasia [MEN]) is envisioned as having one defective gene inherited from the affected parent on chromosome 11, but one copy of the normal gene is present from the other parent. In the monoclonal tumor (benign tumor), a somatic event, here partial chromosomal deletion, removes the remaining normal gene from a cell. In nonhereditary tumors, two successive somatic mutations must occur, a process that takes a longer time. By either pathway, the cell, deprived of growth-regulating influence from this gene, has unregulated growth and becomes a tumor. A different genetic locus also involving loss of a tumor-suppressor gene termed HRPT2 is involved in the pathogenesis of parathyroid carcinoma. (Reproduced with permission from A Arnold: Genetic basis of endocrine disease 5. Molecular genetics of parathyroid gland neoplasia. J Clin Endocrinol Metab 77:1108, 1993.) B. Schematic illustration of the mechanism and consequences of gene rearrangement and overexpression of the PRAD1 protooncogene (pericentromeric inversion of chromosome 11) in parathyroid adenomas. The excessive expression of PRAD1 (a cell cycle control protein, cyclin D1) by the highly active PTH gene promoter in the parathyroid cell contributes to excess cellular proliferation. (Reproduced with permission from J Habener, in L DeGroot, JL Jameson (eds): Endocrinology, 4th ed. Philadelphia, PA: Saunders; 2001.)

A more complex pattern, still incompletely resolved, arises with genetic defects and carcinoma of the parathyroids. This appears to be due to biallelic loss of a functioning copy of a gene, CDC73 (or HRPT2), originally identified as the cause of the HPT-JT syndrome. Several inactivating mutations have been identified in CDC73 (located on chromosome 1q21-31), which encodes a 531-amino-acid protein called parafibromin. The discovery of the genetic mutations that lead to multiple endo crine neoplasias allows genetic testing of suspected probands and fam ily members. Benefits of genetic testing include the ability to verify the clinical diagnosis, identify affected family members, and rule out the genetic variant in family members, who seem to be unaffected. An important contribution from studies on the genetic origin of parathyroid carcinoma has been the realization that the mutations involve a different pathway than that involved with the benign gland enlargements. Unlike the pathogenesis of genetic alterations seen in colon cancer, where lesions evolve from benign adenomas to malignant disease by progressive genetic changes, the alterations commonly seen in most parathyroid cancers (HRPT2 mutations) are infrequently seen in sporadic parathyroid adenomas. Study of the parathyroid cancers found in some patients with the HPT-JT syndrome has led to identification of a much larger role for HRPT2 mutations in most parathyroid carcinomas, including those that arise sporadically, without apparent association with the HPT-JT syndrome. Mutations in the coding region have been identified in 75–80% of all parathyroid cancers analyzed, leading to the conclusion that, with addition of presumed mutations in the noncoding regions, this genetic defect may be seen in essentially all parathyroid carcino mas. Of special importance was the discovery that, in some sporadic parathyroid cancers, germline mutations have been found; this, in turn, has led to careful investigation of the families of these patients and a new clinical indication for genetic testing in this setting. Abnormalities at the Rb gene were the first to be noted in para thyroid cancer. The Rb gene, a tumor-suppressor gene located on Benign tumor PTH Coding PTH Coding PTH 5' Regulatory Break Centromere PTH 5' Regulatory Break PRAD1 PRAD1 Inverted Normal Parathyroid carcinoma

chromosome 13q14, was initially associated with retinoblastoma but has since been implicated in other neoplasias, including parathyroid carcinoma. Early studies implicated allelic deletions of the Rb gene in many parathyroid carcinomas and decreased or absent expression of the Rb protein.

However, because there are often large deletions in chromosome 13 that include many genes in addition to the Rb locus (with similar findings in some pituitary carcinomas), it remains pos sible that other tumor-suppressor genes on chromosome 13 may be playing a role in parathyroid carcinoma. Overall, it seems there are multiple factors in parathyroid cancer, in addition to the HRPT2 and Rb gene, although the HRPT2 gene muta tion is the most invariant abnormality. RET encodes a tyrosine kinase type receptor; specific inherited germline mutations lead to a constitu tive activation of the receptor, thereby explaining the autosomal domi nant mode of transmission and the relatively early onset of neoplasia. In the MEN 2 syndrome, the RET protooncogene may be responsible for the earliest disorder detected, the polyclonal disorder C-cell hyper plasia, which then is transformed into a clonal outgrowth—a medul lary carcinoma with the participation of other, still uncharacterized genetic defects. In some parathyroid adenomas, activation of a protooncogene occurs (Fig. 422-3B). A reciprocal translocation involving chromo some 11 was identified as a somatic event that juxtaposes the PTH gene promoter upstream of CCND1, which encodes a cyclin D protein that plays a key role in normal cell division. This translocation plus other mechanisms that cause an equivalent overexpression of cyclin D1 are found in 20–40% of parathyroid adenomas. Mouse models have confirmed the role of several of the major iden tified genetic defects in parathyroid disease and the MEN syndromes. Loss of the MEN1 gene locus and overexpression of the CCND1 pro tooncogene or the mutated RET protooncogene have been analyzed by genetic manipulation in mice, with the expected onset of parathyroid tumors or medullary thyroid carcinoma, respectively. Pathology Adenomas are most often located in the inferior para thyroid 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 pre dominant in both hyperplasia and adenoma. With chief cell hyperpla sia, 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. Parathyroid carcinoma is often not aggressive. Long-term survival without recurrence is common if at initial surgery the entire gland is removed without rupture of the capsule. Recurrent parathyroid carcinoma is usually slow growing with local spread in the neck, and surgical correction of recurrent disease may be feasible. Occasion ally, however, parathyroid carcinoma is more aggressive, with distant metastases (lung, liver, and bone) found at the time of initial operation. It may be difficult to appreciate initially that a primary tumor is carci noma; increased numbers of mitotic figures and increased fibrosis of the gland stroma may precede invasion. The diagnosis of carcinoma is often made in retrospect when metastasis occur. Hyperparathyroidism from a parathyroid carcinoma may be indistinguishable from other forms of primary hyperparathyroidism but is usually more severe clinically. A potential clue to the diagnosis is offered by the degree of calcium elevation. Calcium values of 3.5–3.7 mmol/L (14–15 mg/dL) are frequent with carcinoma and may alert the surgeon to remove the abnormal gland with care to avoid capsular rupture. Recent findings concerning the genetic basis of some patients with parathyroid carci noma (distinct from that of benign adenomas) indicate the need, in these kindreds, for family screening (see below). Signs and Symptoms Many patients with primary hyperpara thyroidism are asymptomatic. Manifestations of hyperparathyroid ism involve primarily the kidneys and the skeletal system. Kidney

involvement, due either to deposition of calcium in the renal paren chyma or to recurrent nephrolithiasis, was present in 60–70% of patients prior to 1970. With earlier detection, renal complications occur in <20% of patients in many large series. Renal stones are usually composed of either calcium oxalate or calcium phosphate. In occa sional patients, repeated episodes of nephrolithiasis or the formation of large calculi may lead to urinary tract obstruction, infection, and loss of renal function. Nephrocalcinosis may also cause decreased renal function and phosphate retention.

The distinctive bone manifestation of hyperparathyroidism is osteitis fibrosa cystica, which occurred in 10–25% of patients in series reported 50 years ago. Histologically, the pathognomonic features are an increase in the giant multinucleated osteoclasts in scalloped areas on the surface of the bone (Howship's lacunae) and a replacement of the normal cellular and marrow elements by fibrous tissue. Radiographic changes include resorption of the phalangeal tufts and replacement of the usually sharp cortical outline of the bone in the digits by an irregu lar outline (subperiosteal resorption). In recent years, osteitis fibrosa cystica is very rare in primary hyperparathyroidism, probably due to the earlier detection and therefore milder form of the disease. Disorders of the Parathyroid Gland and Calcium Homeostasis
CHAPTER 422 Dual-energy x-ray absorptiometry of the spine provides reproduc ible quantitative estimates (within a few percent) of spinal bone density. Similarly, bone density in the extremities can be quantified by densi tometry of the hip or of the distal radius at a site chosen to be primarily cortical. Computed tomography (CT) is a very sensitive technique for estimating spinal bone density, but reproducibility of standard CT is no better than 5%. Newer CT techniques (spiral, "extreme" CT) are more reproducible but are currently available in a limited number of medical centers and used for research purposes. Cortical bone density is reduced, while cancellous bone density, especially in the spine, is relatively preserved. In symptomatic patients, dysfunctions of the central nervous system (CNS), peripheral nerve and muscle, gastrointestinal tract, and joints also occur. It has been reported that severe neuropsychiatric manifesta tions may be reversed by parathyroidectomy. When present in symp tomatic patients, neuromuscular manifestations may include proximal muscle weakness, easy fatigability, and atrophy of muscles and may be so striking as to suggest a primary neuromuscular disorder. The distin guishing feature is the complete regression of neuromuscular disease after surgical correction of the hyperparathyroidism. Gastrointestinal manifestations are sometimes subtle and include vague abdominal complaints and disorders of the stomach and pan creas. Again, cause and effect are unclear. In MEN 1 patients with hyperparathyroidism, duodenal ulcer may be the result of associ ated pancreatic tumors that secrete excessive quantities of gastrin (Zollinger-Ellison syndrome). Pancreatitis has been reported in associ ation with hyperparathyroidism, but the incidence and the mechanism are not established. Much attention has been paid in recent years to the manifestations of and optimum management strategies for asymptomatic hyperpara thyroidism. This is now the most prevalent form of the disease. Asymp tomatic primary hyperparathyroidism is defined as biochemically confirmed hyperparathyroidism (elevated or inappropriately normal PTH levels despite hypercalcemia) with the absence of symptoms typi cally associated with more severe hyperparathyroidism and can occur with or without target organ involvement such as renal or bone disease. Five conferences on the topic have been held in the United States over the past two decades, with the most recent in 2022. The published proceedings provide guidelines for diagnosis and treatment of primary hyperparathyroidism. Issues of concern include the potential for cardiovascular dete rioration, the presence of subtle neuropsychiatric symptoms, and the longer-

term status of skeletal integrity in patients not treated surgically. The current consensus is that medical monitoring rather than surgical correction of hyperparathyroidism may be justified in certain patients. The current recommendation is that patients who show mild disease, as defined by the meeting guidelines (Table 422-2), can be safely fol lowed under management guidelines (Table 422-3). There is, however, growing uncertainty about subtle disease manifestations and whether

TABLE 422-2 Guidelines for Surgery in Asymptomatic Primary Hyperparathyroidism PARAMETER GUIDELINE Serum calcium

> 1 mg/dL above normal Renal Creatinine clearance <60 mL/min 24-h urine for calcium >300 mg/d in men or >250 mg/d in women and increased stone risk by biochemical stone risk analysis Presence of nephrolithiasis or nephrocalcinosis by x-ray, ultrasound, or other imaging modalities Skeletal BMD by DXA: T score <–2.5 at any site Vertebral fracture by x-ray or VFA PART 12 Endocrinology and Metabolism Age <50 Abbreviations: BMD, bone mineral density; DXA, dual-energy x-ray absorptiometry; VFA, vertebral fracture assessment. Source: Data from JP Bilezikian et al: Evaluation and management of primary hyperparathyroidism: Summary statement and guidelines from the Fifth International Workshop. JBMR 37:2293, 2022. surgery is therefore indicated in most patients. Among the issues is the evidence of eventual (>8 years) deterioration in bone mineral density after a decade of relative stability. There is concern that this late-onset deterioration in bone density in nonoperated patients could contribute significantly to the well-known age-dependent fracture risk (osteopo rosis). Significant and sustained improvements in bone mineral density are seen after successful parathyroidectomy, and there is some evidence for reduction in fractures. Cardiovascular disease, including left ventricular hypertrophy, car diac functional defects, and endothelial dysfunction, has been reported as reversible in European patients with more severe symptomatic dis ease after surgery, leading to numerous studies of these cardiovascular features in those with milder disease. There are reports of endothelial dysfunction in patients with mild asymptomatic hyperparathyroidism, but the expert panels concluded that more observation is needed, espe cially regarding whether there is reversibility with surgery. A topic of considerable interest and some debate is assessment of neuropsychiatric status and health-related quality of life status in hyperparathyroid patients both before surgery and in response to parathyroidectomy. Several observational studies have suggested improvements in symptom score after surgery. Randomized studies of surgery versus observation, however, have yielded inconclusive results, especially regarding benefits of surgery. Many studies report that hyperparathyroidism is associated with increased neuropsychiatric symptoms, but it is not possible at present to determine which patients might improve after surgery. Diagnosis The diagnosis is typically made by detecting an elevated or inappropriately normal immunoreactive PTH level in a patient with

asymptomatic hypercalcemia (Fig. 422-4) (see “Differential Diagnosis: TABLE 422-3 Guidelines for Monitoring in Patients with Primary Hyperparathyroidism Who Do Not Undergo Parathyroidectomy PARAMETER GUIDELINE Serum calcium and 25OHD Annually Renal eGFR, annually; serum creatinine, annually. Abdominal imaging (x-ray, ultrasound, or CT), if clinically indicated. 24-h urine for calcium, if indicated Creatinine clearance Annually Skeletal DXA every 1–2 years (3 sites) (unless BMD is normal). X-ray or VFA of spine if clinically indicated (e.g., height loss, back pain) Abbreviations: BMD, bone mineral density; CT, computed tomography; DXA, dualenergy x-ray absorptiometry; eGFR, estimated glomerular filtration rate; VFA, vertebral fracture assessment. Source: Data from JP Bilezikian et al: Evaluation and management of primary hyperparathyroidism: Summary statement and guidelines from the Fifth International Workshop. JBMR 37:2293, 2022.

