Calcium ion plays a key role in many fundamental biologic processes including muscle contraction, blood coagulation, enzyme activity, neural excitability, hormone release, and membrane permeability, in addition to being an essential structural component of the skeleton. Therefore, the precise control of calcium ion in extracellular fluids is vital to the health of humans and animals. To maintain a constant concentration of blood calcium, despite marked variations in intake and excretion, endocrine control mechanisms have evolved that consist primarily of the interactions of three major hormones. Although the direct roles of parathyroid hormone (PTH), calcitonin (CT), and vitamin D frequently are emphasized in the control of blood calcium, other hormones such as adrenal corticosteroids, estrogens, thyroxine, somatotropin, and glucagon may contribute to the maintenance of calcium homeostasis under certain conditions.

The level of total blood calcium in mammals is approximately 10 mg/dl with some variation due to species, age, dietary intake of calcium, and analytical method used to quantitate blood levels. The calcium concentration in the blood is composed of protein-bound and diffusible fractions. Diffusible calcium consists of calcium complexed to anions such as phosphate and citrate plus the biologically active, "free" (ionized) calcium.

Ionized calcium is the physiologically important fraction, but it is infrequently measured, either because of strict collection requirements or the unreliability of ion-specific analyzers. In most laboratories only serum total calcium is measured. Because approximately half of the calcium is protein bound, the interpretation of total calcium depends on the concurrent values for serum albumin and total protein. (154) In human beings, there are significant linear relationships between serum total calcium and albumin and between serum total calcium and total protein. Adjustment formulas have been derived for serum total calcium on the basis of the concentrations of albumin and total protein. (11,155)

The adjustment formulas for calcium have been derived by adding the difference between the y intercept value from the regression line and the normal mean for serum calcium (10.1 mg/dl) to each intercept value. (127,155) The y intercept for albumin in dogs was 6.57 and the difference was 3.53. For serum total protein, the y intercept was 6.81 and the difference was 3.29. The slope of the regression line was multiplied by the absolute value for albumin or serum total protein. The slope
for serum total protein was 0.41, and the slope for albumin was approximately 1, thereby making this step unnecessary. Therefore, the final adjustment formulas in dogs are as follows (127):

\[
\text{adjusted calcium} (\text{mg/dl}) = \text{measured serum total calcium (mg/dl) - serum albumin + 3.5 (g/dl)}
\]

\[
\text{adjusted calcium} (\text{mg/dl}) = \text{measured serum total calcium(mg/dl)- 0.4(total serum protein) + 3.3 (g/dl)}
\]

A positive linear relationship was found between serum total calcium and albumin (Fig. 59-1) for hospitalized dogs (r=0.575; P < 0.001). One third of the variability in calcium was attributable to the change in the concentration of albumin (R^2=0.33). In the study reported by Meuten and co-workers, (127) of the 209 dogs studied had a low concentration of serum albumin (<2.01 g/dl). Of these 14 dogs, 4 (29%) were normocalcemic and 10 (71%) were hypocalcemic (6.9-8.7 mg/dl). After adjustment of total calcium for albumin concentration, 9 of the 10 hypocalcemic dogs had values of calcium within the normal range. (127)

![FIG. 59-1 Significant relationship between serum albumin and total calcium concentrations in hospitalized dogs (r=0.575 P<0.001). The least square regression line (solid line), the 95% confidence limits for the regression line (two broken lines), and the 95% confidence limits for the population (shaded area) are included in the graph. The numbers represent the number of values at superimposed points. As the concentration of albumin increases or decreases, there is a concurrent increase or decrease in serum total calcium. One third of the variability in calcium was attributable to the change in the concentration of albumin (R^2 = 0.33) (Meuten DJ, Chew DJ, Capen CC et al: Relationship of serum total calcium to albumin and total protein in dogs. J Am Vet Med Assoc 180:63, 1982)](image)

In dogs that had hyperalbuminemia (serum albumin concentrations (>3.7 g/dl), the measured and adjusted concentrations of serum total calcium were normal. The mean (and range) for serum albumin concentration in the dogs with hyperalbuminemia was 4 g/dl (3.75-1.1 g/ dl)

A positive linear relationship has been reported between serum total calcium and serum total protein (Fig. 59-2) for dogs (r = 0.411; P <0.001). (127) Approximately 17% of the variability in calcium was attributable to the change in the concentration of serum total protein (R^2=0.169). Seventy-three percent of dogs with a low serum total protein concentration (<5.6 g/dl) had a low serum calcium concentration. After adjustment of total calcium for the concentration of serum total protein, 88% Of the hypocalcemic dogs had values of calcium within the normal range. (127) Dogs with high concentrations of serum total protein (>8 g/dl) had normal measured and adjusted calcium values. The mean serum total protein in these dogs was 8.6 g/dl and the range was 8.0 g-10.8 g/dl. Calcium concentrations >12 mg/dl in dogs were not ascribed to hyperalbuminemia or hyperproteinemia, and total calcium concentrations <6.5 mg/dl were not attributable to hypoalbuminemia or hypoproteinemia. (127)

Approximately 90% of dogs with disorders of calcium metabolism and 86% of young dogs (6 to 24 weeks of age) had calcium values outside the 95% confidence limits calculated for albumin and total protein for hospitalized dogs (Figs. 59-3 and 59-4) (127) Data from 95% of dogs with hypercalcemia of malignancy (i.e., lymphosarcoma, adenocarcinoma of the apocrine glands of the anal sac, and giant cell carcinoma of the lung) were outside the 95% confidence limits for albumin and total protein. Similarly, total serum calcium values in the young dogs were clustered in a relatively uniform group outside the 95% confidence limits. The mean values for young dogs were total calcium 11 mg/dl; albumin 2.7 g/ dl; serum total protein 5.2 g/ dl; and phosphorus 8.4 mg/ dl. Adjusting calcium for albumin resulted in a mean value of 11.9 mg/dl and adjusting for serum total protein gave a mean calcium value of 12.3 mg/dl. Total serum calcium values in dogs with hypoparathyroidism and primary hyperparathyroidism were always outside the 95% confidence limits.(127) Seventy-nine percent of the dogs with
renal disease were reported to have calcium values outside the 95% confidence limits for albumin and total protein, but there often was considerable variation among individual dogs (127).

FIG. 59-2 Significant relationship between total serum protein and total calcium concentrations in hospitalized dogs. The least square regression line (solid line), the 95% confidence limit for the regression line (two broken lines), and the 95% confidence limits for the population (shaded area) are included in the graph. The numbers represent the number of values at superimposed points. Approximately 17% of the variability in calcium was attributable to the change in the concentration of serum total protein ($R^2=0.169$). (Meuten DJ, Chew DJ, Capen CC et al: Relationship of serum total calcium to albumin and total protein in dogs. J Am Vet Med Assoc 180:63, 1982)

FIG. 59-3 Compared with serum total calcium in hospitalized dogs, 91% of dogs with disorders of calcium metabolism and 86% of young dogs were outside the 95% confidence limits for serum albumin. (in hypercalcemia of malignancy; circle, young dogs (6-24 weeks old); X, renal disease; open circle, hypoparathyroidism; triangle, primary hyperparathyroidism). (Meuten DJ, Chew DJ, Capen CC et al: Relationship of serum total calcium to albumin and total protein in dogs. J Am Vet Med Assoc 180:63, 1982)

FIG. 59-4 Compared with serum total calcium in hospitalized dogs, 91% of dogs with disorders of calcium metabolism and 86% of young dogs were outside the 95% confidence limit for serum total protein (a, hypercalcemia of malignancy; closed circle, young dogs (6-24 weeks old), X, renal disease; open circle, hypoparathyroidism; triangle, primary hyperparathyroidism). (Meuten DJ, Chew DJ, Capen CC et al: Relationship of serum total calcium to albumin and total protein in dogs. J Am Vet Med Assoc 180:63, 1982)

PARATHYROID HORMONE
EMBRYOLOGY AND MACROSCOPIC ANATOMY OF PARATHYROID GLANDS
Embryologically, parathyroids are of entodermal origin. They are derived from the third and fourth pharyngeal pouches in close association with primordia of the thymus. The entodermal bud that forms the thyroid gland arises on the midline at the level of the first; pharyngeal pouch. This gives rise to the thyroglossal duct that migrates caudally. The proliferation of cell cords at the distal end of the thyroglossal duct forms the follicles of each thyroid lobe. The area at the base of the tongue marking the origin of the thyroid gland is referred to as the foramen cecum in postnatal life. Calcitonin-secreting C cells of neural crest origin reach the postnatal thyroid gland by migrating into the ultimobranchial body. This last pharyngeal pouch moves caudally in mammals to fuse with the primordia of the thyroid gland and distributes C cells into each thyroid lobe.

Parathyroid glands in most animal species consist of two pairs of glands situated in the anterior cervical region (Fig. 59-5). In the dog and cat both the external and internal parathyroids are close to the thyroid gland. The external parathyroid (III) in the dog is from 2 mm to 5 mm in length and is found in the loose connective tissue cranial and slightly lateral to the anterior pole of the thyroid. The internal parathyroid (IV) is smaller, flatter, and situated on the medial surface of the thyroid beneath the fibrous capsule. The blood supply of the two glands in the dog is separate. The external parathyroid is supplied by a branch
from the cranial thyroid artery, and the internal parathyroid is supplied by minute ramifications of the arterial supply to the thyroid.(182)

FUNCTIONAL CYTOLOGY OF PARATHYROID GLANDS

CHIEF CELLS

Present evidence indicates that the parathyroid glands contain a single basic type of secretory cell concerned with the elaboration on one hormone. The parathyroids of humans and animals are composed of chief cells in various stages of secretory activity and in transition to oxyphil cells in certain species.(25) Experimental and pathologic evidence has accumulated to suggest that certain fine structural characteristics of chief cells are associated with different stages of synthetic and secretory activity (24,170).
Chief cells in the active stage of the secretory cycle occur less frequently in the parathyroid glands of most species under normal conditions. The cytoplasm of active chief cells has an increased electron density owing to the close proximity of organelles, numerous secretion granules, overall density of the cytoplasmic matrix, and loss of glycogen particles and lipid bodies (Fig. 59-7)(170)

Oxyphil cells and transitional forms
A second cell type in the parathyroid glands of certain animal species and humans is the oxyphil cell (Fig. 59-8). Oxyphil cells are not present in the human fetal parathyroid gland. They first appear in late childhood and increase in number with advancing age, often forming nodules in parathyroids of older persons.(138) They are absent in parathyroids of the rat, chicken, and many species of lower animals.(45,69,172)

Oxyphil cells are observed either singly or in small groups interspersed among chief cells. They are larger than chief cells, and their abundant cytoplasmic area is filled with numerous large, often bizarre-shaped mitochondria (Fig. 59-8). Glycogen particles and free ribosomes are interspersed among the mitochondria. Granular endoplasmic reticulum, Golgi apparatuses, and secretory granules are poorly developed in oxyphil cells of normal parathyroid gland,(24) suggesting that oxyphil cells do not have an active function in the biosynthesis of parathyroid hormone. Associated with the marked increase in mitochondria, oxyphil cells have been shown histochemically to have a higher oxidative and hydrolytic enzyme activity than chief cells (Fig. 59-9),(9,83,195)

Cells are observed with cytoplasmic characteristics intermediate between those of chief and oxyphil cells, suggesting that oxyphil cells represent structurally and functionally modified chief cells. These transitional oxyphil cells have numerous mitochondria, but other organelles are present, including granular endoplasmic reticulum, Golgi apparatuses, and secretory granules. The significance of oxyphil cells in the pathophysiology of the parathyroid glands has not been elucidated, but they do not appear to be active in the synthesis of parathyroid hormone.

Oxyphil cells are not altered in response to either short-term hypocalcemia or hypercalcemia in animals,(24) but both oxyphil and transitional forms may be increased in response to long-term stimulation of human parathyroid glands.(179) Occasionally parathyroid adenomas composed predominantly of oxyphil cells and transitional forms have been reported associated with excessive PTH secretion and a syndrome of primary hyperparathyroidism in humans.(3,171) The transitional oxyphil cells...
that constitute these neoplasms have many large mitochondria in their cytoplasm but a more extensive endoplasmic reticulum and well-developed Golgi apparatus with more numerous secretory granules than oxyphil cells in normal parathyroid glands. (7) Therefore, oxyphil cells do not appear to be degenerate chief cells as previously thought but rather are derived from chief cells as the result of aging or some metabolic derangement.