Hyperparathyroidism Hypercalcemia of malignancy Hypoparathyroidism

Parathyroid hormone 1–84 (pg/mL)

0 6

Calcium (mg/dL) FIGURE 422-4 Levels of immunoreactive parathyroid hormone (PTH) detected in patients with primary hyperparathyroidism, hypercalcemia of malignancy, and hypoparathyroidism. Boxed area represents the upper and normal limits of blood calcium and/or immunoreactive PTH. (Reproduced with permission from SR Nussbaum et al (eds): Endocrinology, 4th ed. Philadelphia, PA: Saunders; 2001.) Special Tests,” below). Serum phosphate is usually low but may be nor mal, especially if renal failure has developed. Several modifications in PTH assays have been introduced in efforts to improve their utility in light of information about metabolism of PTH (as discussed above). First-generation assays were based on dis placement of radiolabeled PTH from anti-PTH antibodies that often reacted with PTH fragments. Second-generation, double-antibody, or immunometric assays (one antibody that is usually directed against the carboxyl-terminal portion of intact PTH to capture the hormone and a second enzyme-labeled antibody that is usually directed against the amino-terminal portion of intact PTH) greatly improved the diagnostic discrimination of the tests by eliminating interference from circulating biologically inactive fragments, detected by the original first-generation assays. Third-generation assays, which detect even fewer inactive fragments, may be useful for clinical research studies as in management of chronic renal disease but have not replaced secondgeneration assays, which reliably help make the diagnosis of hypo- and hyperparathyroidism and differentiate this disease from other condi tions of hypo- and hypercalcemia TREATMENT Primary Hyperparathyroidism Surgical excision of the abnormal parathyroid tissue is the defini tive therapy for this disease. As noted above, medical surveillance without operation for patients with mild, asymptomatic disease is, however, still preferred by some physicians and patients, par ticularly when the patients are more elderly. Evidence favoring surgery, if medically feasible, is growing because of concerns about skeletal, cardiovascular, and neuropsychiatric disease, even in mild hyperparathyroidism. Two surgical approaches are generally practiced. The conven tional parathyroidectomy procedure is neck exploration with general anesthesia; however, an outpatient procedure with local anesthesia,

termed minimally invasive parathyroidectomy, is gaining traction though it has not yet replaced the traditional surgical approach. Parathyroid exploration is challenging and should be undertaken by a surgeon experienced in this procedure. Certain features, like multiple abnormal glands in familial cases along with presurgical identification of one enlarged gland using several different imaging methods, can assist in determining the surgical approach. However, some critical decisions regarding management can be made only during the operation. Preoperative imaging, such as neck ultrasounds, 99mTc sestamibi scans with single-photon emission CT (SPECT), C(11) choline PET/CT, and four-dimensional (4D) CT are used to predict the location of an abnormal gland. Intraoperative monitoring of PTH levels by rapid PTH immunoassays may be useful in guiding the surgery and a rapid fall (>50%) to normal levels of PTH is used in many centers to predict successful removal of the culprit gland(s). Multiple-gland hyperplasia, as predicted in familial cases, and reoperation pose more difficult questions of surgical management and increase the risk of developing permanent hypoparathyroid ism. Immediate transplantation of a portion of a removed, minced parathyroid gland into the muscles of the forearm is sometimes performed, with the view that surgical excision is easier from the ectopic site in the arm if there is recurrent hyperfunction. In a minority of cases, if no abnormal parathyroid glands are found in the neck, the issue of further exploration must be decided. There are documented cases of five or six parathyroid glands and of unusual locations for adenomas such as in the mediastinum. A decline in serum calcium often occurs within 24 h after suc cessful surgery; usually, blood calcium falls to low-normal values for 3–5 days until the remaining parathyroid tissue resumes full hormone secretion. Risk factors for acute postoperative hypocalce mia is undermineralized bone matrix leading to “hungry bone” and vitamin D deficiency. With unexpected hypocalcemia, coexistent hypomagnesemia should be considered, as it interferes with PTH secretion and impairs response to PTH (Chap. 421). Transient hypoparathyroidism can occur but typically resolves within days; protracted recovery over several months can occur. Patients are unlikely to develop permanent hypoparathyroidism (often defined as hypoparathyroidism that persists 12 months after surgery) if their PTH levels tested within 12–24 h after surgery are

> 15 pg/mL. Signs of hypocalcemia include symptoms such as muscle twitch ing, a general sense of anxiety, and positive Chvostek’s and Trous seau’s signs coupled with hypocalcemia. Therapy with oral calcium and sometimes low-dose calcitriol is often sufficient. Parenteral calcium therapy should be instituted when severe hypocalcemia is present. The rate and duration of IV therapy are determined by the severity of the symptoms and the response of the serum calcium to treatment. An infusion of 0.5–2 mg/kg per hour or 30–100 mL/h of a 1-mg/mL solution usually suffices to relieve symptoms. Usu ally, parenteral therapy is required for only a few days. If symptoms worsen or if parenteral calcium is needed for >2–3 days, therapy with a vitamin D analogue and/or oral calcium (2–4 g/d) should be started (see below). It is cost-effective to use calcitriol (doses of 0.5–1 μg/d) because of the rapidity of onset of effect and prompt cessation of action when stopped, in comparison to other forms of vitamin D. A rise in blood calcium after several months of treat ment with calcium and calcitriol may indicate restoration of para thyroid function to normal. It is also appropriate to monitor serum PTH serially to estimate gland

> function in such patients. If magnesium deficiency is present, it can complicate the postop erative course since significant magnesium deficiency impairs the secretion of PTH. Hypomagnesemia should be corrected whenever detected, typically with oral magnesium replacement, but paren teral repletion may be necessary. MEDICAL MANAGEMENT Medical monitoring rather than corrective surgery is still accept able, but it is clear that surgical intervention is the more frequently

recommended option for the reasons noted above. Despite the use fulness of the guidelines, the importance of individual patient and physician judgment and preference is clear in all recommendations.

There is no long-term experience regarding specific clinical outcomes such as fracture prevention, but it has been established that bisphosphonates increase bone mineral density significantly without changing serum calcium. Calcimimetics reduce PTH secre tion and thus lower serum calcium but do not affect bone mineral density (BMD). A Scandinavian randomized clinical trial of para thyroidectomy versus observation in patients with mild primary hyperparathyroidism revealed no differences in morbidity or mor tality after 10 years. Disorders of the Parathyroid Gland and Calcium Homeostasis
CHAPTER 422 ■ ■OTHER PARATHYROID CAUSES

OF HYPERCALCEMIA Lithium Therapy Lithium, used in the management of bipolar depression and other psychiatric disorders, causes hypercalcemia in ~10% of treated patients. The hypercalcemia is dependent on con tinued lithium treatment, remitting and recurring when lithium is stopped and restarted. The parathyroid adenomas reported in some hypercalcemic patients with lithium therapy may reflect the presence of an independently occurring parathyroid tumor; a permanent effect of lithium on parathyroid gland growth need not be implicated as most patients have complete reversal of hypercalcemia when lithium is stopped. However, long-standing stimulation of parathyroid cell replication by lithium may predispose to development of adenomas (as is documented in secondary hyperparathyroidism and renal failure). At the levels achieved in blood in treated patients, lithium can be shown in vitro to shift the PTH secretion curve to the right in response to calcium; i.e., higher calcium levels are required to lower PTH secre tion, probably acting at the calcium sensor (see below). This effect can cause elevated PTH levels and consequent hypercalcemia in otherwise normal individuals. Cinacalcet has been used successfully in these patients. Fortunately, there are usually alternative medications for the underlying psychiatric illness. Parathyroid surgery should not be rec ommended unless hypercalcemia and elevated PTH levels persist after lithium is discontinued. ■ ■GENETIC DISORDERS CAUSING HYPERPARATHYROIDISM-LIKE SYNDROMES Familial Hypocalciuric Hypercalcemia FHH (also called famil ial benign hypercalcemia) is inherited as an autosomal dominant trait. Affected individuals are discovered because of asymptomatic hypercal cemia. Most cases of FHH are caused by an inactivating heterozygous CaSR mutations; this disorder, designated as FHH type 1, leads to inappropriately normal or even increased PTH secretion. Other forms of FHH are caused either by heterozygous loss-of-function mutations in GNA11 (encoding Gα11), one of the signaling proteins at the CaSR (FHH2), or by heterozygous mutations in AP2S1 (FHH3). In FHH1, the primary defect is abnormal sensing of the blood cal cium by the parathyroid gland and renal tubule, causing

inappropriate secretion of PTH and excessive reabsorption of calcium in the distal renal tubules. Many different inactivating CaSR mutations have been identified in patients with FHH1. These mutations lower the capacity of the sensor to bind calcium and the mutant receptors function as though blood calcium levels were low; thus, inappropriate secretion of PTH occurs from an otherwise normal gland. Approximately twothirds of patients with FHH have mutations within the protein-coding region of the CaSR gene (FHH1). Others have mutations in GNA11, the gene encoding the alpha-subunit of G11, a G-protein through which the CaSR signals (FHH2). These loss-of-function mutations have simi lar consequences to the loss-of-function mutations in the CaSR. FHH3 is caused by heterozygous mutations of the adaptor protein-2d subunit (AP2S1), which is a component of clathrin-coated vesicles, and critical in clathrin-mediated endocytosis. Since FHH is a life-long disease that cannot be cured by parathy roidectomy, it is critical to distinguish this rare disease from the more common primary hyperparathyroidism. One striking exception to the

FHH1, NSHPT Blomstrand’s lethal chondrodysplasia Jansen’s metaphyseal chondrodysplasia ADH1 Pseudohypoparathyroidism CaSR Ca2+ McCune-Albright syndrome PLC Gq/11 PART 12 Endocrinology and Metabolism PIP2 IP3
Gs PDE G ATP PTH/PTHrP receptor Proto-oncogenes and tumor-supressor genes PTH Transcription factors, e.g. GATA3, GCM2, FAM111A Gq/11 PTHrP Brachydactyly short stature PARATHYROID CELL FIGURE 422-5 Illustration of some genetic mutations that alter calcium metabolism by effects on the parathyroid cell or target cells of parathyroid hormone (PTH) action. Alterations in PTH production by the parathyroid cell can be caused by changes in the response to extracellular fluid calcium (Ca2+) that are detected by the calcium-sensing receptor (CaSR). Furthermore, PTH (or PTH-related peptide [PTHrP]) can show altered efficacy in target cells such as in proximal tubular cells, by altered function of its receptor (PTH/PTHrP receptor) or the signal transduction proteins, G proteins such as Gsα that is linked to adenylate cyclase (AC), the enzyme responsible for producing cyclic AMP (cAMP) (also illustrated are Gαq/Gα11, which activate an alternate pathway of receptor signal transmission involving the generation of inositol triphosphate [IP3] or diacylglycerol [DAG]). Heterozygous loss-of-function mutations in the CaSR cause familial benign hypocalciuric hypercalcemia (FBHH) and homozygous mutations (both alleles mutated) and neonatal severe hyperparathyroidism (NSHPT); heterozygous gain-of-function causes autosomal dominant hypercalciuric hypocalcemia (ADH1). Other defects in parathyroid cell function that occur at the level of gene regulation (oncogenes or tumor-suppressor genes) or transcription factors are discussed in the text. Blomstrand’s lethal chondrodysplasia is due to homozygous or compound heterozygous loss-of-function mutations in the PTH/PTHrP receptor, a neonatally lethal disorder, while pseudohypoparathyroidism involves inactivation at the level of the G proteins, specifically mutations that eliminate or reduce Gsα activity in the kidney (see text for details). Acrodysostosis can occur with (mutant regulatory subunit of PKA) or without hormonal resistance (mutant PDE4D or PDE3A). Jansen’s metaphyseal chondrodysplasia and McCune-Albright syndrome represent gain-of-function mutations in the PTH/PTHrP receptor and Gsα protein, respectively. rule against parathyroid surgery in this syndrome is the occurrence, usually in consanguineous marriages (due to the rarity of the gene mutation), of a homozygous or compound heterozygote state, result ing in severe impairment of CaSR function. In this condition, neonatal severe hypercalcemia, total parathyroidectomy is mandatory, but calci mimetics have been used as a temporary measure. Patients with FHH have lifelong hypercalcemia, which is typi cally mild and about 11 mg/dL. PTH values are often within normal laboratory range (which is inappropriate for hypercalcemia) or mildly elevated. Family history is often positive but can be negative because the patient has a de

novo mutation or the penetrance of the disease is not 100%. Patients with primary hyperparathyroidism have <99% renal calcium reabsorption, whereas most patients with FHH have

> 99% reabsorption. The calcium–to–creatine clearance ratio (CCCR), determined on spot or 24-hour urine, can be used to help differentiate the two disorders, with the CCCR typically <0.01 in FHH and >0.02 in primary hyperparathyroidism. This distinction is far from perfect, and genetic testing is helpful in establishing the diagnosis. Panel testing for hypercalcemic disorders allows the simultaneous sequencing of all genes known to be implicated in hypercalcemia, including the genes causing FHH. Rare but well-documented cases of acquired hypocalciuric hypercal cemia are reported due to antibodies against the CaSR. They appear to be a complication of an underlying autoimmune disorder and respond to therapies directed against the underlying disorder. Jansen's Disease Activating mutations in the PTH/PTHrP recep tor (PTH1R) have been identified as the cause of this rare autosomal dominant syndrome. Because the mutations lead to constitutive activa tion of receptor function, one abnormal copy of the mutant receptor is sufficient to cause the disease, thereby accounting for its dominant mode of transmission. Besides often severe hypercalcemia, patients affected by Jansen's disease have short-limbed dwarfism due to abnor mal regulation of chondrocyte maturation in the growth plates of the

cAMP AMP Acrodysostosis (with or without hormonal resistance) AC Catalytic subunit Regulatory subunit (PRKAR1A) Active PKA cAMP Cellular events, including HDAC4 activation C R R C C R R C Inactive PKA PIP2 IP3 + DAG Acrodysostosis with hormonal resistance PLC TARGET CELL (e.g. kidney, bone, or cartilage) bone that are formed through the endochondral process. In adult life, there are numerous abnormalities in bone, including multiple cystic resorptive areas resembling those seen in severe hyperparathyroidism. Hypercalcemia and hypophosphatemia with undetectable or low PTH levels are typically observed. The pathogenesis of the growth plate abnormalities in Jansen's disease has been confirmed by transgenic experiments in which targeted expression of the mutant PTH/PTHrP receptor to the proliferating chondrocyte layer of growth plate emu lated several features of the human disorder. Other genetic mutations in the parathyroid gland or PTH target cells that affect Ca2+ metabolism are illustrated in Fig. 422-5. ■ ■MALIGNANCY-RELATED HYPERCALCEMIA Clinical Syndromes and Mechanisms of Hypercalcemia

Hypercalcemia due to malignancy is common (occurring in as many as 20% of cancer patients, especially with certain types of tumors such as lung carcinoma), often severe and difficult to manage, and, typically easy to distinguish from primary hyperparathyroidism by a suppressed PTH. Although malignancy is usually clinically obvious or readily detectable by medical history, hypercalcemia can occasionally be due to an occult tumor. Three main mechanisms of hypercalcemia are operative in cancer hypercalcemia. Humoral hypercalcemia of malignancy (HHM) is caused by tumors producing and secreting PTHrP that causes a clinical picture similar to primary hyperparathyroidism with increased bone resorption and hypercalcemia. However, PTH is suppressed. Patients with HHM may have low to normal levels of 1,25(OH)2D, instead of elevated

levels as in true hyperparathyroidism probably reflecting sub tle differences in the activation of the PTH1R by PTHrP versus PTH. Squamous cell carcinomas and renal, bladder, and colorectal cancer are examples of tumors that can cause HHM. Several different assays (single- or double-antibody, different epitopes) have been developed to detect PTHrP and do not cross-react with PTH. Most data indicate that

circulating PTHrP levels are undetectable or low in normal individuals except in pregnancy (high in human milk) and elevated in most cancer patients with the humoral syndrome. Alternatively, local osteolysis leading to release of cytokines (e.g., interleukin 1 and tumor necrosis factor) that activate osteoclasts occurs with hematologic malignancies such as leukemia, lymphoma, and mul tiple myeloma, but also with breast cancer. A third mechanism leading to malignancy-associated hypercalcemia is an increased production and blood level of 1,25(OH)2D, produced by abnormal lymphocytes or adjacent macrophages in lymphoma but also in ovarian dysgerminomas. The etiologic mechanisms in cancer hypercalcemia may be multiple, even in the same patient. For example, in breast carcinoma (metastatic to bone) and in a distinctive type of T-cell lymphoma/leukemia initi ated by human T-cell lymphotropic virus 1, hypercalcemia is caused by direct local lysis of bone as well as by a humoral mechanism involving excess production of PTHrP. Hyperparathyroidism has been reported to coexist with the humoral cancer syndrome, and rarely, ectopic hyperparathyroidism due to tumor elaboration of true PTH is reported. TREATMENT Malignancy-Related Hypercalcemia Treatment of the hypercalcemia of malignancy is first directed to control of tumor; reduction of tumor mass usually corrects hypercalcemia. If a patient has severe hypercalcemia yet has a good chance for effective tumor therapy, treatment of the hypercalcemia should be vigorous while awaiting the results of definitive therapy (see “General Approach to Hypercalcemic States” below). If hyper calcemia occurs in the late stages of a tumor that is resistant to antitumor therapy, the treatment of the hypercalcemia should be judicious as high calcium levels can have a mild sedating effect. Standard therapies for hypercalcemia (discussed below) are appli cable to patients with malignancy. ■ ■VITAMIN D–RELATED HYPERCALCEMIA Vitamin D–mediated hypercalcemia can be due to excessive inges tion of vitamin D analogues or abnormal metabolism of the vitamin. Abnormal metabolism of the vitamin is usually acquired in association with a widespread granulomatous disorder. Vitamin D metabolism is carefully regulated, particularly the activity of renal 1α-hydroxylase, the enzyme responsible for the production of 1,25(OH)2D

(Chap. 421). The regulation of 1α-hydroxylase in sites other than the renal tubule differs and lacks the negative feedback regulations; these phenomena may explain the occurrence of hypercalcemia secondary to excessive 1,25(OH)2D production in patients with sarcoidosis or lymphoma. Vitamin D Intoxication Chronic ingestion of >10 times the normal physiologic requirement of vitamin D (amounts >10,000 U/d) is usually required to produce significant hypercalcemia in otherwise healthy individuals. The stated upper limit of safe dietary intake is 2000 U/d (50 μg/d) in adults because of concerns about potential toxic effects of cumulative supraphysiologic doses. These recommendations are now regarded as too restrictive, since some estimates are that, in elderly individuals in northern latitudes, ≥2000 U/d may be necessary to avoid vitamin D insufficiency. Hypercalcemia in vitamin D intoxication is due to an excessive bio logic action of the vitamin, perhaps the consequence of increased levels of 25(OH)D rather than merely increased levels of the active metabo lite 1,25(OH)2D (the latter may not be frankly elevated in vitamin D intoxication). These actions lead to both increased intestinal absorp tion of calcium and increased release of

calcium from bone. 25(OH) D has definite, if low, biologic activity in the intestine and bone. The production of 25(OH)D is less tightly regulated than is the production of 1,25(OH)2D. Hence, concentrations of 25(OH)D can be elevated severalfold in patients with excess vitamin D intake.

The diagnosis is substantiated by documenting elevated levels of 25(OH)D >100 ng/mL. Hypercalcemia is usually controlled by restric tion of dietary calcium intake and appropriate attention to hydration. These measures, plus discontinuation of vitamin D, usually lead to resolution of hypercalcemia. However, because of the increased bone resorption caused by high levels of vitamin D, simple cessation of cal cium intake is often insufficient therapy. Further, 25(OH)D stores in fat may be substantial, and vitamin D intoxication may persist for weeks after vitamin D ingestion is terminated. Such patients are responsive to glucocorticoids, which in doses of 40–100 mg/d of prednisone or its equivalent, usually return serum calcium levels to normal over several days; severe intoxication may require intensive therapy.

Disorders of the Parathyroid Gland and Calcium Homeostasis
CHAPTER 422 Sarcoidosis and Other Granulomatous Diseases In patients with sarcoidosis and other granulomatous diseases, such as tuberculo sis and fungal infections, excess 1,25(OH)2D is synthesized in macro phages or other cells in the granulomas. Indeed, increased 1,25(OH)2D levels have been reported in anephric patients with sarcoidosis and hypercalcemia. Macrophages obtained from granulomatous tissue convert 25(OH)D to 1,25(OH)2D at an increased rate. There is a posi tive correlation in patients with sarcoidosis between 25(OH)D levels (reflecting vitamin D intake) and the circulating concentrations of 1,25(OH)2D, whereas normally, there is no increase in 1,25(OH)2D with increasing 25(OH)D levels due to multiple feedback controls on renal 1α-hydroxylase (Chap. 421). The usual regulation of active metabolite production by calcium and phosphate or by PTH does not operate in these patients. Instead, macrophages increase their produc tion of the vitamin D receptor and of the 1α-hydroxylase in response to tumor necrosis factor and other inflammatory stimuli. PTH levels are usually low and 1,25(OH)2D levels are elevated, but primary hyper parathyroidism and sarcoidosis may coexist in some patients. Management of the hypercalcemia can often be accomplished by avoiding excessive sunlight exposure and limiting vitamin D and cal cium intake. Presumably, however, the abnormal sensitivity to vitamin D and abnormal regulation of 1,25(OH)2D synthesis will persist as long as the disease is active. Alternatively, glucocorticoids in the equivalent of 100 mg/d of hydrocortisone or equivalent doses of glucocorticoids may help control hypercalcemia. Glucocorticoids appear to act by blocking excessive production of 1,25(OH)2D, as well as the response to it in target organs. Hypercalcemia of Infancy Several variants of this rare abnor mality of calcium homeostasis are now known. For example, Williams' syndrome is an autosomal dominant disorder characterized by multiple congenital development defects, including supravalvular aortic steno sis, intellectual disability, and an elfin facies, in association with hyper calcemia due to abnormal sensitivity to vitamin D. The hypercalcemia associated with the syndrome was first recognized in England, where it was thought, incorrectly, to be caused by the fortification of milk with vitamin D. The cardiac and developmental abnormalities were independently described, but the connection between these defects and hypercalcemia was not described until later. Levels of 1,25(OH)2D can be elevated, ranging from 46 to 120 nmol/L (150–500 pg/mL). The mechanism of the abnormal sensitivity to vitamin D and of the increased circulating levels of 1,25(OH)2D is still unclear. Studies suggest that genetic mutations involving microdeletions at the elastin locus and perhaps other genes on chromosome 7 may play a role in the pathogenesis. Another genetic cause of hypercalcemia that

starts in infancy is 24-hydroxylase deficiency that impairs catabolism of 1,25(OH)2D caused by biallelic inactivating mutations in CYP24A1. Another rare cause of hypercalcemia involves mutation in the renal sodiumdependent phosphate transporters that lead to increased production of 1,25(OH)2D leading to hypercalcemia (NPT2a mutations lead to more severe hypercalcemia than NPT2c mutations). ■ ■HIGH-BONE-TURNOVER STATES Hyperthyroidism As many as 20% of hyperthyroid patients have high-normal or mildly elevated serum calcium concentrations;

hypercalciuria is even more common. The hypercalcemia is due to increased bone turnover, with bone resorption exceeding bone forma tion. Usually, the diagnosis is obvious, but signs of hyperthyroidism may occasionally be occult, particularly in the elderly (Chap. 396). Hypercalcemia is managed by treatment of the hyperthyroidism.