**BIOSYNTHESIS OF PTH**

Recent evidence suggests that a larger biosynthetic precursor is first synthesized on ribosomes of the rough endoplasmic reticulum in chief cells.(6,40,76,78,80,82,109,121,157,179) Pre-proparathyroid hormone (pre-proPTH) is the initial translational product synthesized on ribosomes. It is composed of 115 amino acids and contains a "signal" or leader sequence of 25 hydrophobic amino acid residues that may facilitate the penetration and subsequent vectorial discharge of the nascent peptide into the cisternal space of the rough endoplasmic reticulum(75,89) (Fig. 59-10). Pre-proPTH is rapidly converted (within one minute or less of its synthesis) to proparathyroid hormone (proPTH) by proteolytic cleavage of the NH2-terminal sequence of 25 amino acids.(81)

The intermediate precursor, proPTH, is composed of 90 amino acids and moves within membranous channels of the endoplasmic reticulum to the Golgi apparatus (Fig. 59-10). Enzymes with trypsinlike and carboxypeptidase B-like activity within membranes of the Golgi apparatus cleave a hexapeptide from the NH2-terminal (biologically active) end of the molecule forming active PTH.76 79,122 Active PTH is packaged into membranelimited, macromolecular aggregates in the Golgi apparatus for subsequent storage in chief cells. Under certain conditions of increased demand, PTH may bypass packaging in the Golgi apparatus and be released directly from chief cells.

Biologically active PTH secreted by chief cells is a straight-chain polypeptide consisting of 84 amino acid residues with a molecular weight of approximately 9500 daltons.(19) Molecular fragments (Cand N-terminal) of PTH are formed in the peripheral circulation, liver, at the target cells of the hormone, and possibly within chief cells. The immunoheterogeneity created by the multiple circulating fragments of PTH has caused significant problems in the development and application of highly specific radioimmunoassays to clinical diagnostic problems.(5) Current evidence suggests it is in the Golgi apparatus that PTH (184 amino acid sequence) is cleaved enzymatically from proPTH and packaged into mature secretory or storage granules.(40,65) As the Golgi apparatus subsequently involutes, acid phosphatase activity appears in its membranes, and acid phosphatase-positive lysosomal bodies are formed in the Golgi complex.(177) During the involuting phase the PTH (1-84 amino acid sequence) packaged in granules moves from the Golgi region and is stored in the cytoplasm prior to secretion from chief cells. Low ambient calcium levels speed up the rate of secretion of PTH and shorten the resting phase of chief cells; conversely, high ambient calcium levels suppress the rate of hormone secretion and lengthen the resting phase of the secretory cycle.
STORAGE AND SECRETION OF PTH

Secretory ("storage") granules have been demonstrated readily at the level of ultrastructure within chief cells of the parathyroid glands in all animal species examined (Fig. 59-11)(2,31,170) Roth and associates(173) localized PTH within chief cells of bovine parathyroids to the small membrane-limited secretory granules by immunocytochemical techniques using rabbit antiserum and peroxidase-labeled goat anti-rabbit globulin. The rabbit antiserum used in these studies recognized multiple antigenic determinants of bovine PTH including the biologically active N-terminal of the molecule. Reaction product was not deposited over the larger acid phosphatase-positive lysosomal bodies in chief cells.

Secretory granules in chief cells also contain a parathyroid secretory protein (PSP) in addition to PTH. Kemper and co-workers(110) reported that bovine parathyroids incubated in vitro secrete a protein that is distinct from both proPTH and PTH. It is a large protein (two or more subunits of molecular weight 70,000 daltons) and constitutes about 50% of the total protein secreted by the parathyroid. PSP may accompany PTH in the intracellular transport pathway through cytoplasmic organelles and is associated predominantly with the particulate fraction of chief cells.(81) Secretion of PSP is stimulated or inhibited in parallel with that of PTH by varying the concentration of calcium in the incubation medium. The coordinated secretion of PSP and PTH in response to changes in levels of ambient calcium suggests that both molecules are present in the membrane-limited secretion granules in chief cells. Although the function of PSP is uncertain at present, it appears to represent a "binding protein" for PTH and may be analogous in function to the neurophysins secreted with oxytocin and vasopressin by the neurohypophyseal system.(59)

The PTH-containing secretory granules migrate peripherally in chief cells, and their limiting membrane fuses with the plasma membrane of the cell. An internal cytoskeleton composed of microtubules and contractile filaments has been reported to be important in control of the peripheral movement of secretory granules and liberation of secretory products from other endocrine cells (e.g., beta cells of the pancreatic islets).(116) The presence of peripheral microfilaments in chief cells as well as the attachment of granules to the plasma membrane by stalklike condensations of cytoplasmic material in some species suggests that a similar secretory mechanism exists in parathyroid glands.(211)

Secretory granules appear to be extruded from chief cells by exocytosis into perivascular spaces.(24,60,61) Numerous small spherules of similar size have been observed by scanning electron microscopy to protrude from secretory surfaces of chief cells into perivascular spaces (Fig. 59-12).(24) Thiele and Wermbter(193) used freeze-fracture techniques to demonstrate secretory granules being discharged from chief cells by exocytosis in the human parathyroid gland.

CONTROL OF PTH SECRETION

Secretory cells in the parathyroids store relatively small amounts of preformed hormone but are capable of responding to minor fluctuations in calcium ion concentration by rapidly altering the rate of hormonal secretion(158) and more slowly by altering the rate of hormonal synthesis.(172) In contrast to most endocrine organs, which are under complex controls, the parathyroids have a unique feedback control system that relies primarily on the concentration of calcium (and to a lesser

FIG. 59-11 Mature secretory (storage) granule in the feline parathyroid gland is surrounded by a closely applied limiting membrane (arrow) and is composed of fine dense particles. Secretory granules contain biologically active parathyroid hormone and parathyroid secretory protein. (original magnification x 315,000) (Capen CC, Rowland GN: The ultrastructure of the parathyroid glands of young cats. Anat Rec 162:327, 1968)

FIG. 59-12 Scanning electron micrograph of the secretory surface of active chief cells in the parathyroid gland illustrating secretory granules (arrowheads) budding into the perivascular space. Chief cells are polyhedral, and distinct cell boundaries can be visualized (arrows). (original magnification x 3000)
If the blood calcium level is elevated by the intravenous infusion of calcium, there is a rapid and pronounced reduction in circulating levels of immunoreactive parathyroid hormone (iPTH) (Fig. 59-13). Conversely, if the blood calcium level is lowered by ethylenediaminetetra-acetic acid EDTA, there is a brisk and substantial increase in iPTH levels. The concentration of blood phosphorus has no direct regulatory influence on the synthesis and secretion of PTH; however, certain disease conditions characterized by hyperphosphatemia in both animals and humans are associated clinically with hyperparathyroidism. An elevated blood phosphorus level may lead indirectly to parathyroid stimulation by virtue of its ability to lower the blood calcium level according to the mass-law equation when the serum is saturated with respect to these two ions. If the blood phosphorus level is elevated significantly by an infusion of phosphate and calcium administered simultaneously in amounts to prevent the accompanying reduction of the blood calcium level, plasma iPTH levels remain within the normal range. In addition, hyperphosphatemia suppresses the rate of formation of the biologically active, hormonal form of vitamin D (1,25-dihydroxycholecalciferol 1,25-diOH-CC) in the kidney, which further contributes to the development of hypocalcemia and parathyroid stimulation.

Magnesium ion has an effect on PTH secretory rate similar to that of calcium but not equipotent. The more potent effects of calcium ion in the control of PTH secretion together with its preponderance over magnesium in the extracellular fluid suggest a secondary role for magnesium in parathyroid control.

Calcium ion controls not only the rates of biosynthesis and secretion of PTH but also other metabolic and intracellular degradative processes within chief cells. An increased calcium ion concentration in extracellular fluids rapidly inhibits the uptake of amino acids by chief cells, synthesis of proPTH and conversion to PTH, and secretion of stored PTH. The shifting of the percent of flow of proPTH from the degradative pathways to the synthetic route represents a key adaptive response of the parathyroid gland to a low-calcium diet. Parathyroids from rats fed a low-calcium (0.02%) diet convert approximately 40% of proPTH to PTH compared with a 20% conversion in rats fed a control diet. During periods of long-term calcium restriction, the enhanced synthesis and secretion of PTH would be accomplished by an increased capacity of the entire pathway in individual chief cells and through hyperplasia of active chief cells. Recently synthesized and processed active PTH may be released directly in response to increased demand and bypass the chief cell's storage pool of mature secretory granules in the cytoplasm. Bypass secretion of calcium can be stimulated only by a low circulating concentration of calcium ion and not by other secretagogues for PTH (Fig. 59-14). Degradation of "mature PTH" by lysosomal enzymes occurs after prolonged exposure of chief cells to a highcalcium environment.


FIG. 59-14 Bypass secretion of parathyroid hormone in response to increased demands signaled by a decreased blood calcium ion concentration. Recently synthesized and processed active PTH (1-84) may be released directly and not enter the chief cell's storage pool of mature ("old") secretory granules in the cytoplasm. Parathyroid hormone from the storage pool can be mobilized by cyclic adenosine monophosphate (cAMP), -agonists (such as epinephrine, norepinephrine, and isoproterenol), as well as by lowered blood calcium ion, whereas secretion from the pool of recently synthesized PTH can be stimulated only by a decreased calcium ion concentration. (Cohn DV, MacGregor RR: The biosynthesis, intracellular processing, and secretion of parathormone. Endocrine Rev 2:1, 1981)
BIOLOGIC ACTION OF PTH

PTH is the principal hormone involved in the minute-to-minute fine regulation of blood calcium in mammals.(4) It exerts its biologic actions by directly influencing the function of target cells primarily in bone and kidney, and indirectly in the intestine, to maintain plasma calcium at a level sufficient to ensure the optimal functioning of a wide variety of body cells.

The action of PTH on bone is to mobilize calcium from skeletal reserves into extracellular fluids. The administration of PTH causes an initial decline followed by a sustained increase in circulating levels of calcium. This transitory decrease in the blood calcium level is considered to be the result of a sequestration of calcium phosphate in bone and soft tissues(153) The subsequent increase in the blood calcium level results from a direct or indirect interaction of PTH with osteoblasts, osteocytes and osteoclasts in bone.

The response of bone to PTH is biphasic. The immediate effects are the result of increasing the activity of existing osteoclasts and osteocytes present in bone. This rapid effect of PTH depends upon the continuous presence of hormone and results in an increased flow of calcium from deep in bone to bone surfaces through the coordinated action of osteocytes and endosteal lining cells (inactive osteoblasts) (Fig. 59-15). This osteocyte-osteoblast "pump" is concerned with movement of calcium from the bone fluid to the extracellular fluid compartment.

The late effects of PTH on bone are potentially of a greater magnitude of response and are not dependent upon the continuous presence of hormone. Osteoclasts appear to be primarily responsible for the long-term action of PTH by increasing bone resorption and overall bone remodeling. This is interesting in light of recent findings which have failed to demonstrate receptors for PTH on osteoclasts but receptors were present on osteoblasts. If the increase in PTH is sustained, the active osteoclast pool in bone is increased by activation of osteoprogenitor cells in the endosteal and other bone-cell envelopes and recruitment of circulating mononuclear macrophages.(163,164) The plasma membrane of osteoclasts in intimate contact with the resorbing bone surface is modified to form a series of membranous projections, referred to as the brush ("ruffled") border (Fig. 59-16). This area of active bone resorption is isolated from the extracellular fluids by adjacent transitional ("sealing") zones, thereby localizing the lysosomal enzymes and acidic environment to the immediate area undergoing dissolution. The mineral and organic components (e.g., hydroxyproline) released from bone are phagocytized by osteoclasts and moved across the cell in transport vesicles to be released into the extracellular fluid compartment.

A long-term increase in PTH secretion also may result in the formation of greater numbers of osteoblasts with a resultant increase in osteoid formation as well as resorption. However, resorption is usually greater than formation, leading to a net negative skeletal balance.

PTH has a rapid (within 5 to 10 minutes) and direct effect on renal tubular function, leading to decreased reabsorption of phosphate and phosphaturia. The site of action of PTH on blocking tubular reabsorption of phosphate has been localized to the proximal tubule of the nephron. In addition, PTH leads to an increased urinary excretion of potassium, bicarbonate, sodium, cyclic adenosine monophosphate, and amino acids.