Immobilization Immobilization is a rare cause of hypercalcemia in adults in the absence of an associated disease but may cause hyper calcemia in children and adolescents, particularly after spinal cord injury and paraplegia or quadriplegia. With resumption of ambulation, the hypercalcemia in children usually returns to normal. The mechanism appears to involve a disproportion between bone formation and bone resorption; the former decreased and the latter increased. Hypercalciuria and increased mobilization of skeletal cal cium can develop in normal volunteers subjected to extensive bed rest, although hypercalcemia is unusual. Immobilization of an adult with a disease associated with high bone turnover, however, such as Paget’s disease, may cause hypercalcemia. PART 12 Endocrinology and Metabolism Thiazides Administration of thiazides can cause hypercalcemia in patients with high rates of bone turnover. Commonly, thiazides are associated with aggravation of hypercalcemia in primary hyperparathy roidism, but this effect can be seen in other high-bone-turnover states as well. The mechanism of thiazide action is complex. Chronic thiazide administration leads to reduction in urinary calcium; the hypocalciuric effect appears to reflect the enhancement of proximal tubular resorp tion of sodium and calcium in response to sodium depletion. Some of this renal effect is due to augmentation of PTH action and is more pronounced in individuals with intact PTH secretion. However, thia zides cause hypocalciuria in hypoparathyroid patients if sodium intake is restricted. This finding is the rationale for the use of thiazides as an adjunct to therapy in hypoparathyroid patients, as discussed below. Thi azide administration to normal individuals causes a transient increase in blood calcium (usually within the high-normal range) that reverts to preexisting levels after a week or more of continued administration. If hormonal function and calcium and bone metabolism are normal, homeostatic controls are reset to counteract the mild calcium-elevating effect of the thiazides. In the presence of hyperparathyroidism or increased bone turnover from another cause, homeostatic mechanisms are ineffective. The abnormal effects of the thiazide on calcium metabo lism disappear within days of cessation of the drug. Vitamin A Intoxication Vitamin A intoxication is a rare cause of hypercalcemia and is most commonly a side effect of dietary faddism (Chap. 344). Calcium levels can be elevated into the 3- to 3.5-mmol/L (12–14 mg/dL) range after the ingestion of 50,000–100,000 units of vitamin A daily (10–20 times the minimum daily requirement). Typi cal features of severe hypercalcemia include fatigue, anorexia, and, in some, severe muscle and bone pain. Excess vitamin A intake is pre sumed to increase bone resorption. The diagnosis can be established by history and by measurement of vitamin A levels in serum. Diagnostic challenges may arise in CKD where mildly elevated vitamin A levels are often seen with no asso ciation to hypercalcemia. Occasionally, skeletal x-rays reveal periosteal calcifications, particularly in the hands. Withdrawal of the vitamin is usually associated with prompt disappearance of the

hypercalcemia and reversal of the skeletal changes. As in vitamin D intoxication, administration of 100 mg/d hydrocortisone or its equivalent leads to a rapid return of the serum calcium to normal.
■ ■HYPERCALCEMIA ASSOCIATED WITH

CHRONIC KIDNEY DISEASE The pathogenesis of secondary hyperparathyroidism in CKD is mul tifactorial and includes resistance to PTH and an increase in FGF23, which, in turn, inhibits the renal 1a-hydroxylase, thus reducing 1,25(OH)2D levels and leading to further increases of PTH. Occasional patients develop severe manifestations of secondary hyperparathyroidism, including hypercalcemia, pruritus, extraskeletal calcifications, and painful bones, despite aggressive medical efforts to suppress the hyperparathyroidism. It is now recognized that a

true clonal outgrowth (irreversible) can arise in long-standing, inad equately treated CKD. PTH hypersecretion no longer responsive to medical therapy, a state of severe hyperparathyroidism in patients with CKD that requires surgery, has been referred to as tertiary hyperparathyroidism. TREATMENT Hypercalcemia in Tertiary Hyperparathyroidism Medical therapy to reverse secondary hyperparathyroidism in CKD includes reduction of excessive blood phosphate by restriction of dietary phosphate, the use of nonabsorbable phosphate binders, and careful, selective addition of calcitriol (0.25–2 µg/d) or related analogues. Calcium carbonate became preferred over aluminumcontaining antacids to prevent aluminum-induced bone disease. However, synthetic gels that also bind phosphate (such as sevelamer; Chap. 322) are now widely used, with the advantage of avoiding not only aluminum retention but also excess calcium loading, which may contribute to cardiovascular calcifications. Intravenous cal citriol (or related analogues), administered as several pulses each week, helps control secondary hyperparathyroidism. Aggressive but carefully administered medical therapy can often, but not always, reverse hyperparathyroidism and its symptoms and manifestations. Parathyroid surgery is necessary to control tertiary hyperpara thyroidism. Based on genetic evidence from examination of tumor samples in these patients, the emergence of autonomous parathy roid function is due to a monoclonal outgrowth of one or more previously hyperplastic parathyroid glands. The adaptive response has become an independent contributor to disease; this finding seems to emphasize the importance of optimal medical manage ment to reduce the proliferative response of the parathyroid cells that enables the irreversible genetic change. ■ ■OTHER CAUSES OF HYPERCALCEMIA Aluminum Intoxication Aluminum intoxication (and often hypercalcemia as a complication of medical treatment) in the past occurred in patients on chronic dialysis; manifestations included acute dementia and unresponsive and severe osteomalacia. Bone pain, multiple nonhealing fractures, particularly of the ribs and pelvis, and a proximal myopathy occur. Hypercalcemia develops when these patients are treated with vitamin D or calcitriol because of impaired skeletal responsiveness. Aluminum is present at the site of osteoid min eralization, osteoblastic activity is minimal, and calcium incorporation into the skeleton is impaired. The disorder is now rare because of the avoidance of aluminum-containing antacids or aluminum excess in the dialysis regimen. Milk-Alkali Syndrome The milk-alkali syndrome is due to exces sive ingestion of calcium and absorbable antacids such as milk or cal cium carbonate. It is much less frequent since proton pump inhibitors and other treatments became available for peptic ulcer disease. For a time, the increased use of calcium carbonate in the management of secondary hyperparathyroidism led to reappearance of the syndrome. Several clinical presentations—acute, subacute, and chronic—have been described, all of which feature hypercalcemia, alkalosis, and renal failure. The chronic form of the disease, termed Burnett’s syndrome, is associated with irreversible renal damage. The acute syndromes

reverse if the excess calcium and absorbable alkali are stopped. Individual susceptibility is important in the pathogenesis, as some patients are treated with calcium carbonate and alkali regimens with out developing the syndrome. One variable is the fractional calcium absorption as a function of calcium intake. Some individuals absorb a high fraction of calcium, even with intakes ≥2 g of elemental calcium per day, instead of reducing calcium absorption with high intake, as occurs in most normal individuals. Resultant mild hypercalcemia after meals in such patients is postulated to contribute to the generation of alkalosis. Development of hypercalcemia causes increased sodium excretion and some depletion of total-body water. These phenomena

and perhaps some suppression of endogenous PTH secretion due to mild hypercalcemia lead to increased bicarbonate resorption and to alkalosis in the face of continued calcium carbonate ingestion. Alkalo sis per se selectively enhances calcium resorption in the distal nephron, thus aggravating the hypercalcemia. The cycle of mild hypercalcemia → bicarbonate retention → alkalosis → renal calcium retention → severe hypercalcemia perpetuates and aggravates hypercalcemia and alkalosis as long as calcium and absorbable alkali are ingested. ■ ■DIFFERENTIAL DIAGNOSIS OF HYPERCALCEMIA Differential diagnosis of hypercalcemia is best achieved by using clinical criteria, but immunometric assays to measure PTH are especially useful in distinguishing among major causes (Fig. 422-6). The clinical features that deserve emphasis are the presence or absence of symptoms or signs of disease and evidence of chronicity. If one discounts fatigue or depression, >90% of patients with primary hyperparathyroidism have asymptomatic hypercalcemia; symptoms of malignancy are usually present in cancer-associated hypercalcemia. Disorders other than hyperparathyroidism and malignancy cause <10% of cases of hypercalcemia, and some of the nonparathyroid causes are associated with clear-cut manifestations such as renal failure. Hyperparathyroidism is the likely diagnosis in patients with chronic hypercalcemia. If hypercalcemia has been manifesting for >1 year, malignancy as the underlying cause is very unlikely. A striking feature of malignancy-associated hypercalcemia is the rapidity of the course, 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 primary hyperparathyroidism from all other causes of hypercalce mia (exceptions are very rare reports of ectopic production of excess PTH by nonparathyroid tumors). Patients with hyperparathyroidism have elevated (or nonsuppressed) PTH levels despite hypercalcemia, whereas patients with malignancy and the other causes of hyper calcemia (except for disorders mediated by PTH such as lithiuminduced hypercalcemia) have very low or undetectable levels. Intact PTH assays, based on the double-antibody method for PTH, exhibit very high sensitivity (especially if serum calcium is simultaneously Hypercalcemia Acute (or unknown) duration Chronic duration (months) PTH high PTH high PTH low PTH low 1° Hyperpara- thyroidism Consider MEN syndromes Consider malignancy PTHrP assay Clinical evaluation FIGURE 422-6 Algorithm for the evaluation of patients with hypercalcemia. PTH levels (high or low) should be interpreted in the context of serum calcium levels, as they may be inappropriately high or low for the level of serum calcium. See text for details. FHH, familial hypocalciuric hypercalcemia; MEN, multiple endocrine neoplasia; PTH, parathyroid hormone; PTHrP, parathyroid hormone–related peptide; Vit, vitamin.

evaluated) and specificity for the diagnosis of primary hyperparathy roidism (Fig. 422-4).