Although the effect of PTH on the tubular reabsorption of phosphate has been considered to be of major importance, evidence has accumulated recently suggesting that the ability of PTH to enhance the renal absorption of calcium is of considerable importance in the maintenance of calcium homeostasis. This effect of PTH upon tubular reabsorption of calcium appears to be due to a direct action on the distal convoluted tubule. The urinary excretion of magnesium, ammonia, and titratable acidity also is decreased by PTH. The other important effect of PTH on the kidney is in the regulation of the conversion of 25-hydroxycholecalciferol (25-OHCC) to biologically active 1,25-DiOH-CC and other metabolites of vitamin D.
PTH is secreted continuously from chief cells under normal conditions. In the liver, peripheral circulation, and at target cells, PTH (1-84 amino acid sequence) is cleaved into a smaller (approximately 1/3 of molecule) amino (N-) terminal fragment (biologically active portion) and a larger carboxyl (C-) terminal fragment (biologically inactive portion). The kidney also is a major organ for the degradation of PTH. Biologically active PTH from peritubular capillaries is degraded by specific proteases on the surface of renal tubular cells. In addition, both biologically active (NH2N34) and inactive (34N84 COOH) fragments may be degraded intracellularly by lysosomal enzymes within renal tubular cells.

FIG. 59-16 Osteoclastic osteolysis on a bone surface (S) with release of calcium and phosphorus into the extracellular fluid. The brush ("ruffled") border (B) is a specialized area of the plasma membrane of the osteoclast that is in intimate contact with the underlying bone mineral (S). Adjacent transitional ("sealing") zones isolate the area of bone surface undergoing active resorption and provide a mechanism for localizing the lysosomal enzymes and acidic environment required for the dissolution of bone mineral. (Fetter AW, Switzer WP, Capen CC: Electron microscopic evaluation of bone cells in pigs with experimental Bordetella rhinitis [turbinate osteoporosis]. Am J vet Res 36:15, 1975)

SUBCELLULAR MECHANISM OF ACTION OF PTH
The calcium-mobilizing and phosphaturic activities of PTH appear to be mediated through the intracellular accumulation of 3',5'adenosine monophosphate (cAMP) and cytosol calcium in target cells. Binding of PTH to specific receptors on target cells results in the activation of adenylate cyclase in the plasma membrane (Fig. 59-17). The adenylate cyclase catalyzes the conversion of ATP to cAMP in target cells. Cyclic 3',5'-AMP accumulation in target cells functions as an intracellular mediator or second messenger of PTH action, resulting in an increased permeability for calcium ion. The resultant increase in cytosol calcium content in combination with the cAMP accumulation initiates the synthesis and release of lysosomal enzymes and triggers other biochemical reactions in osteolytic cells that result eventually in breakdown of both the inorganic and organic phases of bone.

FIG. 59-17 Mechanism of parathyroid hormone action. The biologically active end of the hormone (PTH 1-34) binds to specific receptors (R) on the surface of target cells. The receptor hormone complex is coupled to the catalytic subunit of adenylate cyclase in the cell membrane by a nucleotide regulatory (N-) protein. This results in the intracellular accumulation of cyclic adenosine monophosphate (cAMP), which serves as the "second messenger" for polypeptide hormones such as PTH in target cells and results in expression of the biologic response of the hormone.

PTH also contributes to the regulation of the rate of formation of 1,25-Dihydroxyvitamin D3, the principal metabolically active form of vitamin D3, by kidney mitochondria. The active metabolites of vitamin D make bone cells more sensitive to the direct effects of PTH ("permissive effect") and greatly enhance the gastrointestinal absorption of calcium, thereby amplifying the effect of PTH upon plasma calcium concentration.
CALCITONIN
Calcitonin (thyrocalcitonin, CT) was discovered by Copp and coworkers\(^\text{44}\) in experiments designed to test the McLean-Urist hypothesis of negative feedback control of blood calcium by PTH. They perfused the parathyroid-thyroid complex of dogs with alternating intervals of blood with low and high calcium concentrations and measured the effects on calcium levels in peripheral blood (Fig. 59-18). Two findings from these experiments were difficult to explain based upon the existing concept of a single hormone controlling the concentration of blood calcium. First, the fall in systemic calcium levels following perfusion of the thyroid-parathyroid complex with high calcium concentrations was more rapid and of greater magnitude than expected from only an inhibition of PTH secretion. Second, thyro-parathyroidectomy following the last low-calcium perfusion resulted in a continued progressive rise in blood calcium levels rather than the expected fall after removal of the source of PTH. These and subsequent experiments lead to development of the concept of a second calcium-regulating hormone secreted by the parathyroid-thyroid complex in response to hypercalcemia that lowered the plasma calcium concentration.

![FIG. 59-18 Experiment of Copp and associates that led to the discovery of calcitonin. Perfusion of the thyroid-parathyroid complex in dogs with a high calcium concentration in the blood resulted in a more rapid and greater decline in peripheral calcium concentration than was expected by the inhibition of PTH secretion alone. Thyroidectomy following the last calcium infusion resulted in a progressive hypercalcemia rather than the expected decline in blood calcium following removal of the source of PTH. (copp DH, Cameron EC, Cheney BA et al: Evidence for calcitonin: A new hormone from the parathyroid that lowers blood calcium. Endocrinology 70:638, 1962)](image)

C CELLS IN THYROID
CT has been shown to be secreted by a second endocrine cell population in the mammalian thyroid gland. C (parafollicular) cells are distinct from follicular cells in the thyroid, which secrete thyroxine and triiodothyronine.\(^\text{105}\) They are situated either within the follicular wall between follicular cells (Fig. 59-19) or as small groups of cells between follicles. C cells do not border the follicular colloid directly, and their secretory polarity is oriented toward the interfollicular capillaries. The distinctive feature of C cells is the presence of numerous small membrane-limited secretory granules in the cytoplasm (Fig. 59-19). Immunocytochemical techniques have localized the CT activity of C cells to these secretory granules.\(^\text{46}\)

![FIG. 59-19 Electron micrograph illustrates a C cell in the wall of a thyroid follicle wedged between several follicular cells. The cytoplasm of the C cell has many calcitonin-containing secretion granules (s) and a prominent Golgi apparatus (G) for the packaging of hormone. Follicular cells (F) line the follicle and extend microvilli (arrow) into the colloid (c). The secretory polarity of C cells is directed toward interfollicular capillaries (E) rather than toward the follicular lumen, as is that of follicular cells. (original magnification x 7700)](image)
CHEMISTRY
CT is a polypeptide hormone composed of 32 amino acid residues arranged in a straight chain with a 1-7 disulfide linkage. It is a smaller molecule than PTH (84 amino acids) and there is evidence that CT is synthesized as part of a larger procalcitonin molecule as described with proPTH. The complete sequence of 32 amino acids and the disulfide bond are essential for full biologic activity of CT. The structure of CT differs considerably among species. For example, the CT molecules of five selected animal species share only 9 of the 32 amino acid residues (Fig. 59-20). Radioimmunoassays to measure circulating levels of CT, therefore, are highly species-specific.

FIG. 59-20 Amino acid sequence of the calcitonin molecule from five species. The nine residues in the chain of 32 amino acids shared by the calcitonin molecule in all five species are indicated by the vertical bars. (Foster GV, Byfield PGH, Gudmundsson TV: Calcitonin. Clin Endocrinol Metab 1:93 124, 1972)

REGULATION OF CT SECRETION
The concentration of calcium ion in plasma and extracellular fluids is the principal physiologic stimulus for the secretion of CT by C cells. CT is secreted continuously under conditions of normocalcemia, but the rate of secretion of CT is increased greatly in response to elevations in blood calcium levels. Magnesium ion concentration has an effect on CT secretion similar to that of calcium, but these effects are observed only under experimental conditions with nonphysiologic levels of magnesium. Substantial amounts of CT are stored in the cytoplasm of C cells in the form of membrane-limited secretory granules (see Fig. 59-19). In response to hypercalcemia there is a rapid discharge of stored hormone from C cells into interfollicular capillaries (Fig. 59-21). If the hypercalcemic stimulus is sustained, this is followed by an increased development of cytoplasmic organelles concerned with the synthesis and secretion of CT (Fig. 59-22). Hyperplasia of C cells occurs in response to long-term hypercalcemia. When the blood calcium level is lowered, the stimulus for CT secretion is diminished and numerous secretory granules accumulate in the cytoplasm of C cells.

FIG. 59-21 Degranulated C cell within the follicular wall of the thyroid gland of an animal receiving pharmacologic doses of vitamin D. The cytoplasmic area of the degranulated C cells is reduced and depleted of secretory granules but contains a small Golgi apparatus (G) and scattered mitochondria (M). An intervening rim of follicular cell cytoplasm separates the C cell from colloid (C) of the thyroid follicle. An interfollicular capillary (CP) is present at the right. (N. nucleus) (original magnification x 11,000) (Young DM, Capen CC: Fine structure of parafollicular cells of cows fed a calcium-deficient diet and vitamin D. Virchows Arch Abt B Zellpath 8:288, 1971)

The storage of large amounts of preformed hormone in C cells and rapid release in response to moderate elevations in blood calcium levels probably are a reflection of the physiologic role of CT as an "emergency" hormone to protect against the development of hypercalcemia. CT secretion is increased in response to a high-calcium meal often before a significant rise in the plasma calcium level can be detected. The cause of this increase in CT secretion could be due either to a small undetectable rise in plasma-ionized calcium or to a direct stimulation of certain gastrointestinal hormones by the oral calcium load, which in turn act as secretagogues for CT release from the thyroid gland (Fig. 59-23). Gastrin, pancreozymin, and glucagon all have been demonstrated to stimulate CT release under experimental conditions in animals. These findings suggest that gastrointestinal hormones may be important in triggering the early release of CT to prevent the development of hypercalcemia following ingestion of a high-calcium meal.
The administration of CT or stimulation of endogenous secretion results in the development of varying degrees of hypocalcemia and hypophosphatemia. These effects of CT on plasma calcium and phosphorus levels are most evident in young animals or in older animals with increased rates of skeletal remodeling. CT exerts its function by interacting with target cells primarily in bone and kidney, and to a much lesser extent, the intestine.

The actions of PTH and CT on bone resorption are antagonistic (both osteocytic and osteoclastic osteolysis), but their actions on decreasing the renal tubular reabsorption of phosphorus are synergistic. The hypocalcemic effects of CT are primarily the result of decreased entry of calcium from the skeleton into plasma owing to a temporary inhibition of PTH-stimulated bone resorption. The hypophosphatemia develops as the result of a direct action of CT, which increases the rate of movement of phosphate out of plasma into soft tissue and bone; it is also the result of inhibition of bone resorption. The action of CT is not dependent on vitamin D, since it acts both in vitamin D-deficient animals and following the administration of large doses of vitamin D.

Specific structural alterations are produced in osteoclasts by CT. Osteoclasts withdraw from resorptive surfaces, and the brush border and transitional zone become atrophic. In addition, there is a decrease in the rate of activation of osteoprogenitor cells to preosteoclasts and osteoclasts, resulting in fewer osteoclasts in bone. Although CT can block bone resorption completely, the inhibition is a transitory effect. The continuous administration of CT in vivo and in vitro in the presence of PTH leads to an "escape phenomenon" whereby the effects of PTH on increasing bone resorption become manifest in the presence of CT.

CT and PTH both decrease renal tubular reabsorption of phosphate, leading to phosphaturia; however, the adenylate cyclase-linked receptors for CT are found in the ascending limb of Henle and distal convoluted tubule. In addition, CT results in diuresis of sodium, chloride, and calcium, whereas PTH infusion leads to renal retention of calcium and hydrogen ions.

CT and PTH provide a dual negative feedback-control mechanism to maintain the concentration of calcium in extracellular fluids within narrow limits. Present evidence suggests that PTH is the major factor concerned with the minute-to-minute regulation of blood calcium levels under normal conditions. This probably is related to the fact that in most higher mammals,
living in a relatively low calcium-high phosphorus environment, protection against the development of hypocalcemia by PTH is a life-sustaining function. CT appears to function more as an emergency hormone to prevent the development of hypercalcemia during the rapid postprandial absorption of calcium, and to protect against excessive loss of calcium and phosphorus from the maternal skeleton during pregnancy.

CHOLECALCIFEROL (VITAMIN D)
Cholecalciferol is the third major hormone involved in the regulation of calcium metabolism and skeletal remodeling. Although cholecalciferol has been considered to be a vitamin for a long time, recent evidence suggests it can correctly be considered a hormone. Cholecalciferol is ingested in small amounts in the diet and can be synthesized in the epidermis from precursor molecules (e.g., 7-dehydrocholesterol) through a previtamin D3 intermediate form (Fig. 59-24). This reaction is catalyzed by ultraviolet irradiation (wavelength 290-320 nm) from the sun. A high affinity vitamin D-binding protein (DBP) transports cholecalciferol from the skin into the blood.

In response to prolonged exposure to sunlight, previtamin D3 is converted to lumisterol and tachysterol (Fig. 59-25). Because the DBP has no affinity for lumisterol and minimal affinity for tachysterol, the translocation of these photoisomers into the circulation is negligible, and they are sloughed off with the natural turnover of the skin.

METABOLIC ACTIVATION OF VITAMIN D
Vitamin D must be metabolically activated before it can produce its known physiologic functions in target cells. Vitamin D3 from dietary sources is absorbed by facilitated diffusion and bound to an a2-globulin in the blood for transport. Endogenous cholecalciferol synthesized in the skin from 7-dehydrocholesterol also is bound to an a2-globulin for transport to the liver.

The first step in the metabolic activation of vitamin D is the conversion of cholecalciferol to 25-OH-CC in the liver (Fig. 59-26). The enzyme responsible for controlling this reaction is the hepatic microsomal enzyme, calciferol-25-hydroxylase, associated with the endoplasmic reticulum. Considerably larger amounts of protein-bound 25-OH-CC circulate than with the more hydroxylated metabolites such as 1,25-DiOH-CC, which are present in extremely low levels in the blood.

This first metabolite of cholecalciferol (25-OH-CC) is transported to the kidney and undergoes further transformation to a more polar and active metabolite (Fig. 59-26). The principal active metabolite of 25-OH-CC formed in the kidney is 1,25-DiOH-CC, but other metabolites are formed such as 24,25-DiOH-CC and 1,24,24TriOH-CC. This rate of formation of 1,25 DiOH-CC is catalyzed by 25-hydroxycholecalciferol-lahydroxylase in renal mitochondria, primarily in proximal convoluted tubules (Fig. 59-27). The conversion of 25-OH-CC to 1,25-DiOH-CC is the rate-limiting step in vitamin D metabolism and is the primary reason for the delay between vitamin D administration and expression of its biologic effects.
The control of this final step in the metabolic activation of vitamin D is complex and appears to be regulated in part by the plasma calcium concentration and its influence on the rates of secretion of PTH (67, 77, 165) (Fig. 59-28). PTH and conditions that stimulate its secretion (e.g., low blood calcium levels) increase the transformation of 25-OH-CC to 1,25-DiOH-CC. Low blood phosphorus levels increase the formation of 1,25-DiOH-CC, whereas high blood phosphorus levels suppress the activity of the la-hydroxylase (Fig. 59-28).

The rates of synthesis of 24,25-DiOH-CC and 1,25-DiOH-CC appear to be reciprocally related and controlled by similar factors. (48, 51-53) When 1,25-DiOH-CC synthesis increases, the synthesis of 24,25-DiOH-CC declines and vice versa (see Fig. 59-26). (188) In certain animal species 24,25-DiOH-CC may play a role in bone formation, (151) egg hatchability, (91) and with 1,25-DiOH-CC may exert negative feedback control on the parathyroid gland. (17, 54, 133, 203) The parathyroids selectively localize 1,25-DiOH-CC and contain specific cytoplasmic and nuclear receptors for the active metabolite of vitamin D. (103) Under experimental conditions, the administration of either 1,25-DiOH-CC or cholecalciferol decreases parathyroid weight and the DNA content of stimulated glands, but lower doses of 1,25-DiOH-CC require 24,25-DiOH-CC to lower parathyroid weight significantly in vitamin D-deficient chicks. (30, 92) Therefore, a negative feedback loop appears to exist whereby vitamin D metabolites (either alone or in combination) directly interact with parathyroid chief cells to diminish the secretion of PTH, which in turn diminishes the formation of 1,25-DiOH-CC (Fig. 59-29).
Other hormones may increase the activity of renal 1-α-hydroxylase and the formation of 1,25-DiOH-CC under certain conditions. Prolactin, estradiol, and possibly somatotropin enhance 1-α-hydroxylase activity (see Fig. 59-28).(123) Increased secretion of these hormones, either alone or in combination, appears to be important in the efficient adaptation to the major calcium demands during life (e.g., growth, lactation, and pregnancy).

**CHEMISTRY**

The chemical structure of cholecalciferol (vitamin D3) resembles other steroid hormones. It is a secosteroid in which one of the rings of the basic steroid nucleus has undergone fission by breakage of a carbon-carbon bond. (141) Photoactivation by ultraviolet irradiation (290-320 nm) of 7-dehydrocholesterol in the skin results in a cleavage between the 9 and 10 carbons and unfolding of the B ring of the basic steroid nucleus (see Fig. 59-24).(88,96,100) During metabolic activation of cholecalciferol, hydroxy groups are attached successively to the steroid nucleus by specific hydroxylases at positions 25 and 1 in the liver and kidney to form the hormonal or biologically active form of vitamin D.

There are a number of other sterols closely related to cholecalciferol. Vitamin D2 is formed by the irradiation of the plant sterol referred to as ergosterol. When irradiated ergosterol is ingested and absorbed from the intestine, it undergoes a series of steps of metabolic activation similar to those described for cholecalciferol. Another related sterol of considerable therapeutic interest is dihydrotachysterol. The A ring of the steroid nucleus in this compound is rotated so that the hydroxyl in position 3 occupies a position sterically equivalent to the hydroxyl position 1 of 1,25-DiOH-CC. Current evidence suggests the dihydroxytachysterol undergoes metabolic transformation to 25-dihydrotachysterol, but subsequent hydroxylation of position 1 does not occur.< P>

**SUBCELLULAR MECHANISM OF ACTION OF ACTIVE VITAMIN D METABOLITES**

Vitamin D and its active metabolites function to increase the absorption of calcium and phosphorus from the intestine, thereby maintaining adequate levels of these electrolytes in the extracellular fluids in order to permit the appropriate mineralization of bone matrix.(150) From a functional point of view, vitamin D can be thought to act in such a way as to cause the retention of sufficient mineral ions to ensure the mineralization of bone matrix, whereas PTH maintains the proper ratio of calcium to phosphate in extracellular fluids.

![FIG. 59-30 Molecular mechanism of action of 1,25-dihydroxycholecalciferol in the intestine. The active metabolite of vitamin D is transported to the intestine by a vitamin D-binding protein (DBP). The hydrophilic steroid penetrates the plasma membrane, binds to a cytoplasmic receptor, and is transported to the nucleus, where it interacts with the nuclear chromatin to increase the formation of mRNA. The mRNA becomes associated with ribosomes on the endoplasmic reticulum and directs the synthesis of new proteins, such as calcium binding protein (CABP). The CABP is involved in the transcellular transport of calcium to the basilar aspects of the intestinal absorptive cells where calcium ion is exchanged for sodium and enters the extracellular fluid compartment.](image)

The major target tissue for 1,25-DiOH-CC is the mucosa of the small intestine where it increases the active transcellular transport of calcium (proximal part) and phosphorus (distal part). Following synthesis in the kidney, 1,25-DiOH-CC is transported by a DBP to specific target cells in the intestine (Fig. 59-30) and bone. Free 1,25-DiOH-CC penetrates the plasma membrane of target cells and initially binds to cytoplasmic receptors in cells of the intestine (Fig 59-30)(20) Subsequently, the hormone receptor complex is transferred to the nucleus and 1,25-DiOH-CC binds to specific receptors in the nuclear chromatin. Here it stimulates gene expression with increased messenger ribonucleic acid (mRNA) formation, which directs
the synthesis of vitamin D-dependent proteins such as calcium binding protein (CaBP cholecalcin) and calcium ATPase by intestinal cells.(87,201)

Intestinal absorptive cells are responsive to 1,25-DiOH-CC and are concerned with the transport of calcium from the lumen to the blood stream. The luminal surface (brush border) of absorptive cells is highly specialized and has numerous microvilli, which greatly increase the intestinal surface area (Fig 59-31) In response to 1,25-DiOHCC, intestinal absorptive cells synthesize a specific CaBP.(192,200) The highest concentration of CaBP in absorptive cells is in the cytosol near the terminal web and in the basal cellular region. (194) CaBP in mammals has a molecular weight of between 24,000 daltons and 28,000 daltons and has been isolated from several tissues (eg., small intestine, kidney, parathyroid gland, and the shell gland of laying hens) across which significant amounts of calcium are transported. In addition, vitamin D-dependent CaBP has been demonstrated in bone, particularly in the spongiosa and cartilaginous growth plate.(36)

The absorptive capacity of the intestine for calcium is a direct function of the amount of CaBP present (104,201) The administration of vitamin D or feeding low-calcium diets has been shown to stimulate the synthesis of CaBP, which contributes to the increased intestinal absorption of calcium. The physiologic functions of CaBP appear to be related to the transcellular transport of calcium from the luminal to basilar border of intestinal absorptive cells and the regulation intracellular calcium concentration.(194) At the basilar aspect of intestinal absorptive cells, calcium is exchanged for sodium and enters the extracellular fluids.

In addition to this effect on mineralization of bone matrix, vitamin D is necessary for osteoclastic resorption and calcium mobilization from bone in adults. Small amounts of vitamin D or its active metabolite are necessary to permit osteolytic cells to respond to PTH (permissive effect) under physiologic conditions. Both 1,25-DiOH-CC(206) and 25-OH-CC and cholecalciferol in pharmacologic doses will stimulate osteoclastic mobilization of bone calcium and the resorption of bone. On a weight basis 1,25-DiOH-CC and cholecalciferol in pharmacologic doses will stimulate osteoclastic mobilization of bone calcium and the resorption of bone. On a weight basis 1,25-DiOH-CC is about 100 times more potent in stimulating bone resorption in vitro than 25-OH-CC (160,167)

Adult intact female dogs administered intermittent low doses of 1,25-DiOH-CC (1,25 ug daily for 6 days and withdrawn for 14 days for 3 complete cycles) had elevations in levels of blood calcium and phosphorus and increased urinary hydroxyproline excretion.(93,94) In cortical bone (11th rib) there was a mixed decrease in activation frequency, bone formation rate, osteoid seam thickness, seam circumference, and mean appositional rate. Although recruitment of new remodeling sites was decreased after administration of 1,25-DiOH-CC, previously existing remodeling units continues to completion. These effects resulted in a preponderance of mature osteons in normal cortical bone.(94)(94) In trabecular bone of the iliac crest in dogs, 1-25-DiOH-CC stimulated the resorption rate and depressed the formation rate. (93) Trabecular resorption surfaces, osteoid volume and thickness, and mineralization lagtime were decreased by administration of 1,25-DiOH-CC localizes in the nucleus of tubular cells (185,186) Vitamin D-dependent CaBP is present primarily in cells of the distal convoluted tubule in most animal species.(191)
SECTION TWO
METABOLIC BONE DISEASE

- Secondary Hyperthyroidism
- Primary Hyperthyroidism
- Hypercalcemia of Malignancy (Pseudohyperparathyroidism)
- Hypoparathyroidism
- Hypocalcemia Syndromes Associated with Parturition
- Hypercalcitoninism
- Hypocalcitoninism

SECONDARY HYPERPARATHYROIDISM
RENAL HYPERPARATHYROIDISM
Secondary hyperparathyroidism as a complication of chronic renal failure is a metabolic state characterized by an excessive, but not autonomous, rate of PTH secretion. This disorder is encountered frequently in dogs and occurs occasionally in cats. The secretion of hormone by the hyperplastic parathyroid glands usually remains responsive to fluctuations in blood calcium levels. The primary etiologic mechanism in this disorder is longstanding, progressive renal disease resulting in severely impaired function. Chronic renal insufficiency in older dogs results from interstitial nephritis (Fig. 59-32), glomerulonephritis, nephrosclerosis, or amyloidosis. Chronic renal disease with periglomerular and interstitial fibrosis in Norwegian elkhounds has been reported to be familial. Several congenital anomalies such as cortical hypoplasia, polycystic kidneys, and bilateral hydronephrosis may result in renal insufficiency in younger dogs.