In summary, PTH values are elevated in >90% of parathyroid-related causes of hypercalcemia, undetectable or low in malignancy-related, 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 but can be due to heterotopic antibodies. Immunoassays for PTHrP are helpful in diagnosing cer tain types of malignancy-associated hypercalcemia. Although FHH is parathyroid-related, the disease should be managed distinctively from primary hyperparathyroidism. Clinical features, family history, and the low urinary calcium excretion can help make the distinction, and genetic testing confirms the diagnosis. Because the incidence of malignancy and hyperparathyroidism both increase with age, they can coexist as two independent causes of hypercalcemia. Disorders of the Parathyroid Gland and Calcium Homeostasis CHAPTER 422 1,25(OH)2D levels are in the upper range of normal or frankly ele vated 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 hyperpara thyroidism 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. 422-6. If the patient is asymptomatic and there is evidence of chronicity to the hypercalcemia, hyperparathyroidism is likely the cause and FHH needs to be excluded. If PTH levels (usually measured at least twice) are elevated, the clinical impression is confirmed, and little additional diagnostic 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 suppressed then a thorough workup must be undertaken for malignancy, which may include 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 Key historical considerations • Confirm if ↑Ca2+ chronic • Clues from history and physical findings Screen negative Other causes Granulomatous disease FHH Milk-alkali syndrome Medications (lithium, thiazides) Immobilization Vit D or Vit A intoxication Adrenal insufficiency Hyperthyroidism Hyperpara- thyroidism or MEN syndromes (consider FHH)

in some patients with metastases such as in multiple myeloma. Finally, if a patient with chronic hypercalcemia is asymptomatic and malig nancy 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 General Approach to Hypercalcemic States PART 12 Endocrinology and Metabolism The approach to medical treatment of hypercalcemia varies with its severity. Mild hypercalcemia, <3 mmol/L (12 mg/dL), can usually be managed by hydration. More severe hypercalcemia (levels of 3.2–3.7 mmol/L [13–15 mg/dL]) must be managed more aggres sively; above that level, hypercalcemia can be life-threatening and requires emergency measures (Table 422-4). By using a combina tion of approaches in severe hypercalcemia, the serum calcium concentration can be decreased within 24–48 h in most patients, enough to relieve acute symptoms, prevent death from

hypercalce mic 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 pathogen esis 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 restriction of dietary calcium is beneficial. Decreased renal function or ECF depletion decreases urinary cal cium excretion. In such situations, rehydration may rapidly reduce or reverse the hypercalcemia, even though increased bone resorp tion persists. As outlined below, the more severe the hypercalcemia, the greater the need for a combination of therapies. Rapid-acting (hours) approaches—rehydration, forced diuresis, and calcitonin— can be used with the most effective antiresorptive agents such TABLE 422-4 Therapies for Severe Hypercalcemia ONSET OF ACTION DURATION OF ACTION ADVANTAGES DISADVANTAGES TREATMENT Most Useful Therapies IV hydration with normal saline Hours During infusion Rehydration invariably needed Volume overload Forced diuresis; normal 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 Zoledronate 1–2 days

> 3 weeks Same as for pamidronate (lasts longer) Denosumab 1–2 days 3 weeks Strongest antiresorptive Occasional severe hypocalcemia, rarely jaw necrosis, skin infections Special Use Therapies Calcitonin Hours 1–2 days Rapid onset of action; useful as adjunct in severe hypercalcemia Phosphate oral 24 h During use Chronic management (with hypophosphatemia); low toxicity if P <4 mg/dL 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 Source: Data from JP Bilezikian et al: Evaluation and management of primary hyperparathyroidism: Summary statement and guidelines from the Fifth International Workshop. JBMR 37:2293, 2022.

as bisphosphonates (since severe hypercalcemia usually involves excessive bone resorption). HYDRATION, INCREASED SALT INTAKE, AND MILD

AND FORCED DIURESIS The first principle of treatment is to restore normal hydration. Many hypercalcemic patients are dehydrated because of vomiting, inanition, and/or hypercalcemia-induced defects in urinary con centrating ability. The resultant drop in glomerular filtration rate is accompanied by an additional decrease in renal tubular sodium and calcium clearance. Restoring a normal ECF volume corrects these abnormalities and increases urine calcium excretion by 2.5–7.5 mmol/d (100–300 mg/d). Increasing urinary sodium excretion to 400–500 mmol/d increases urinary calcium excretion even further than simple rehydration. After rehydration has been achieved, saline can be administered, or furosemide or ethacrynic acid can be given to depress the tubular reabsorptive mechanism for cal cium (care must be taken to prevent dehydration). The combined

use of these therapies can increase urinary calcium excretion to

≥12.5 mmol/d (500 mg/d) in most hypercalcemic patients. Since this is a substantial percentage of the exchangeable calcium pool, the serum calcium concentration usually falls 0.25–0.75 mmol/L (1–3 mg/dL) within 24 h. Precautions should be taken to prevent potassium and magnesium depletion; calcium-containing renal calculi are a potential complication. Under life-threatening circumstances, the preceding approach can be pursued more aggressively, but the availability of effective agents to block bone resorption (such as bisphosphonates) has reduced the need for extreme diuresis regimens (Table 422-4). Depletion of potassium and magnesium is inevitable unless replace ments are given; pulmonary edema can be precipitated. The poten tial complications can be reduced by careful monitoring of central venous pressure and plasma or urine electrolytes; catheterization of the bladder may be necessary. Dialysis treatment may be needed when renal function is compromised. BISPHOSPHONATES The bisphosphonates are analogues of pyrophosphate, with high affinity for bone, especially in areas of increased bone turnover, Fever in 20%, hypophosphatemia, hypocalcemia, hypomagnesemia, rarely jaw necrosis Same as pamidronate above Rapid tachyphylaxis Limited use except as adjuvant or chronic therapy Useful in renal failure; onset of effect in hours; can immediately reverse life-threatening hypercalcemia Complex procedure, reserved for extreme or special circumstances

where they are powerful inhibitors of bone resorption. These boneseeking compounds are stable in vivo because phosphatase enzymes cannot hydrolyze the central carbon-phosphorus-carbon bond. The bisphosphonates are concentrated in areas of high bone turnover and are taken up by and inhibit osteoclast action; the mechanism of action is complex. The bisphosphonate molecules that contain amino groups in the side chain structure (see below) interfere with prenylation of proteins and can lead to cellular apoptosis. The highly active non-amino-group–containing bisphosphonates are also metabolized to cytotoxic products. A number of second- or third-generation compounds have become the mainstays of antiresorptive therapy for treatment of hypercalcemia and osteoporosis. The newer bisphosphonates have a highly favorable ratio of blocking resorption versus inhibiting bone formation; they inhibit osteoclast-mediated skeletal resorption yet do not cause mineralization defects at ordinary doses. Though the bisphosphonates have similar structures, the routes of administra tion, efficacy, toxicity, and side effects vary. Compounds commonly used are pamidronate, alendronate, and zoledronate. The IV use of pamidronate and zoledronate is approved for the treatment of hypercalcemia; between 30 and 90 mg pamidronate, given as a single IV dose over a few hours, returns serum calcium to normal within 24–48 h with an effect that lasts for weeks in 80–100% of patients. Zoledronate given as an infusion in doses of 5 mg has a more rapid and more sustained effect that lasts longer than pami dronate in direct comparison. These drugs are used extensively in cancer patients. Absolute survival improvements are noted with pamidronate and zoledronate in multiple myeloma, for example. However, though rare, osteone crosis of the jaw, especially after dental surgery, mainly in cancer patients treated with multiple doses of the more potent bisphospho nates, and atypical femoral fractures are potential side effects. DENOSUMAB Denosumab is the most recent antiresorptive therapy to be approved for the treatment of hypercalcemia, a monoclonal antibody that binds to RANK ligand (RANKL) and prevents it from binding to the receptor RANK on osteoclast precursors and mature osteo clasts. The inhibition of differentiation, activation, and function of osteoclasts leads to a reduction in bone resorption. It has a pro found suppressive effect on biochemical markers of bone resorption and is the most powerful antiresorptive agent currently available. Repeated doses of

denosumab, 120 mg given subcutaneously, may be effective in patients with hypercalcemia of malignancy who are not controlled by bisphosphonates. There are currently uncertain ties how to manage rebound effects (fractures, hypercalcemia) after stopping denosumab, but antiresorptives such as alendronate and zoledronic acid can mitigate these effects. OTHER THERAPIES Calcitonin acts within a few hours of its administration, princi pally through receptors on osteoclasts, to block bone resorption. Calcitonin, after 24–48 h of use, is no longer effective in lowering calcium. Tachyphylaxis, a known phenomenon with this drug, seems to explain the results since the drug is initially often effective. Therefore, in life-threatening hypercalcemia, calcitonin can be used effectively within the first 24–48 h in combination with rehydra tion and saline diuresis while waiting for more sustained effects from simultaneously administered antiresorptives. Usual doses of calcitonin are 2–8 U/kg of body weight IV, SC, or IM every 6–12 h. Glucocorticoids have utility, especially in hypercalcemia compli cating certain malignancies. They increase urinary calcium excre tion and decrease intestinal calcium absorption when given in pharmacologic doses, but they also cause negative skeletal calcium balance. In normal individuals and in patients with primary hyper parathyroidism, glucocorticoids neither increase nor decrease the serum calcium concentration. In patients with hypercalcemia due to certain osteolytic malignancies, however, glucocorticoids may be effective as a result of antitumor effects. The malignancies in

which hypercalcemia responds to glucocorticoids include mul tiple myeloma, leukemia, Hodgkin’s disease, other lymphomas, and carcinoma of the breast, at least early in the course of the disease. Glucocorticoids are also effective in treating hypercalcemia due to vitamin D intoxication and sarcoidosis. Glucocorticoids are also useful in the rare form of hypercalcemia, now recognized in certain autoimmune disorders in which inactivating antibodies against the receptor imitate FHH. Elevated PTH and calcium levels are effec tively lowered by the glucocorticoids. In all the preceding situations, the hypocalcemic effect develops over several days, and the usual glucocorticoid dosage is 40–100 mg prednisone (or its equivalent) daily in divided doses. The side effects of chronic glucocorticoid therapy may be acceptable in some circumstances.

 For patients with hypercalcemia due to CYP24A1 mutations, avoidance of sun, vitamin D intake, and reducing calcium intake are recommended. Fluconazole and ketoconazole, inhibitors of CYP27B1, and rifampin (an inducer of CYP3A4) have been reported to be beneficial; particular attention should be given to potential side effects of each of these medications. Dialysis is often the treatment of choice for severe hypercalcemia complicated by renal failure, which is difficult to manage medi cally. Peritoneal dialysis with calcium-free dialysis fluid can remove 5–12.5 mmol (200–500 mg) of calcium in 24–48 h and lower the serum calcium concentration by 0.7–2.2 mmol/L (3–9 mg/dL). Large quantities of phosphate are lost during dialysis, and serum inorganic phosphate concentration usually falls, potentially aggra vating hypercalcemia. Therefore, the serum inorganic phosphate concentration should be measured after dialysis, and phosphate sup plements should be added to the diet or to dialysis fluids if necessary. Phosphate therapy, PO or IV, has a limited role in certain cir cumstances (Chap. 421). Correcting hypophosphatemia lowers the serum calcium concentration by several mechanisms, includ ing bone/calcium exchange. The usual oral treatment is 1–1.5 g phosphorus per day for several days, given in divided doses. It is generally believed, but not established, that toxicity does not occur if therapy is limited to restoring serum inorganic phosphate con centrations to normal. Raising the serum inorganic phosphate concentration above nor mal decreases serum calcium levels, sometimes strikingly. Intrave nous

phosphate is one of the most dramatically effective treatments available for severe hypercalcemia but is toxic and even dangerous (fatal hypocalcemia). For these reasons, it is used rarely and only in severely hypercalcemic patients with cardiac or renal failure where dialysis, the preferable alternative, is not feasible or is unavailable. SUMMARY The various therapies for hypercalcemia are listed in Table 422-4. The choice depends on the underlying disease, the severity of the hypercalcemia, the serum inorganic phosphate level, and the renal, hepatic, and bone marrow function. Mild hypercalcemia (≤3 mmol/L [12 mg/dL]) can usually be managed by hydration. Severe hyper calcemia (≥3.7 mmol/L [15 mg/dL]) requires rapid correction. IV pamidronate or zoledronate or subcutaneous denosumab should be administered. In addition, for the first 24–48 h, aggressive sodium-calcium diuresis with IV saline should be given. Following rehydration, furosemide or ethacrynic acid can be added, but only if appropriate monitoring is available and cardiac and renal function are adequate. For intermediate degrees of hypercalcemia between 3 and 3.7 mmol/L (12 and 15 mg/dL), vigorous hydration is recom mended. Depending on symptoms and underlying causes, this may be combined with antiresorptives and other previously mentioned treatments. ■ ■HYPOCALCEMIA (See also Chap. 57). Pathophysiology Chronic hypocalcemia is less common than hyper calcemia; causes include CKD, hereditary and acquired hypoparathy roidism, vitamin D deficiency, PTH resistance, and hypomagnesemia.