When the renal disease progresses to the point at which there is significant reduction in glomerular filtration rate, phosphorus is retained and progressive hyperphosphatemia develops (Fig. 59-33). Although the concentration of blood phosphorus has no direct regulatory influence on the synthesis and secretion of PTH, it may, when elevated, contribute to parathyroid stimulation by virtue of its ability to lower blood calcium levels. Parathyroid stimulation in patients with chronic renal disease can be attributed directly to the hypocalcemia. Recent evidence suggests that impaired intestinal absorption of calcium due to an acquired defect in vitamin D metabolism plays a significant role in the development of hypocalcemia in chronic renal insufficiency and uremia. Chronic renal disease interferes with the production of 1,25-DiOH-CC by the kidney, thereby diminishing intestinal calcium transport and resulting in development of hypocalcemia (Fig. 59-33).

All parathyroids are considerably enlarged (Fig. 59-34) as a result initially of hypertrophy of chief cells and subsequently of hyperplasia, as compensatory mechanisms to increase hormonal synthesis and secretion in response to the hypocalcemic stimulus. Although the parathyroids are not autonomous, the concentration of PTH in the peripheral blood in canine and human patients with chronic renal failure may exceed that of primary hyperparathyroidism (130) PTH increases osteoclastic resorption (205) and bone remodeling (144,145,196) resulting in release of stored calcium from bone. The longstanding increase in bone resorption that attempts to return serum calcium levels to normal eventually results in the metabolic bone disease associated with chronic renal insufficiency. Progressive glomerular and tubular dysfunction with loss of target cells interferes with an expression of the phosphaturic response by the increased circulating PTH in renal disease. Phosphate is
retained and the blood concentration continues to rise in spite of the secondary hyperparathyroidism (see Fig. 59-33).

Although skeletal involvement is generalized in hyperparathyroidism, it does not affect all parts uniformly. Lesions become apparent earlier and reach a more advanced stage in certain areas, such as cancerous bone of the skull. In dogs with longstanding renal disease, the increased osteoclastic resorption results in the formation of cystic (radiolucent areas) in bones of the skull giving a "moth-eaten" appearance (Figs. 59-35 and 59-36), similar to that of primary hyperparathyroidism. Resorption of alveolar socket bone and loss of lamina dura dentes occurs early and results in loose teeth, which may be dislodged easily and interfere with mastication (Fig. 59-37). The nasal cavity may be impinged upon owing to partial collapse of surrounding poorly mineralized bone and displacement of the medial nasal septum.

Cancerous bone of the maxilla (Fig. 59-38) and mandible also is a site of predilection in hyperparathyroidism. As a result of the accelerated resorption, bone of the mandibles becomes softened and readily pliable ("rubber jaw disease"; Fig. 59-39), and the jaws fail to close properly. This often results in drooling of saliva and protrusion of the tongue. The severely demineralized mandibles are predisposed to fractures and displacement of teeth from alveolar sockets. Long bones of the abaxial skeleton are affected less dramatically. Lameness, stiff gait, and the occurrence of fractures after relatively minor trauma may result from increased bone resorption.
The predominant clinical signs of vomiting, dehydration, polydipsia, depression, and an ammonia odor to the breath are related to progressive renal insufficiency and uremia. A spectrum of skeletal lesions of secondary hyperparathyroidism may be present, ranging from minor changes with early (or mild) renal disease to the severe fibrous osteodystrophy of advanced renal failure. Histologic evaluation of the skeleton in dogs with chronic renal disease reveals that a high percentage have generalized fibrous osteodystrophy. The volume of affected bones is usually normal (isostotic fibrous osteodystrophy), particularly in older dogs because of the slow onset of renal failure and lower metabolic activity of bones. Hyperostotic bone lesions, such as facial swellings, may be seen in younger dogs in whom deposition of osteoid by hyperplastic osteoblasts (stimulated by high blood phosphorus levels) and repair by proliferation of fibrous connective tissue exceed the rate of resorption, resulting in a greater than normal bone volume.

Serum should be analyzed for calcium, phosphorus, and alkaline phosphatase. Results of a single determination of these parameters must be interpreted with an appreciation that considerable variation exists, depending upon the stage of the disease, because of the body's compensatory mechanisms (see Fig. 59-33). The blood calcium level is variable but usually is in the low normal range because of mobilization of skeletal reserves. Most cases of chronic renal failure either have a normal or low serum calcium concentration with varying degrees of elevation in blood phosphorus values. However, 5% to 10% of dogs with chronic renal failure have serum calcium values of 12 mg/dl or greater.

Pathogenic mechanisms that have been suggested to explain the development of hypercalcemia in certain cases of chronic renal failure include decreased excretion of calcium by the diseased kidney, decreased renal tubular degradation of PTH, PTH-induced hypercitricemia with a consequent increase in complexed calcium, autonomous transformation or overcompensation by the parathyroid gland, and an exaggerated response to vitamin D with increased intestinal calcium absorption. In our experience, microscopic evaluation has failed to reveal evidence of autonomous or overcompensated parathyroid glands in dogs with hypercalcemia associated with chronic renal disease.

A transient and mild hypercalcemia has been observed in chronic renal failure in dogs following a precipitous decline in the blood phosphorus value through treatments with intestinal binding agents (e.g., aluminum hydroxide) and fluid therapy. This may be a consequence of a reciprocal movement of calcium from the bone fluid to the extracellular fluid space in response to the rapid lowering of circulating phosphorus levels. Persistent hypercalcemia has been reported in human patients during the diuretic phase of acute renal failure associated with rhabdomyolysis and is thought to be caused by mobilization of calcium from soft tissues, where it was initially deposited during oliguria. Dogs have been observed recovering from the oliguric phase of acute primary renal failure who developed hypercalcemia during diuresis. The hypercalcemia resolved without specific treatment.

Alkaline phosphatase activity may be elevated in animals with overt bone disease and renal hyperparathyroidism. Urinary excretion of calcium and phosphorus is decreased in patients with chronic renal disease.

The aim of treatment of renal hyperparathyroidism ideally would be to interrupt the progression of kidney disease and restore or replace renal function to a semblance of normal. Because of the stage at which the diagnosis is established in animals and the progressive nature of the disease, treatment is directed realistically toward reducing the excretory load and providing substances (such as sodium chloride or bicarbonate, and water) that the failing kidney is unable to conserve. A K/D prescription diet with supplemental calcium (gluconate or lactate) and vitamin D may diminish the severity of
hyperparathyroidism and accompanying bone lesions. Recent evidence in human patients suggests that 1,25DiOH-CC or 1\(^{\alpha}\)hydroxycholecalciferol has considerable potential in the therapy of impaired intestinal absorption of calcium, hypocalcemia, and osteomalacia associated with chronic renal disease.

**NUTRITIONAL HYPERPARATHYROIDISM**

The increased secretion of PTH in this metabolic disorder is a compensatory mechanism directed against a disturbance in mineral homeostasis induced by nutritional imbalances. The disease occurs commonly in dogs, cats (Fig. 59-40), certain primates, and laboratory animals, as well as in many farm animals. Dietary mineral imbalances of etiologic importance in the pathogenesis of nutritional secondary hyperparathyroidism are a low content of calcium; excessive phosphorus with normal or low calcium; and inadequate amounts of cholecalciferol (vitamin D3) in New World nonhuman primates housed indoors without exposure to sunlight. The significant end result is hypocalcemia, which results in parathyroid stimulation (Fig. 59-41).

A diet low in calcium fails to supply the daily requirement, even though a greater proportion of ingested calcium is absorbed and hypocalcemia develops.(32,175) Ingestion of excessive phosphorus results in increased intestinal absorption and elevation of blood phosphorus levels. Hyperphosphatemia does not stimulate the parathyroid gland directly but does so indirectly by virtue of its ability to lower blood calcium levels (see Fig. 59-33). In response to the nutritionally induced hypocalcemia, all parathyroid glands undergo cellular hypertrophy and hyperplasia (Figs. 59-42 and 59-43). The expanded cytoplasmic area of hyperactive chief cells contains large mitochondria, prominent Golgi complexes, and lamellar arrays of rough endoplasmic reticulum but few PTH-containing secretory granules (Fig. 59-44).(32) Plasma membranes of adjacent hyperactive chief cells are intricately interdigitated (Fig. 59-44) Since kidney function is normal, the increased levels of PTH result in diminished renal tubular reabsorption of phosphate and increased reabsorption of calcium, returning blood levels toward normal (see Fig. 59-41). In addition, osteoclastic bone resorption is accelerated, and release of calcium elevates blood calcium levels to the low normal range. Continued ingestion of the unbalanced diet sustains the state of compensatory hyperparathyroidism, leading to progressive development of the metabolic bone disease.

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The disease develops in young pups and kittens fed a predominantly meat diet. For example, beef heart or liver contains minimal amounts of calcium (7-9 mg per 100 g) and has a markedly imbalanced calcium/phosphorus ratio (1:20 to 1:50). The feeding of a monotonous meat diet to dogs of any age results in secondary hyperparathyroidism with the development of skeletal disease of varying severity. The low calcium content and unfavorable calcium/phosphorus ratio of nonsupplemented all-meat diets are unable to fulfill the daily requirements for either growing pups (528 mg of calcium and 440 mg of phosphorus/kg of body weight/day) or adult dogs (264 mg of calcium and 220 mg of phosphorus/kg of body weight/day).
The diet of kittens up to 6 months of age should supply 200 mg to 400 mg of calcium and approximately 200 μg of iodine daily, and from 10,000 IU to 15,000 IU of vitamin A weekly. (175) The addition of iodine to allmeat diets prevents the development of thyroid hyperplasia in cats but not the skeletal disease.

Kittens that are fed beef heart exclusively develop locomotor disturbances within 4 weeks. The predominant clinical signs are a reluctance to move, posterior lameness, and an incoordinated gait. The kittens often assume a standing position with characteristic deviation of the paws. The skeletal disease becomes progressively more severe after 5 to 14 weeks. The cortex of long bones is greatly thinned owing to the increased resorption, and the medullary cavity is widened (Fig. 59-45). The kittens become quiet and reluctant to play. They assume a sitting position or are in sternal recumbency with the hindlegs abducted at the pelvis. Normal activities may result in the sudden onset of severe lameness due to incomplete or folding fractures of one or more bones. In kittens that are fed beef heart, the high content of digestible protein (over 50% on a wet basis) and fat promotes rapid growth. These animals appear well nourished and their coat maintains a good luster.

Various terms have been used to describe this metabolic disorder in cats, including osteogenesis imperfecta, juvenile osteoporosis, and paper-bone or Siamese cat disease. In general, kittens are more susceptible to this disorder and develop more severe skeletal lesions than adult cats fed a similar diet. Adult cats fed a beef heart diet develop osteoporosis slowly after a period of months in response to increased PTH secretion, whereas the skeletons of kittens develop severe generalized osteitis fibrosa within a few weeks. The disease develops rapidly in kittens because the dietary imbalance is wide and their nutritional secondary hyperparathyroidism has been reported frequently in Siamese and Burmese kittens, but skeletal lesions can be induced readily in other breeds. The indulgence of fussy eating habits with undesirable diets by their owners, rather than a genetic predisposition, probably accounts for the higher incidence of the disease in the Siamese and Burmese breeds.

FIG. 59-43 Chief cell hypertrophy and hyperplasia in the parathyroid gland of a cat with nutritional secondary hyperparathyroidism. The hyperactive chief cells are enlarged, lightly eosinophilic, and closely packed together, with narrow perivascular spaces (arrow). (H&E, x 315)

FIG. 59-44 Hyperactive chief cells in the parathyroid gland of an experimental cat fed a low-calcium diet for 9 weeks. The plasma membranes of adjacent hyperactive chief cells are intricately interdigitated (arrows). The cytoplasm of the chief cells contains lamellar arrays of endoplasmic reticulum, prominent Golgi complexes (G) with numerous prosecretory granules, filamentous mitochondria, and aggregations of ribosomes. Mature secretory granules are infrequent (arrowhead) and situated near the periphery of the chief cells in response to the diet-induced hypocalcemia. (original magnification x 9600) (Capen CC, Rowland GN: Ultrastructural evaluation of the parathyroid glands of young cats with experimental hyperparathyroidism. Z Zellforsch Mikrosk Anat 90:495, 1968)

FIG. 59-45 Radiograph of a kitten with nutritional secondary hyperparathyroidism illustrates generalized skeletal demineralization with bilateral folding fractures of the femur (arrows), thin Vortices of long bones, and a fracture of the pelvis near the acetabulum.
The skeletal metabolic rate is high. Resorption proceeds at a faster rate than repair by fibrous connective tissue proliferation and results in a decreased bone volume (hypostotic fibrous osteodystrophy). Fractures of long bones are bridged by a poorly mineralized fibrous callus in untreated animals. Vertebral fractures with compression of the spinal cord and paralysis are common in kittens (Fig. 59-46) but infrequent in adult cats.

Lameness is the initial functional disturbance in growing dogs and may vary from a slight limp to complete inability to walk. The bones are painful on palpation, and folding fractures of long bones and vertebrae are not uncommon. Clinical signs usually are related to resorption of jaw bones in adult dogs. PTH-stimulated resorption of alveolar socket bone results in loss of lamina dura dented loosening and subsequent loss of teeth from their sockets, and recession of gingiva with partial root exposure in advanced cases.

In order to establish a definite diagnosis the diet should be evaluated for calcium, phosphorus, and vitamin D content in patients (particularly young and rapidly growing animals) with skeletal disease. In nutritional hyperparathyroidism, there is radiographic evidence of generalized skeletal demineralization, loss of lamina dura dented subperiosteal cortical bone resorption, bowing deformities, and multiple folding fractures of long bones (see Fig. 59-45) due to intense localized osteoclast proliferation (Fig. 59-47). Laboratory parameters used to assess renal function should be within normal limits in patients with nutritional hyperparathyroidism.

Analysis of the serum for calcium, phosphorus, and alkaline phosphatase should be undertaken with an appreciation that one determination may be of limited diagnostic value. Since the body's compensatory mechanisms with this disease are complex and operational when the animal is seen for the first time, serum calcium and phosphorus levels usually are in a low normal range. Alkaline phosphatase activity often is elevated in animals with overt bone disease. The increased PTH secretion acts on the normal kidneys to increase phosphate and decrease calcium excretion in the urine (see Fig. 59-41).

The aim of treatment of nutritional hyperparathyroidism is to decrease PTH secretion by correcting the dietary mineral imbalance or deficiency. Kittens and pups with the disease should be fed a diet that fulfills their high demand for animal protein and meets the daily requirements for calcium and phosphorus. Calcium gluconate, lactate, or carbonate, alone or in combination, should be used as dietary supplements to achieve a 2:1 calcium/phosphorus ratio during the healing phase in young animals with severe bone disease. Additional vitamin D usually is not necessary but may be indicated in severely affected animals to increase intestinal absorption of calcium. Calcium gluconate should be given parenterally if the appetite is depressed. The feeding of excessive amounts of calcium for prolonged periods should be avoided both therapeutically and under normal conditions because it may retard growth and alter remodeling of bone in young dogs.

Affected animals should be confined for at least 3 weeks after initiation of the supplemental diet. The response to therapy is rapid, and within a week the animals become more active and their attitude improves. Jumping or climbing must be prevented because the skeleton is still susceptible to fractures. The restrictions need be less rigid after 3 weeks, but confinement with limited movement is indicated until the skeleton returns to normal. Improvement of the skeleton during dietary supplementation can be followed radiographically. Fracture calluses become radiodense and the overall mineral density and cortical bone thickness increase progressively with treatment. The skeleton is usually healed after feeding the
supplemental diet (calcium/phosphorus ratio of 2:1) for 8 to 9 weeks. Subsequently, the diet should supply the total daily requirement of calcium and phosphorus and be balanced at about 1.2:1.0. Even advanced cases respond favorably to dietary supplementation. Good nursing care is essential to prevent complications such as decubital ulcers, constipation, and additional fractures. Healed pelvic fractures may predispose to dystocia and obstipation. Hypoplasia of the pelvic lumen of cats is not uncommon. These animals may develop megacolon secondary to the pelvic constriction.

**FIG. 59-48 Alterations in levels of serum calcium and phosphorus in response to an autonomous secretion of parathyroid hormone in primary hyperparathyroidism.**

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**PRIMARY PARAHYPTERTHYROIDISM**

In primary hyperparathyroidism PTH is produced in excess of normal by a functional lesion in the parathyroid gland. This disease is encountered infrequently in older dogs (35,72,114,118,156,183) Primary hyperparathyroidism does not appear to be a sequela of long-standing secondary hyperparathyroidism in animals. The normal control of PTH secretion by the concentration of blood calcium is lost in primary hyperparathyroidism. Hormone secretion is autonomous, and the parathyroid produces excessive hormone in spite of the increased blood calcium.4 PTH acts on cells of the renal tubules initially to promote the excretion of phosphate and retention of calcium. A prolonged increased secretion of PTH results in accelerated osteocytic and osteoclastic bone resorption (Fig. 59-48). Mineral is removed from the skeleton and replaced by immature fibrous connective tissue. The bone lesion of fibrous osteodystrophy is generalized throughout the skeleton but is accentuated in local areas such as in the cancerous bone of the skull.

The lesion in the parathyroid gland responsible for the excessive secretion of PTH in dogs usually is an adenoma composed of active chief cells.(27) Adenomas are usually single, light brown-red, and usually located in the cervical region near, but sharply demarcated from, the thyroid gland (Fig. 59-49); however, they may be present in the anterior mediastinum near the base of the heart. Parathyroid neoplasms in the precardial mediastinum are derived from ectopic parathyroid anlage displaced into the thorax with the expanding thymus during embryonic development. Histopathologic demonstration of a rim of normal tissue and fibrous capsule in an enlarged parathyroid suggests a diagnosis of adenoma rather than hyperplasia (Fig. 59-50). Thyroid C cells are markedly hyperplastic in response to the long-term hypercalcemia and appear as small white foci in the thyroid gland (see Fig. 59-49). The hyperplastic C cells often displace the colloidcontaining follicles lined by follicular cells.

**FIG. 59-49 Chief cell adenoma removed surgically from a dog with primary hyperparathyroidism. The parathyroid adenoma (A) is sharply demarcated from the adjacent thyroid by a thin fibrous capsule (arrows). There are multiple foci of C-cell hyperplasia (C) in the thyroid gland, stimulated by the long term hypercalcemia.**

**FIG. 59-50 Photomicrograph illustrates a thin fibrous capsule (arrows) surrounding the chief cell adenoma (see Fig. 59-49) that separates the tumor from the adjacent thyroid gland. Thin strands of fibrous connective tissue (arrowheads) extend from the capsule into the adenoma. (H&E, x 42)**

Chief cell carcinomas are infrequent causes of primary hyperparathyroidism. Carcinomas tend to be larger than adenomas and fixed to the underlying tissues owing to local infiltration of neoplastic chief cells.

In primary hyperparathyroidism functional disturbances often are observed as the result of weakening of bones by excessive...
osteoclastic resorption. Lameness due to severe demineralization (Fig. 59-51) or fractures of long bones occurs after relatively minor physical trauma. Compression fractures of weakened vertebral bodies may exert pressure on the spinal cord and nerves, resulting in motor or sensory dysfunction.

Facial hyperostosis with partial obliteration of the nasal cavity by poorly mineralized woven bone and highly vascular fibrous connective tissue and loss or loosening of teeth in alveolar sockets have been observed in dogs with primary hyperparathyroidism (Fig. 59-52). This may result in an inability to close the mouth properly and the development of areas of ulceration of the gingival mucosa. The abnormal accumulations of woven bone may partially occlude the nasal cavity (Fig. 59-53) and are composed of spicules of poorly mineralized osteoid, numerous capillaries, and immature connective tissue fibers (Fig. 59-54). Active osteoblasts are embedded in the woven bone and are surrounded by abundant collagen fibers of the osteoid, but there are only occasional initial foci of mineralization (Fig. 59-55). Numerous granules of amorphous calcium phosphate are present within hyperactive osteoblasts in the woven bone (Fig. 59-56). The maxilla and rami of mandibles often are coarsely thickened by the formation of excessive woven bone. Bones of the skull are thinned markedly by the increased resorption and have a characteristic moth-eaten appearance radiographically.

Primary hyperparathyroidism should be included in the differential diagnosis of older dogs with a clinical history of severe generalized skeletal demineralization and normal renal function. Radiographic evaluation reveals areas of subperiosteal
cortical resorption, loss of lamina dura dentes, soft tissue mineralization, bone cysts, a generalized decrease in bone density, and in advanced cases, Fractures. Hypercalcemia results in anorexia, vomiting, constipation, and generalized muscular weakness due to decreased neuromuscular excitability.

Quantitation of total blood calcium is the most important and practical laboratory test to aid in establishing the diagnosis of primary hyperparathyroidism. Although other laboratory findings may be variable, hypercalcemia is a consistent finding and results from accelerated release of calcium from bone. The blood calcium level of normal adult animals is near 10 mg/dl with some variation depending upon the analytical method employed as well as the age and diet of the animal. Calcium values consistently above 11.5 mg/dl should be considered to be in the hypercalcemic range. Dogs with primary hyperparathyroidism usually have a greatly elevated blood calcium level (12-20 mg/dl or above). The blood phosphorus level is low or in the low normal range (4 mg/dl or less) because of inhibition of renal tubular reabsorption of phosphorus by excess PTH (see Fig. 59-48).

The urinary excretion of phosphorus and often of calcium is increased and may result in nephrocalcinosis and urolithiasis (Fig. 59-57). Accelerated bone matrix catabolism is reflected by an increased excretion of hydroxyproline in the urine. The activity of alkaline phosphatase may be elevated in the serum of animals with overt bone disease. The increased activity of this enzyme is thought to result from a compensatory increase in osteoblasts along trabeculae as a response to mechanical stress in bones weakened by excessive resorption. In humans the detection of elevated circulating levels of PTH by radioimmunoassay has greatly facilitated the early diagnosis of hyperparathyroidism.

The objective of treatment of primary hyperparathyroidism is to eliminate the source of excessive PTH production. An attempt should be made to identify all four parathyroid glands before excising any tissue. A correlation often exists in humans between tumor size and the severity of hypercalcemia and bone disease. Single or multiple adenomas should be removed in toto. In case all identifiable glands in the cervical region appear to be of normal or smaller size and a diagnosis has been established with reasonable certainty, surgical exploration of the thorax near the base of the heart may be necessary to localize the neoplasm.

Surgical removal of the functional parathyroid lesion results in a rapid decrease in circulating PTH levels, since the half-life of PTH in plasma is approximately 20 minutes. It should be emphasized that plasma calcium levels in patients with overt bone disease may decrease rapidly and be subnormal within 12 to 24 hours postsurgery, resulting in severe hypocalcemic tetany. Hypocalcemia also has been observed in dogs with primary hyperparathyroidism following infarction of a functional chief cell adenoma due to excessive palpation. Serum calcium levels should be monitored frequently following surgical removal of a parathyroid neoplasm. Postoperative hypocalcemia (5 mg/dl and lower) can be the result of the following: depressed secretory activity of chief cells due to long-term suppression by the chronic hypercalcemia or injury to the remaining parathyroid tissue during surgery; abruptly decreased bone resorption as a result of lowered PTH levels; and accelerated mineralization of osteoid matrix formed by the hyperplastic osteoblasts that was prevented previously from undergoing mineralization by the elevated PTH levels. Infusions of calcium gluconate to maintain the serum calcium level between 7.5 mg and 9.0 mg/dl plus feeding highcalcium diets and administering supplemental vitamin D therapy will correct this serious postoperative complication. If hypercalcemia persists for a week or more after surgery or recurs after initial improvement, the presence of a second adenoma or metastases from a carcinoma should be suspected.
Since many of the severe effects of hypercalcemia are accentuated by dehydration, disturbances in fluid balance should be corrected in all instances. Replacement fluids such as isotonic lactated Ringer's or 0.9% sodium chloride solutions should be administered intravenously.

Calciuresis may be enhanced by administering 0.9% sodium chloride intravenously, since the additional sodium presented to the renal tubules diminishes calcium reabsorption. In cases of hypercalcemic crisis, intravenous administration of sodium bicarbonate may be of value in temporarily reducing the toxic effects of elevated ionized calcium concentration. The beneficial effect is related to diminution in the level of ionized calcium associated with alkalosis induced by sodium bicarbonate.

Other causes of hypercalcemia that must be considered in differential diagnosis of primary hyperparathyroidism are vitamin D intoxication, malignant neoplasms with osseous metastases, and PTH like activity ("pseudohyperparathyroidism") or other boneresorbing substances produced by malignant neoplasms ("hypercalcemia of malignancy") of nonparathyroid origin without metastases to bone.