Acute rather than chronic hypocalcemia is seen in critically ill patients or as a consequence of certain medications and often does not require specific treatment. Transient hypocalcemia is seen with severe sepsis, burns, acute kidney injury, and extensive transfusions with citrated blood. Although as many as one-half of patients in an intensive care setting are reported to have calcium concentrations of <2.1 mmol/L (8.5 mg/dL), most do not have a reduction in ionized calcium. Patients with severe sepsis may have a decrease in ionized calcium (true hypocalcemia), but in other severely ill individuals, hypoalbuminemia is the primary cause of the reduced total calcium concentration. Alkalosis increases calcium binding to proteins.

Medications such as protamine, heparin, and glucagon may cause transient hypocalcemia. These forms of hypocalcemia are usually not associated with tetany and resolve with improvement in the overall medical condition. The hypocalcemia after repeated transfusions of citrated blood usually resolves quickly. PART 12 Endocrinology and Metabolism Patients with acute pancreatitis have hypocalcemia that persists dur ing the acute inflammation and varies in degree with disease severity. The cause of hypocalcemia remains unclear but may include saponifi cation and systemic inflammation. PTH values are reported to be low, normal, or elevated, and both resistance to PTH and impaired PTH secretion have been postulated. Chronic hypocalcemia, however, is usually symptomatic and requires treatment. Neuromuscular and neurologic manifestations of chronic hypocalcemia include tingling, muscle spasms, carpopedal spasm, and, in extreme cases, laryngeal spasm and convulsions. Increased intracranial pressure occurs in some patients with longstanding hypocalcemia, often in association with papilledema. Mental changes include irritability, depression, and psychosis. The QT interval on the electrocardiogram is prolonged, in contrast to its shortening with hypercalcemia. Arrhythmias occur, and digitalis effectiveness may be reduced. Intestinal cramps and chronic malabsorption may occur. Chvostek’s or Trousseau’s sign can be used to confirm latent tetany; the latter is more specific and sensitive for hypocalcemia. Classification of Hypocalcemia The classification of hypocalce mia shown in Table 422-5 is based on an organizationally useful prem ise that hypocalcemia may be primarily due to one of the two main calcium-regulating hormones, PTH and vitamin D, or other causes. PTH-related Hereditary or

acquired forms of hypoparathyroidism have a number of common components. The disease is rare with esti mates from all causes to be ~25–35 patients/100,000 of the population (based on U.S. and Danish estimates). Symptoms of untreated hypo calcemia are shared by both types of hypoparathyroidism, although the onset of hereditary hypoparathyroidism can be more gradual and associated with other developmental defects. Basal ganglia calcification and extrapyramidal syndromes are more common and earlier in onset in hereditary hypoparathyroidism. Acquired hypoparathyroidism sec ondary to surgery in the neck is the most common cause of hypopara thyroidism, but the frequency of surgically induced parathyroid failure has diminished as a result of improved surgical techniques that spare the parathyroid glands and increased use of nonsurgical therapy for hyperthyroidism. PHP, an example of resistance to PTH action rather than a failure of production by the parathyroid gland, may share several features with hypoparathyroidism, including extraosseous calcification and extrapyramidal manifestations such as choreoathetotic movements and dystonia but circulating PTH is increased rather than decreased in the other conditions. Papilledema, raised intracranial pressure, and lenticular cataracts may occur in both hereditary and acquired hypoparathyroidism, as do chronic changes in fingernails and hair, the latter usually reversible with treatment of hypocalcemia. Certain skin manifestations, includ ing alopecia and candidiasis, are characteristic of hereditary hypo parathyroidism associated with autoimmune polyglandular failure

(Chap. 401). Hypocalcemia associated with hypomagnesemia is associated with both deficient PTH release and impaired responsiveness to the hor mone and is reversible with normalization of serum magnesium. Patients with hypocalcemia secondary to hypomagnesemia have low

TABLE 422-5 Functional Classification of Hypocalcemia (Excluding Neonatal Conditions) 1. PTH-Related a. Absence of parathyroid glands or inactive PTH i. Congenital: 22q11 deletion syndrome (DS), isolated hypoparathyroidism, PTH mutations, mutations in specific transcription factors (GCM2, GATA3) ii. Destruction of glands: postsurgical, APECED, infiltrative disorders b. Impaired secretion i. Congenital: autosomal-dominant hypocalcemia ii. Functional: hypomagnesemia, hypermagnesemia c. Target organ resistance i. Pseudohypoparathyroidism ii. Hypomagnesemia 2. Vitamin D–related a. Vitamin D deficiency: nutritional deficiency, impaired cutaneous production, malabsorption b. Accelerated loss: impaired enterohepatic recirculation; increased metabolism due to anticonvulsants or antituberculosis therapy (e.g., rifampin) c. Impaired 25-hydroxylation: severe liver disease, CYP2R1 mutations d. Impaired 1a-hydroxylation: renal insufficiency, azole antifungal medications that inhibit CYP27B1 (e.g., ketoconazole), genetic 1α hydroxylase deficiency, FGF23-related (TIO, XLH, CKD) e. Target organ resistance: VDR mutations 3. Others a. Impaired bone resorption: denosumab, antiresorptives b. Excessive deposition into the skeleton: hungry bone syndrome (e.g., after parathyroidectomy for primary hyperparathyroidism), osteoblastic malignancies c. Chelation: infusion of citrated blood products or EDTA, phosphate infusion d. Critical illness: pancreatitis, ICU patients Abbreviations: 22q11DS, 22q11 deletion syndrome; APECED, autoimmune polyendocrinopathy candidiasis ectodermal dystrophy; CKD, chronic kidney disease; EDTA, ethylenediaminetetraacetic acid; FGF23, fibroblast growth factor 23; ICU, intensive care unit; PTH, parathyroid hormone; TIO, tumor-induced osteomalacia; VDR, vitamin D receptor; XLH, X-linked hypophosphatemic rickets. levels of circulating PTH, indicative of diminished hormone release despite a maximum physiologic stimulus by hypocalcemia. Hyperma gnesemia, which can be iatrogenic, may inhibit PTH release leading to hypocalcemia. GENETIC CAUSES Hereditary hypoparathyroidism can occur as an isolated entity without other endocrine or

dermatologic manifestations or in association with other abnormalities. Hypoparathyroidism Associated with Other Abnormalities Hypoparathyroidism associated with defective development of both the thymus and the parathyroid glands is termed DiGeorge syndrome, velocardiofacial syn drome, or 22q11 deletion syndrome. Congenital cardiovascular, facial, and other developmental defects are present, and patients may die in early childhood with severe infections, hypocalcemia and seizures, or cardiovascular complications. Patients can survive into adulthood, and milder, incomplete forms may become manifest in childhood or adolescence. Most cases are sporadic, but autosomal dominant forms involving microdeletions of chromosome 22q11.2 or point mutations in the transcription factor TBX1 within that chromosomal region exist. Another autosomal dominant developmental defect with hypoparathy roidism, deafness, and renal dysplasia (HDR) is caused by mutations in the transcription factor GATA3 (chromosome 10p14), which is important in embryonic development and is expressed in develop ing kidney, ear structures, and the parathyroids. Autosomal recessive disorders comprising hypoparathyroidism include Kenney-Caffey syn drome type 1, which also features short stature, osteosclerosis, and thick cortical bones, and the related Sanjad-Sakati syndrome, which also exhibits growth failure and other dysmorphic features. Both syndromes involve mutations in a chaperone protein called TBCE (chromosome 1q42-q43), which is relevant to tubulin function. FAM111A defects (chromosome 11q12.1) were identified as the cause of Kenney-Caffey syndrome type 2.

Hypoparathyroidism that can occur in association with a mono genetic autoimmune syndrome involving failure of the adrenals, the ovaries, the immune system, and the parathyroids in association with recurrent mucocutaneous candidiasis, alopecia, vitiligo, and pernicious anemia is commonly referred to as polyglandular autoimmune type 1 deficiency or autoimmune polyendocrinopathy candidiasis ectodermal dystrophy (APECED) (Chap. 401). This disorder is caused by muta tions in the AIRE gene (chromosome 21q22.3). A stop codon mutation occurs in many Finnish families with the disorder, while another muta tion (Y85C) is typically observed in Jews of Iraqi and Iranian descent. Hypoparathyroidism is also seen in two disorders associated with mitochondrial dysfunction and myopathy, one termed Kearns-Sayre syndrome (KSS), with ophthalmoplegia and pigmentary retinopathy, and the other termed MELAS syndrome (mitochondrial encephalopa thy, lactic acidosis, and stroke-like episodes). Mutations or deletions in mitochondrial genes have been identified. Isolated Hypoparathyroidism Several forms of hypoparathyroidism, each rare in frequency, are seen as isolated defects; the genetic mechanisms are varied. The inheritance includes autosomal dominant, autosomal recessive, and X-linked modes. PTH Mutations Several autosomal defects involving the preproPTH sequence or the mature PTH have been recognized. The dominant forms are caused by point mutations in a critical region involved in intracellular transport of the hormone precursor. For example, an Arg for Cys mutation interferes with processing of the precursor and is believed to trigger an apoptotic cellular response, hence acting as a dominant negative. Recessive forms require both PTH alleles encoding the prepro sequence to be mutated. Only three homozygous mutations affecting the mature PTH have been described that lead to an autoso mal recessive form of hypoparathyroidism. The defect for an X-linked recessive form of hypoparathyroidism has been localized to chromo some Xq26-q27, perhaps involving the SOX3 gene. CaSR Mutations Different gain-of-function mutations in the CaSR gene have been found in one form of hypocalcemia termed autosomal dominant hypocalcemia (ADH) type 1. The mutant receptor senses the ambient calcium level as excessive and suppresses PTH secretion, lead ing to hypocalcemia. The hypocalcemia is aggravated by constitutive receptor activity in the renal tubule causing excretion of inappropri ate amounts of calcium. Recognition of

the syndrome is important because efforts to treat the hypocalcemia with vitamin D analogues and increased oral calcium exacerbate the already excessive urinary calcium excretion leading to irreversible renal damage from stones and ectopic calcification. The orally available negative allosteric modulator (NAM) on the CaSR encaleret has been shown to normalize serum and urine calcium, as well as serum phosphate and magnesium in a phase 2 trial in patients with ADH1. Other Causes of Isolated Hypoparathyroidism These include homozygous, inac tivating mutations in the parathyroid-specific transcription factor GCM2 or heterozygous point mutations in this protein, which have a dominant-negative effect on the wild-type protein and thus lead to an autosomal dominant form of hypoparathyroidism. Furthermore, heterozygous mutations in Gα11, one of the two signaling proteins downstream of the CaSR, have been identified as a cause of autoso mal dominant hypocalcemia, now referred to as ADH type 2. The Bartter syndrome is a group of disorders associated with disturbances in electrolyte and acid-base balance, sometimes with nephrocalcino sis and other features. Several types of ion channels or transporters are involved. Curiously, Bartter syndrome type V has electrolyte and pH disturbances but is caused by a gain-of-function mutation in the CaSR. The defect may be more severe than in ADH1 and explains the additional features seen beyond hypocalcemia and hypercalciuria. As with autoimmune disorders that block the CaSR (discussed above under hypercalcemic conditions), there are autoantibodies that at least transiently activate the CaSR, leading to suppressed PTH secretion and hypocalcemia. Acquired chronic hypoparathyroidism is usually the result of inad vertent surgical removal of or damage to all the parathyroid glands; in some instances, not all the tissue is removed, but the remainder

undergoes vascular supply compromise secondary to fibrotic changes in the neck after surgery. In the past, the most frequent cause of acquired hypoparathyroidism was surgery for hyperthyroidism. Hypo parathyroidism can also occur after surgery for hyperparathyroidism when the surgeon, facing the dilemma of removing too little tissue and thus not curing the hyperparathyroidism, removes too much. Parathy roid function may not be totally absent in all patients with postopera tive hypoparathyroidism.