The hypercalcemia of hypervitaminosis D may be of a magnitude similar to that in primary hyperparathyroidism but is accompanied by varying degrees of hyperphosphatemia and normal serum alkaline phosphatase activity. Skeletal disease usually is not present, since the increased concentrations of blood calcium and phosphorus are derived principally from augmented intestinal absorption rather than bone resorption.(29,199)

Malignant neoplasms with osseous metastases may cause moderate hypercalcemia and hypercalciuria, but the alkaline phosphatase activity and serum phosphorus are usually normal or slightly elevated. These changes are believed to be due to release of calcium and phosphorus into the blood from areas of bone destruction at rates greater than can be cleared by the kidney and intestine. Bone involvement is more sharply demarcated and localized to the area of metastases. Osteolysis associated with tumor metastases has been shown to be the result not only of a physical disruption of bone by proliferating neoplastic cells but also of the local production of humoral substances that stimulate bone resorption, such as prostaglandins and osteoclast-activating factor. Multiple myeloma and lymphosarcoma with widespread bone marrow infiltration have been associated with hypercalcemia. Myeloma patients with hypercalcemia may have increased binding of calcium to an abnormal quantity of globulin in addition to the increased amount of ionized calcium from bone dissolution.

Hypercalcemia also may be caused by multifocal osteolytic lesions associated with septic emboli, complete immobilization, osteosarcoma, hypoadrenocorticism (Addison's-like disease),(137,193) hypocalcitoninism due to a destructive thyroid disease, occasional cases of chronic renal disease, hemoconcentration, and hyperproteinemia. Metastatic tumors to bone are not encountered commonly in dogs or cats with malignant neoplasms but may be associated with hypercalcemia at certain stages of tumor growth. Primary bone tumors occasionally may be associated with hypercalcemia.(149) Bacterial or fungal osteomyelitis and neonatal septicemia in puppies with septic emboli and lysis of bone are sporadic causes of hypercalcemia. Skeletal radiographs are indicated to document the sites and severity of multifocal bone lesions.

Hypercalcemia may be detected occasionally in dehydrated animals. The magnitude of elevation in blood usually is mild and is attributed to fluid volume contraction that results in hyperproteinemia and an increased relative concentration of ionized and nonionized calcium. The hypercalcemia rapidly resolves following fluid therapy. The majority of dehydrated animals do not develop hypercalcemia.

Prolonged immobilization can lead to hypercalcemia as a consequence of continued bone resorption associated with diminished bone accretion. Hypercalcemia of this type occurs infrequently in animals that cannot move around freely because of extensive musculoskeletal or neurologic injury.

Hypercalcemia has been reported in experimentally adrenalectomized dogs and in some cases of naturally occurring Addison's-like disease in dogs.(137,198) The magnitude of elevation in serum calcium values may exceed 26 mg/dl under experimental conditions, whereas dogs with Addison's-like disease evaluated in our hospital have had blood calcium values up to 15 mg/ dl. Experimental evidence suggests that the type of hypercalcemia associated with hypoadrenocorticism is unusual in that the ionized calcium fraction remains normal while the nonionized calcium fraction increases. If the ionized calcium does indeed remain normal, it follows that this type of hypercalcemia should not be deleterious to the animal. The elevated calcium value rapidly returns to normal following treatment for hypoadrenocorticism.
HYPERCALCEMIA OF MALIGNANCY (PSEUDOHYPERPARATHYROIDISM)

Pseudohyperparathyroidism is a metabolic disorder in which PTH-like polypeptides or other bone-resorbing substances are secreted in excessive amounts by malignant tumors of nonparathyroid origin. Criteria for the diagnosis of pseudohyperparathyroidism include the following: (1) persistent hypercalcemia and hypophosphatemia; (2) absence of radiographic or pathologic evidence of tumor metastases in bone; (3) atrophy of parathyroid glands and C-cell hyperplasia in the thyroid gland; (4) remission of hypercalcemia when the tumor is destroyed or excised; (5) demonstration of immunologically or biologically active PTH-like polypeptides or other boneresorbing substances in the tumor tissue; and (6) exacerbation of hypercalcemia if the tumor recurs following therapy. Tumor cells in human beings and animals have been shown to produce several humoral substances that induce calcium mobilization from bone, including PTH-like polypeptides, prostaglandins (PGE2), osteoclast-activating factor, colony-stimulating activity, and transforming growth factors.(135,136)

Hypercalcemia and hypophosphatemia develop in dogs and humans with various malignant neoplasms in the absence of bone metastases and functional lesions in the parathyroid glands. Present evidence suggests that the hypercalcemia is the result of ectopic secretion of bone-resorbing substances by anaplastic tumor cells,(184) most likely by the mechanism of genetic derepression.

Rijnberk and co-workers(168,169) described a syndrome of pseudohyperparathyroidism in elderly female dogs associated with perirectal adenocarcinomas. The dogs had persistent hypercalcemia and hypophosphatemia that returned to normal following surgical excision of the neoplasm in the perirectal area. The hypercalcemia persisted following removal of the parathyroid glands. Immunoreactive PTH levels were within the normal range for the dog but were inappropriately high for the degree of hypercalcemia.

HYPERCALCEMIA ASSOCIATED WITH APOCRINE ADENOCARCINOMA

Meuten and co-workers(128) reported detailed clinical, macroscopic, and histopathologic features of adenocarcinomas arising from the apocrine gland of the anal sac in 36 dogs. This unique syndrome occurred in aged (mean 10 years), predominantly female (92%) dogs and was characterized by persistent hypercalcemia (91%) and hypophosphatemia (71%). Serum calcium values ranged from 11.4 mg to 24.0 mg/dl with a mean of 16.2 mg/dl. Tumor ablation resulted in a prompt return to normocalcemia, but the hypercalcemia recurred with tumor regrowth, suggesting the neoplastic cells were producing a humoral substance that increased calcium mobilization. All tumors had histopathologic features of malignancy and 96% had metastasized to iliac and sublumbar lymph nodes.

Functional disturbances in dogs with pseudohyperparathyroidism include generalized muscular weakness, anorexia, vomiting, bradycardia, depression, polyuria, and polydipsia. These clinical signs are the result primarily of severe hypercalcemia and complicate the problems associated with the malignant neoplasm.

FIG. 59-58 Hypercalcemia of malignancy. Perirectal region of a dog with hypercalcemia and a small adenocarcinoma (arrow) derived from apocrine glands of the anal sac. (A, anus; T, tail)

FIG. 59-59 Transverse section of perineum from a female dog with hypercalcemia and an adenocarcinoma derived from apocrine glands of the anal sac. Anal sacs (A) are present on both sides of the rectum (R). A tumor nodule (arrows) 1 cm in diameter arising in the wall of the left anal sac protrudes into its lumen. The scale represents 1 cm. (Meuten DJ, Cooper BJ, Capen CC et al: Hypercalcemia associated with an adenocarcinoma derived from the apocrine glands of the anal sac. Vet Pathol 18:454, 1981)
Apocrine adenocarcinomas develop as a firm mass (81% unilateral) in the perirectal area, ventral-lateral to the anus, in close association with the anal sac, but are not attached to the overlying skin (Figs. 59-58 and 59-59). This unique neoplasm that develops from apocrine glands of the anal sac (Fig. 59-60) forms distinctive glandular acini with projections of apical cytoplasm extending into a lumen (Fig. 59-61) and is histologically distinct from the more common perianal (circumanal) gland tumor. The majority of neoplasms were histologically bimorphic with glandular and solid areas (Fig. 59-62). The solid pattern of arrangement of neoplastic cells was characterized by sheets, microlobules, and packets separated by a thin fibrovascular stroma. Pseudorosettes were common in solid areas adjacent to small blood vessels.

FIG. 59-60 Photomicrograph illustrates close anatomical relationship of apocrine adenocarcinoma (T) to normal apocrine glands (G) in the wall of the anal sac. The anal sac (A) is lined by stratified squamous epithelium. (H&E, x 125) (Meuten DJ, Cooper BJ, Capen CC et al: Hypercalcemia associated with an adenocarcinoma derived from the apocrine glands of the anal sac. Vet Pathol 18:454, 1981)

FIG. 59-61 Photomicrograph of biopsy of an adenocarcinoma arising from apocrine glands in the wall of the anal sac in a dog with pseudohyperparathyroidism and persistent hypercalcemia. The glandular acini are lined by single or multiple layers of columnar neoplastic cells with characteristic apical projection of cytoplasm into the lumen (arrowheads). The acini contain varying amounts of colloidlike material and occasional inflammatory cells. (H&E, x 315) (Meuten DJ, Cooper BJ, Capen CC et al: Hypercalcemia associated with an adenocarcinoma derived from the apocrine glands of the anal sac. Vet Pathol 18:454, 1981)

FIG. 59-62 Photomicrograph of biopsy illustrates characteristic bimorphic growth pattern in adenocarcinoma derived from apocrine glands of the anal sac with adjacent solid areas (S) and acini (A) formed by neoplastic cells. (H&E, x 125) (From Meuten DJ, Cooper BJ, Capen CC et al: Hypercalcemia associated with an adenocarcinoma derived from the apocrine glands of the anal sac. Vet Pathol 18:454, 1981)

FIG. 59-63 Electron micrograph of an adenocarcinoma derived from apocrine glands of the anal sac in a dog with hypercalcemia. Tall columnar cells with microvilli (V) and a prominent basement membrane (left) line the tubule. Adjacent tumor cells are joined by tight junctions and desmosomes (D). A Golgi apparatus (G) is present in most cells. Tumor cells contain scattered mitochondria and many small electron-dense granules (arrows). (original magnification x 3900) (Meuten DJ, Capen CC, Kociba GJ et al: Ultrastructural evaluation of an adenocarcinoma-derived from apocrine glands of the anal sac associated with hypercalcemia in dogs. Am J Pathol 107: 167, 1982)

The tumor cells in adenocarcinomas derived from apocrine glands of the anal sac ultrastructurally contained a well-developed rough endoplasmic reticulum, clusters of free ribosomes, large mitochondria, and prominent Golgi apparatuses (Fig. 59-63). Small, membrane-limited secretory granules often were present in the apical cytoplasm of neoplastic cells (Figs. 59-64 and 59-65). These granules were of similar size and electron density as PTH-containing storage granules in chief cells of normal
parathyroid glands; however, additional studies are required to determine if they contain hormonal activity.

The parathyroid glands were small and difficult to locate or not visible macroscopically in 69% of dogs reported by Meuten and coworkers. Atrophic parathyroid glands in dogs with apocrine adenocarcinomas were characterized by narrow cords of inactive chief cells with an abundant fibrous connective tissue stroma and widened perivascular spaces (Fig. 59-66). The inactive chief cells had a markedly reduced cytoplasmic area, prominent hyperchromatic nuclei, and were closely packed together (Fig. 59-67). These findings were interpreted to suggest that the apocrine adenocarcinomas were not producing a substance that stimulated PTH secretion but rather the parathyroid glands were responding to the persistent hypercalcemia by undergoing trophic atrophy. Thyroid parafollicular (C) cells often responded to the persistent elevation in blood calcium levels by undergoing diffuse or nodular hyperplasia.

Skeletal demineralization in dogs with pseudohyperparathyroidism was mild in comparison with other causes of hypercalcemia and usually undetectable by conventional roentgenographic methods. Neoplastic cells from the perirectal adenocarcinomas rarely metastasized to bone (1 of 36 dogs) and caused osteolysis. Variable numbers of osteoclasts have been detected on bone surfaces in dogs with marked hypercalcemia, possibly reflecting different states in the course of the disease and phases of bone remodeling activity (Fig. 59-68). Osteolytic osteolysis was not detected microscopically, and the cement lines were smooth and linear.
Histomorphometric analysis indicated that dogs with apocrine adenocarcinomas and hypercalcemia had significantly decreased trabecular bone volume as compared with age-matched control dogs (Table 59-1). Total resorptive surface (Howship's lacunae with and without osteoclasts) was increased significantly, as were the number of osteoclasts per millimeter of trabecular bone. By comparison, dogs with primary hyperparathyroidism also had significantly increased total resorptive surface and numbers of osteoclasts (Table 59-1).(130)

The mean concentration of iPTH in the plasma of dogs with hypercalcemia and apocrine adenocarcinomas was reported by Meuten and co-workers(130) to be 168 + 40 pg/ml with a range of undetectable to 266 pg/ml (Fig. 59-69). The concentration of iPTH in dogs with apocrine adenocarcinomas was not significantly different from the concentration in control dogs (322 + 33 pg/ml) or normocalcemic tumor controls (264 + 46 pg/ml) but was decreased significantly compared with that of dogs with primary hyperparathyroidism. The concentration of iPTH in dogs with renal failure was markedly increased compared with that of control dogs (Fig. 59-69). Plasma iPTH levels were undetectable in dogs with primary hypoparathyroidism but increased in dogs with primary hyperparathyroidism (mean: 1540 pg/ml) (Fig. 59-69). Urea-hydrochloric acid extracts from apocrine adenocarcinoma, tumors from normocalcemic control dogs, and lymph nodes from control dogs without tumors were assayed for iPTH before and after precipitation with trichloroacetic acid. Immunoreactive PTH was not detected in tissue extracts from any tumor or lymph node. The iPTH concentrations in extracts of parathyroid glands from adult dogs were greater than 200.