Very rare causes of acquired chronic hypoparathyroidism include radiation-induced damage subsequent to radioiodine therapy of hyper thyroidism and glandular damage in patients with hemochromatosis or hemosiderosis after repeated blood transfusions. Disorders of the Parathyroid Gland and Calcium Homeostasis
CHAPTER 422 Transient hypoparathyroidism is frequent following surgery for hyperparathyroidism. After a variable period of hypoparathyroidism, normal parathyroid function may return due to hyperplasia or recov ery of remaining tissue. Occasionally, recovery occurs months after surgery. TREATMENT Acquired and Hereditary Hypoparathyroidism Conventional treatment has involved increasing serum calcium by administration of active vitamin D (calcitriol) combined with oral calcium supplementation. In many patients, blood calcium and phosphate levels are maintained satisfactorily, but some patients show a tendency to alternate between hypocalcemia and hyper calcemia, thus requiring close monitoring. Treatment with active vitamin D (calcitriol or alpha-calcidol) is preferred over high-dose plain vitamin D, which was standard in the past, particularly since calcitriol is cleared much more rapidly from the circulation than vitamin D. PTH analogues are being incorporated into the range of treatment options for this disease (see below). Oral calcium and vitamin D increase serum calcium but do not address other functions of PTH. This current standard of care treatment exacerbates hypercalciuria, does not normalize hyper phosphatemia,

and does not normalize the low bone turnover of hypoparathyroidism. Because of the hypercalciuria, blood calcium levels should be maintained at the lower end of the normal range or just below normal in these patients to avoid excessive urinary calcium excretion; otherwise, nephrocalcinosis and kidney stones can develop, and the risk of CKD is increased. Thiazide diuretics lower urine calcium by as much as 100 mg/d in hypoparathyroid patients on calcium and vitamin D, provided they are maintained on a low-sodium diet. Until recently, hypoparathyroidism was the only endocrine dis order not being treated with the missing hormone. After the ini tial experimental use of PTH(1–34), the synthetic PTH fragment used in treatment of osteoporosis, showed promise, full-length PTH(1–84) has been shown to be effective and was approved by the U.S. Food and Drug Administration for therapy of hypopara thyroidism. The effective half-life of these PTH analogues is not long enough to achieve effective PTH effects over 24 h with one injection. Moreover, they are not approved or no longer available in the United States. Long-acting PTH molecules have been developed and are in clinical trials. Palopegteriparatide, an inactive prodrug that is given as an SC injection once daily and releases PTH(1–34) from an inert carrier in a sustained manner, showed normaliza tion of blood and urine calcium in a phase 3 clinical trial and is approved in the US and Europe. Eneboparatide, a biased peptide agonist to the PTH receptor with a prolonged intracellular signal ing, showed normalization of blood and urine calcium in patients with hypoparathyroidism in a phase 2 clinical trial and is currently undergoing a phase 3 trial. HYPOMAGNESEMIA Severe hypomagnesemia (<0.4 mmol/L; <0.8 meq/L) is associated with hypocalcemia (see above). Restoration of the total-body magnesium deficit leads to rapid reversal of hypo calcemia. There are at least two causes of the hypocalcemia in severe

hypomagnesemia—impaired PTH secretion and reduced responsive ness to PTH. For further discussion of causes and treatment of hypomagnesemia, see Chap. 421.

PTH levels are undetectable or inappropriately low in severe hypo magnesemia despite the stimulus of severe hypocalcemia, and acute repletion of magnesium leads to a rapid increase in PTH level. Serum phosphate levels are often not elevated, in contrast to the situation with acquired or idiopathic hypoparathyroidism, probably because phosphate deficiency is often seen in hypomagnesemia. In addition to diminished PTH secretion, some patients with low calcium and mag nesium levels show a blunted peripheral response to exogenous PTH as documented by subnormal response in urinary phosphorus and urinary cyclic AMP excretion. PART 12 Endocrinology and Metabolism TREATMENT Hypomagnesemia Repletion of magnesium cures the condition. Repletion should be parenteral. Attention must be given to restoring the intracellular deficit, which may be considerable. After IV magnesium admin istration, serum magnesium may return transiently to the normal range, but unless replacement therapy is adequate, serum magne sium will again fall. If the cause of the hypomagnesemia is renal magnesium wasting, magnesium may have to be given long-term to prevent recurrence (Chap. 421). PTH TARGET ORGAN RESISTANCE PHP refers to a group of distinct inherited disorders that resemble hypoparathyroidism (in which PTH synthesis is deficient) and is manifested by hypocalcemia and hyper phosphatemia yet elevated PTH levels. Patients affected by PHP type Ia (PHP1A) develop symptoms and signs of hypocalcemia in association with distinctive skeletal and devel opmental defects, referred to as Albright’s hereditary osteodystrophy (AHO). The hypocalcemia is due to a deficient PTH response in the proximal renal tubules, probably leading to insufficient 1,25(OH)2D production and thus impaired intestinal calcium absorption. Further more, PTH resistance in this portion of the kidney impairs urinary phosphate excretion, thus leading to elevated serum phosphate levels. Patients

affected by PHP type Ib (PHP1B) also present with hypocal cemia and hyperphosphatemia but less frequently with obvious AHO features. In response to the hypocalcemia observed in either disorder, PTH levels increase, leading to parathyroid hyperplasia and, in some cases, to autonomous PTH secretion. Studies, both clinical and basic, have clarified some aspects of these disorders, including the variable clinical spectrum, the pathophysiology, the genetic defects, and their mode of inheritance. A working classification of the various PHP forms is given in

Table 422-6. The classification scheme is based on the signs of ineffec tive PTH action (low calcium and high phosphate), low or normal uri nary cyclic AMP response to exogenous PTH, the presence or absence of AHO, and assays to measure the concentration of the Gsα subunit. TABLE 422-6 Classification of Pseudohypoparathyroidism (PHP) and Pseudopseudohypoparathyroidism (PPHP) HYPOCALCEMIA, HYPERPHOSPHATEMIA RESPONSE OF URINARY cAMP TO PTH SERUM PTH TYPE PHP1A Yes ↓ ↑ Yes Yes Yes PPHP No Normal Normal Yes Yes No PHP1B Yes ↓ ↑ No Yes (less frequently and usually less severe) PHP2 Yes Normal (but ↓ phosphaturic response) Acrodysostosis due to PRKAR1A mutations with hormonal resistance Yes Normal (but ↓ phosphaturic response) Abbreviations: ↓, decreased; ↑, increased; AHO, Albright’s hereditary osteodystrophy; cAMP, cyclic adenosine monophosphate; PTH, parathyroid hormone.

Using these criteria, there are four types: PHP types Ia and Ib (PHP1A and PHP1B); pseudopseudohypoparathyroidism (PPHP), and PHP type II (PHP2). Another classification has been proposed recently, which is being debated. PHP1A and PHP1B Individuals with PHP type I (PHP1), the most com mon of the disorders, show deficient urinary cyclic AMP excretion in response to administration of exogenous PTH. Patients with PHP1 are divided into PHP1A and PHP1B. Most patients with PHP1A show evidence for AHO and reduced amounts of Gsα protein/activity, as previously determined in readily accessible tissues such as erythro cytes, lymphocytes, or fibroblasts. Only some PHP1B patients show typical AHO features, but they usually have normal Gsα activity. PHP1C, sometimes listed as a third form of PHP1, is really a variant of PHP1A, although the mutant Gsα shows normal activity in certain in vitro assays. Most patients who have PHP1A reveal characteristic features of AHO, which consist of short stature, early-onset obesity, round face, obesity, skeletal anomalies (brachydactyly), intellectual impairment, and/or heterotopic calcifications. Patients have low calcium and high phosphate levels, as with true hypoparathyroidism. PTH levels, how ever, are elevated, reflecting resistance to hormone action. In addition, hormonal resistance is observed at other Gsα-coupled receptors, par ticularly at the TSH receptor, leading to elevated levels of this hormone. Calcium and phosphate deposits are frequently found in the basal ganglia. The typical shortening of metacarpal and metatarsal bones is caused by premature closing of the epiphyses and is probably a particu larly sensitive sign of overall advanced skeletal maturation resulting in adult short stature. INHERITANCE AND GENETIC DEFECTS Multiple defects at the GNAS locus have now been identified in PHP1A, PHP1B, and PPHP patients. This gene, which is located on chromosome 20q13.3, encodes the α-subunit of the stimulatory G protein (Gsα), among other products (see below). Mutations involving the GNAS exons encoding Gsα, which are the cause of PHP1A and PPHP, include abnormalities at splice junc tions, point mutations, insertions, and/or deletions that all result in a Gsα protein with defective function, resulting in a 50% reduction of in vitro Gsα activity in erythrocytes or other cells. While PHP1A is caused by inactivating Gsα mutations on the maternal allele, PPHP is caused by the same or similar mutations on the paternal GNAS allele (Fig. 422-7). The Gsα transcript is biallelically expressed in most tissues; however, expression from paternal allele is silenced through as-of-yet-

unknown mechanisms in some tissues, including proximal renal tubules, thyroid, and pituitary. Consequently, inheritance of a molecular defect involv ing the paternal exons encoding Gsα has no implications with regard to hormone function, while inactivating Gsα mutations involving the maternal GNAS allele lead to little or no Gsα protein in these tissues (Chap. 479). Thus, females affected by either PHP1A or PPHP will have offspring with PHP1A, if these children inherit the allele carrying the GNAS mutation; in contrast, if the mutant allele is inherited from a male affected by either disorder, the offspring will exhibit PPHP. How ever, patients affected by both disease subtypes develop some but not Gs` SUBUNIT DEFICIENCY AHO RESISTANCE TO HORMONES OTHER THAN PTH Yes (in some patients) ↑ No No No ↑ No Yes Yes

PTH PHP-Ia (+ AHO) Urinary cyclic AMP/ phosphate PTH PPHP (+ AHO) FIGURE 422-7 Paternal imprinting of renal parathyroid hormone (PTH) resistance (GNAS gene for Gs` subunit) in pseudohypoparathyroidism (PHP1A and PHP1B). An impaired excretion of urinary cyclic AMP and phosphate is observed in patients with PHP type I. In the renal cortex, there is selective silencing of paternal Gsα expression; consequently, mutations involving the maternal GNAS exons encoding Gsα or loss of methylation at GNAS exon A/B leads to reduced or completely absent Gsα protein in this portion of the kidney. The disease becomes manifest only in patients who inherit the defective gene from an obligate female carrier (left). If a genetic defect involving GNAS exons encoding Gsα is inherited from an obligate male carrier of the mutation (PHP1A or PPHP patient), no biochemical abnormality is encountered, and the administration of PTH causes an appropriate increase in the urinary cyclic AMP and phosphate concentration (pseudoPHP [PPHP]; right). Both patterns of inheritance lead to some but not all features of Albright’s hereditary osteodystrophy (AHO), most likely because of haploinsufficiency; for example, Gsα protein derived from both parental GNAS alleles must be active for normal bone development. Maternal inheritance of a mutation (deletion, duplication, or inversion within or upstream of the GNAS locus) causes AD-PHP1B, while paternal inheritance does not lead to any detectable abnormality. all AHO features, making it likely that Gsα haploinsufficiency becomes apparent during embryonic or postnatal development. The complex mechanisms that control the GNAS gene contributed particularly to challenges involved in unraveling the pathogenesis of PHP1B. Analysis of families in which multiple members are affected by PHP1B, as well as studies of the complex parent-specific methylation of four regions within the complex GNAS locus, revealed that the autoso mal dominant forms of PHP1B (AD-PHP1B) are caused by microdele tions, duplications, retrotransposon insertions, or inversions within or upstream of the GNAS locus. These genetic mutations are associated with a loss of DNA methylation at one or several loci on the maternal GNAS allele (Table 422-6). These abnormalities in methylation silence maternal Gsα expression, thus leading in the proximal renal tubules— where Gsα appears to be expressed predominantly from the maternal allele—to PTH resistance. While most cases of AD-PHP1B are by now resolved at the molecular level, the genetic defect responsible for the sporadic variant of PHP1B (sporPHP1B), the most frequent form of PHP1B, remains to be defined, except for those sporPHP1B cases that are caused by paternal uniparental isodisomy/heterodisomy of chro mosome 20q (patUPD20q). PHP1B patients, who rarely develop an AHO phenotype as severe as in PHP1A, develop hypocalcemia and hyperphosphate mia caused by PTH resistance and thus elevated PTH levels. The previously used Ellsworth-Howard test to assess the presence or absence of hormone resistance is used much less frequently, largely because of routinely available sensitive PTH assays (Table 422-6). As for PHP1A, these endocrine abnormalities become apparent only if disease-causing mutations are inherited maternally. Bone responsiveness may be excessive rather than blunted in PHP1B (and in PHP1A) patients, based on case reports

that have empha sized an osteitis fibrosa–like pattern in several PHP1B patients. Some patients present with PTH resistance in the absence of AHO features and without GNAS methylation changes; it remains unclear

why this PHP variant readily resolves upon treatment with vitamin D supplements.

PHP2 refers to patients with hypocalcemia and hyperphosphate mia, who have normal urinary cyclic AMP excretion, but an impaired urinary phosphaturic response to PTH. In one PHP2 variant, referred to as acrodysostosis with hormonal resistance, patients have a het erozygous defect in the regulatory subunit of PKA (PRKAR1A) that mediates the response to PTH distal to cyclic AMP production. Acrodysostosis without or with only mild hormonal resistance can be caused by heterozygous mutations in the cyclic AMP–selective phos phodiesterase 4D. Patients with one variant of acrodysostosis that is associated with hypertension, were shown to have heterozygous phos phodiesterase 3A mutations. Disorders of the Parathyroid Gland and Calcium Homeostasis CHAPTER 422 The diagnosis of these hormone-resistant states can usually be made when there is a positive family history for signs and symptoms of hypocalcemia with or without AHO features. In both categories— PHP1A and PHP1B—serum PTH levels are elevated, particularly when patients start to experience hypocalcemia during childhood. In PHP1A and PHP1B, the response of urinary cyclic AMP to the administration of exogenous PTH is blunted. The diagnosis of PHP2, in the absence of acrodysostosis, is more complex, and vitamin D deficiency must be excluded before such a diagnosis can be entertained. TREATMENT Pseudohypoparathyroidism Treatment of PHP is similar to that of hypoparathyroidism, except that calcium and activated vitamin D analogues are usually given at higher doses to maintain blood calcium levels within the nor mal range and PTH levels in the upper end of normal or slightly elevated. Patients with PHP1 show no PTH resistance in the distal tubules—hence, urinary calcium clearance is typically not elevated, and these individuals are not at risk of developing nephrocalcino sis, as are patients with hypoparathyroidism, unless overtreatment occurs, for example, after the completion of pubertal development and skeletal mutation, when calcium and 1,25(OH)2D treatment should be reduced. Variability in response makes it necessary to establish the optimal regimen for each patient. Vitamin D Related • VITAMIN D DEFICIENCY DUE TO INADEQUATE

DIET AND/OR SUNLIGHT Vitamin D deficiency due to inadequate intake of dairy products enriched with vitamin D, lack of vitamin supplementation, and reduced sunlight exposure in the elderly, par ticularly during winter in northern latitudes, is more common in the United States than previously recognized. Biopsies of bone in elderly patients with hip fracture (documenting osteomalacia) and abnor mal levels of vitamin D metabolites, PTH, calcium, and phosphate indicate that vitamin D deficiency may occur in as many as 25% of elderly patients, particularly in northern latitudes in the United States. Concentrations of 25(OH)D are low or low-normal in these patients. Quantitative histomorphometric analysis of bone biopsy specimens from such individuals reveals widened osteoid seams consistent with osteomalacia (Chap. 421). PTH hypersecretion compensates for the tendency for the blood calcium to fall but also increases renal phos phate excretion and thus causes osteomalacia. Treatment involves adequate replacement with vitamin D and cal cium until the deficiencies are corrected. Severe hypocalcemia rarely occurs in moderately severe vitamin D deficiency of the elderly, but vitamin D deficiency must be considered in the differential diagnosis of mild hypocalcemia. Mild hypocalcemia, secondary hyperparathyroidism, severe hypo phosphatemia, and a variety of nutritional deficiencies occur with gastrointestinal diseases.

Hepatocellular dysfunction can lead to reduc tion in 25(OH)D levels, as in portal or biliary cirrhosis of the liver, and malabsorption of vitamin D and its metabolites, including 1,25(OH)2D, may occur in a variety of bowel diseases, hereditary or acquired. Depending on the disorder, vitamin D or its metabolites can be given parenterally, guaranteeing adequate blood levels of active metabolites.

DEFECTIVE VITAMIN D METABOLISM • Anticonvulsant Therapy Anticonvul sant therapy with any of several agents induces acquired vitamin D deficiency by increasing the conversion of vitamin D to inactive com pounds and/or causing resistance to its action. The more marginal the vitamin D intake in the diet, the more likely that anticonvulsant therapy will lead to abnormal mineral and bone metabolism.

Vitamin D–Dependent Rickets Type I Vitamin D–dependent rickets type I, pre viously termed pseudo-vitamin D–resistant rickets, is caused by homo zygous or compound heterozygous mutations in the gene CYP27B1 encoding 25(OH)D-1α-hydroxylase. It differs from true vitamin D–resistant rickets (vitamin D–dependent rickets type II, see below) in that it is typically less severe and the biochemical and radiographic abnormalities can be readily reversed with physiologic doses of the vitamin's active metabolite, 1,25(OH)2D (Chap. 421). Clinical features include hypocalcemia, often with tetany or convulsions; hypophospha temia due to secondary hyperparathyroidism; and thus, osteomalacia and increased levels of alkaline phosphatase. PART 12 Endocrinology and Metabolism Vitamin D–Dependent Rickets Type II Vitamin D–dependent rickets type II results from end-organ resistance to the active metabolite 1,25(OH)2D. The clinical features resemble those of the type I disorder and include hypocalcemia, hypophosphatemia, secondary hyperparathy roidism, and rickets but also partial or total alopecia. Plasma levels of 1,25(OH)2D are elevated, in keeping with the refractoriness of the end organs. This disorder is caused by homozygous or compound heterozygous mutations in the gene encoding the vitamin D receptor; treatment requires regular, usually nocturnal calcium infusions, which normalize PTH levels, thus reducing urinary phosphate excretion and thereby improving rickets and thus growth, but do not restore hair growth (Chap. 421). CKD Improved medical management of CKD allows many patients to survive for decades and, hence, provides time enough to develop features of renal osteodystrophy, which must be controlled to avoid additional morbidity. Impaired production of 1,25(OH)2D is a principal factor that causes calcium deficiency, secondary hyperparathyroidism, and bone disease; hyperphosphatemia, which lowers further blood calcium lev els, typically occurs only in the later stages of the disease. Low levels of 1,25(OH)2D due to increased FGF23 production in bone (and possibly other tissues) are critical in the development of hypocalcemia. It is nota ble that FGF23 levels are often dramatically elevated in end-stage kidney disease (ESKD). The uremic state also causes impairment of intestinal absorption by mechanisms other than defects in vitamin D metabolism. Nonetheless, treatment with supraphysiologic amounts of vitamin D or calcitriol can correct impaired calcium absorption. Increased FGF23 lev els are seen already during the early CKD stages and have been reported to correlate with kidney disease progression, increased mortality, and left ventricular hypertrophy. Strategies involving different oral phos phate binders have therefore been pursued to lower intestinal phosphate absorption early during the course of kidney disease and to thereby lower FGF23 levels. However, these approaches have been largely disappoint ing. Furthermore, there is concern as to whether supplementation with activated vitamin D analogues increases further the circulating FGF23 levels and their "off-target" effects in CKD patients. TREATMENT Chronic Kidney Disease Therapy of CKD (Chap. 322) involves appropriate management of patients prior to dialysis and adjustment of regimens once dialysis is

initiated. Attention should be paid to restriction of phosphate in the diet; avoidance of aluminum-containing phosphate-binding antacids; provision of an adequate calcium intake by mouth, usually around 1 g/d; and supplementation with 0.25–1 μg/d calcitriol or other activated forms of vitamin D. The aim of therapy is to restore normal calcium balance to prevent osteomalacia and severe second ary hyperparathyroidism (it is usually recommended to maintain PTH levels between 100 and 300 pg/mL) and, in light of evidence of genetic changes and monoclonal outgrowths of parathyroid glands

in CKD patients, to prevent secondary hyperparathyroidism from becoming autonomous hyperparathyroidism. Reduction of hyper phosphatemia and restoration of normal intestinal calcium absorp tion by calcitriol can improve blood calcium levels and reduce the manifestations of secondary hyperparathyroidism. Since adynamic bone disease can occur in association with low PTH levels, it is important to avoid excessive suppression of the parathyroid glands while recognizing the beneficial effects of controlling the secondary hyperparathyroidism. These patients should be closely monitored with intact PTH assays. Oral phosphate-binding agents such as sevelamer lower blood phosphate levels in ESKD, but their use in earlier CKD stages does not seem to be beneficial in lowering blood phosphate levels and to prevent the rise in FGF23. Other Causes Treatment of patients using antiresorptives, such as bisphosphonates and denosumab, my result in hypocalcemia. Risk factors for this condition include vitamin D deficiency, low calcium intake, or advanced chronic kidney disease. Increased enteric loss of 25-hydroxyvitamin D and 1,25(OH)2D due to intestinal disease and increased metabolism due to anticonvulsants or antituberculosis therapy can also lead to hypocalcemia. Impaired 25-hydroxylation due to severe liver disease or mutations in CYP2R1, the 25-hydroxylase, are rare causes of hypocalcemia. Impaired 1a-hydroxylation is not uncommon and occurs in renal insufficiency, certain antifungals, and FGF23-related disorders. Occasionally, loss of calcium from the ECF is so severe that PTH cannot compensate. Such situations include acute pancreatitis and severe, acute hyperphosphatemia, often in association with renal failure, conditions in which there is rapid efflux of calcium from the ECF. Severe hypocalcemia can occur quickly; PTH rises in response to hypocalcemia but does not return blood calcium to normal. SEVERE, ACUTE HYPERPHOSPHATEMIA Severe hyperphosphate mia is associated with extensive tissue damage or cell destruction

(Chap. 421). The combination of increased release of phosphate from muscle and impaired ability to excrete phosphorus because of renal failure causes moderate to severe hyperphosphatemia, the latter caus ing calcium loss from the blood and mild to moderate hypocalcemia. Hypocalcemia is usually reversed with tissue repair and restoration of renal function as phosphorus and creatinine values return to normal. There may even be a mild hypercalcemic period in the oliguric phase of renal function recovery. This sequence, severe hypocalcemia followed by mild hypercalcemia, reflects widespread deposition of calcium in muscle and subsequent redistribution of some of the calcium to the ECF after phosphate levels return to normal. Other causes of hyperphosphatemia include hypothermia, mas sive hepatic failure, and hematologic malignancies, either because of high cell turnover of malignancy or because of cell destruction by chemotherapy. TREATMENT Severe, Acute Hyperphosphatemia Treatment is directed toward lowering of blood phosphate by the administration of phosphate-binding antacids or dialysis. Although calcium replacement may be necessary if hypocalcemia is severe and symptomatic, calcium administration during the hyperphos phatemic period tends to increase extraosseous calcium deposition and aggravate tissue damage. The levels of 1,25(OH)2D may be low during the hyperphosphatemic phase and return to normal during the oliguric phase of recovery. OSTEITIS FIBROSA AFTER

PARATHYROIDECTOMY Severe hypocalce mia after parathyroid surgery is rare now that osteitis fibrosa cystica is an infrequent manifestation of hyperparathyroidism. When osteitis fibrosa cystica is severe, however, bone mineral deficits can be large. After parathyroidectomy, hypocalcemia can persist for days if cal cium replacement is inadequate. Treatment may require parenteral administration of calcium; addition of calcitriol and oral calcium

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