<table>
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<th>TABLE 59-1</th>
<th>Histomorphometric Evaluation of Lumbar Vertebrae From Dogs With Hypercalcemia and Adenocarcinomas Derived From Apocrine Glands of the Anal Sac Compared With Control Dogs and Dogs With Primary Hyperparathyroidism</th>
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The mean serum concentration of 1,25-dihydroxyvitamin D (1,25DiOH-CC) in dogs with apocrine adenocarcinomas and hypercalcemia was 23 pg/ml with a range of 7 pg to 58 pg/ml (Table 59-2). Although these dogs had hypercalcemia and normophosphatemia, the mean serum 1,25-DiOH-CC concentration was not significantly different from either group of normocalcemic control dogs (Table 59-2). The concentration of 1,25DiOH-CC decreased twofold to eightfold following excision of the apocrine adenocarcinomas (Fig. 59-70). The mean preoperative serum calcium level was 16.5 mg/dl, and the mean preoperative serum 1,25-DiOH-CC concentration was 32 pg/ml, whereas postoperative values were 10 mg/dl and 6 pg/ml, respectively.

Dogs with carcinomas derived from apocrine glands of the anal sac have a significantly greater urine calcium excretion (mean + SE = 0.35 + 0.11 mg/dl glomerular filtrate [GF]) than either control dogs (0.02 + 0.01 mg/dl GF) or normocalcemic tumor-control dogs (0.04 + 0.01 mg/dl GF) and have higher urine calcium levels than dogs with primary hyperparathyroidism (0.12 + 0.06 mg/dl GF) (Fig. 59-71). In addition, the results for fractional excretion of calcium (mean + SE) indicate that the urinary excretion of calcium in dogs with apocrine carcinomas (2.1% + 0.7%) is significantly greater than that of clinically normal dogs (0.2% + 0.05%).

Urinary cAMP per deciliter GF is increased significantly in dogs with carcinomas derived from apocrine glands of the anal sac (mean: 337 + 0.44 nM) compared with that of clinically normal dogs (mean: 1.94 + 0.16 nM) but not compared with that of tumor-control dogs (mean: 2.70 + 0.57 nM) (Fig. 59-71). Urinary excretion of phosphorus and hydroxyproline has been reported to be numerically higher in dogs with apocrine carcinomas than in control dogs, but the differences were not significant (see Fig. 59-71). Significant differences have not been demonstrated in the concentrations of serum albumin, urea nitrogen, alkaline phosphatase, or phosphorus in dogs with apocrine adenocarcinomas (Table 59-2).
Biopsy specimens from adenocarcinomas derived from apocrine glands of the anal sac usually have histologic evidence of malignancy, and 96% metastasize to iliac or lumbar lymph nodes. Invasion of tumor cells usually is present into adjacent tissues and endothelial-lined vessels, forming emboli. Tumor cell emboli appear to be more common in lymphatic vessels than in blood vessels.

Shaded areas for P and CA represent laboratory reference values (mean +/- 2 SD for 100 normal adult dogs). Shaded areas for iPTH and 1,25-(OH)D are mean +/- 1 SD for control dogs. The limits of detectability for iPTH (112 pg/ml) and 1,25(OH)D (4 pg/ml) are indicated by broken lines. (Meuten DJ, Segre GV, Capen CC et al: Hypercalcemia in dogs with adenocarcinoma derived from apocrine glands of the anal sac: Biochemical and histomorphometric investigations. Lab Invest 48:428, 1983)

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FIG. 59-71 Urinary excretion of hydroxyproline, cAMP, and calcium in dogs with apocrine adenocarcinoma of the anal sac compared with that in normocalcemic controls with and without tumors and in dogs with primary hyperparathyroidism. Levels of calcium and cAMP excretion were significantly increased in dogs with apocrine carcinomas compared with those in control dogs without tumors but not compared with those of control dogs with tumors. cAMP excretion was significantly greater (P<0.05) in hyperparathyroid dogs than in any other group. Hydroxyproline excretion in dogs with apocrine carcinomas (19.6 +/- 3.9 ug/dl GF) was greater than in controls (9.3 +/- 1.4 ug/dl GF) but this difference was not significant. Horizontal lines indicate mean for the group. Significant differences (P<0.05) from control dogs are indicated by a and from tumor controls by b. (Meuten DJ, Segre GV, Capen CC et al: Hypercalcemia in dogs with adenocarcinoma derived from apocrine glands of anal sac: Biochemical and histomorphometric investigations. Lab Invest 48:428, 1983)

FIG. 59-72 Photomicrograph of biopsy illustrates tumor cell emboli (arrow) of adenocarcinoma arising from apocrine glands of anal sac in lymphatic. (H&E, x 315) (Meuten DJ, Cooper BJ, Capen CC et al: Hypercalcemia associated with an adenocarcinoma derived from the apocrine glands of the anal sac. Vet Pathol 18:454, 1981)
Renal mineralization has been detected histologically in 90% of dogs with pseudohyperparathyroidism associated with apocrine adenocarcinomas of the anal sac, particularly when the ion product for calcium and phosphorus was 50 or greater. (128) Tubular mineralization was most pronounced near the corticomedullary junction (Fig. 59-73) but also was present in cortical and deep medullary tubules, Bowman's capsule, and glomerular tuft. Mineralization was present less frequently in the fundic mucosa of the stomach and endocardium.(128)

Dogs with adenocarcinomas derived from apocrine glands of the anal sac develop hypercalcemia secondary to the production of humoral factor that appears to be distinct from iPTH or prostaglandin E2. (130) It increases bone resorption and the urinary excretion of calcium and phosphorus. The inappropriate serum concentration of 1,25-DiOH-CC for the degree of hypercalcemia in tumorbearing dogs and the rapid decrease following excision of the tumor suggests that the tumor may secrete a substance or substances that alter the activity of the 1-alpha-hydroxylase in the kidney. The persistent hypercalcemia causes secretory inactivity of the parathyroid glands and decreased production of iPTH. Surgical removal of the tumor usually is followed by an increased secretion of iPTH that prevents the development of postoperative hypocalemia. The unknown humoral factor or factors secreted by this unique adenocarcinoma in dogs are different from PTH in that they are not recognized by an immunoassay that detects canine iPTH, neither do they stimulate renal calcium reabsorption. However, the substances do induce osteoclastic osteolysis and hyperphosphaturia, and they maintain normal serum 1,25DiOH-CC levels in spite of the persistent hypercalcemia. Additional investigations into the pathogenesis of hypercalcemia in dogs with apocrine adenocarcinomas may further the understanding of the mechanisms responsible for cancer-associated hypercalcemia in animals and human beings. (130)

HYPERCALCEMIA ASSOCIATED WITH LYMPHOSARCOMA
Lymphosarcoma is the most common neoplasm associated with hypercalcemia in dogs and cats. (152, 213) Estimates of the prevalence of hypercalcemia in dogs with lymphoma vary from 10% to 40%. Peripheral lymph node enlargement may or may not be detected, but there usually is evidence of anterior mediastinal or visceral involvement. It is not completely resolved whether the hypercalcemia develops from the production of humoral substances by neoplastic cells (e.g., PTH-like polypeptides, prostaglandins, osteoclast-activating factor) or from physical disruption of trabecular bone due to frequent marrow involvement, or both.

Heath and co-workers(90) recently reported that serum iPTH levels were subnormal in hypercalcemic dogs with lymphosarcoma and that plasma immunoreactive PGE2 levels did not differ from those of controls. Culture media from normal lymphoid tissue and control media had no effect on release of 45Ca from prelabeled fetal mouse forelimb bones; however, media from tumor tissue increased 45Ca release. These findings suggest that the local production of bone-resorbing factors (e.g., osteoclastactivating factor) is important in stimulating calcium release from bone in certain dogs with lymphosarcoma and hypercalcemia.

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Heath and co-workers(90) recently reported that serum iPTH levels were subnormal in hypercalcemic dogs with lymphosarcoma and that plasma immunoreactive PGE2 levels did not differ from those of controls. Culture media from normal lymphoid tissue and control media had no effect on release of 45Ca from prelabeled fetal mouse forelimb bones; however, media from tumor tissue increased 45Ca release. These findings suggest that the local production of bone-resorbing factors (e.g., osteoclastactivating factor) is important in stimulating calcium release from bone in certain dogs with lymphosarcoma and hypercalcemia.

FIG. 59-74 Photomicrograph of lumbar vertebra of a dog with hypercalcemia and lymphosarcoma Several large osteoclasts (arrowheads) are present in lacunae along a thin bone trabecula. Hyperplastic osteoblasts (arrows) and prominent osteoid seams are present adjacent to the resorptive surfaces. The marrow contains neoplastic lymphoid cells (N). (von Kossa-tetrachrome, x 700) (Meuten DJ, Kociba GJ, Capen CC et al Hypercalcemia in dogs with lymphosarcoma Biochemical, ultrastructural and histomorphometric investigations. Lab Invest 49:553, 1983)
In a recent study dogs with lymphosarcoma and hypercalcemia were reported to have decreased trabecular bone volume and increased osteoclastic osteolysis compared with control dogs and dogs with normocalcemia and lymphosarcoma (Table 59-3) (129) Only dogs with neoplastic cells in bone marrow had increased osteoclastic bone resorption. Dogs with hypercalcemic lymphosarcoma often had osteoclasts on trabecular bone surfaces opposite a surface lined by osteoid and large columnar osteoblasts (Figs. 59-74 and 59-75). Bone surfaces in normocalcemic control dogs were smooth and lined by flattened osteoblasts but only rarely by osteoclasts (Fig. 59-76). Dogs with lymphosarcoma that were normocalcemic did not have increased bone resorption. Hypercalcemic dogs with lymphosarcoma had decreased concentrations of plasma iPTH and serum 1,25-DiOH-CC compared with normocalcemic dogs with lymphosarcoma and control dogs (Fig. 59-77). The plasma concentration of 13,14-dihydro-15-keto-prostaglandin E2 (PG2E M) was elevated (approximately two-fold) significantly in hypercalcemic dogs with lymphosarcoma compared to controls (Table 59-4). Immunoreactive PTH was not detected in lymphosarcoma tissue.(129)

Urine excretion of calcium, phosphorus, and hydroxyproline was increased in hypercalcemic dogs with lymphosarcoma (Fig. 59-78). (129) Light and electron microscopic examination of parathyroid glands revealed inactive or atrophic chief cells and evidence of secretory inactivity in dogs with lymphosarcoma and hypercalcemia. Ultrastructurally, lymphosarcomas were composed of tumor cells with large nuclei and a paucity of cytoplasmic organelles. Lymphosarcoma in dogs with hypercalcemia appeared to produce a bone-resorbing substance that was immunologically distinct from iPTH and 1,25-DiOH-CC. This factor induced the resorption of bone and the mobilization of calcium only when the bone marrow was infiltrated by tumor cells.
Hypoparathyroidism is a metabolic disorder in which either subnormal amounts of PTH are secreted by pathologic parathyroid glands or the hormone secreted is unable to interact normally with target cells. Hypoparathyroidism has been recognized in dogs, particularly in smaller breeds such as schnauzers and terriers.(23,113,131,178) A variety of pathogenic mechanisms can result in an inadequate secretion of PTH. If the parathyroid glands or their vascular supply have been damaged or inadvertently removed during the course of thyroid surgery, the parathyroid glands may be damaged or inadvertently removed during the course of thyroid surgery. If the parathyroid glands or their vascular supply have been damaged, there often is regeneration of adequate functional parenchyma and subsequent disappearance of clinical signs.

Idiopathic hypoparathyroidism in adult dogs usually is associated with diffuse lymphocytic parathyroiditis resulting in extensive degeneration of chief cells and replacement by fibrous connective tissue. In the early stages of lymphocytic
parathyroiditis, there is infiltration of the gland with lymphocytes and plasma cells and nodular regenerative hyperplasia of remaining chief cells (Fig. 59-79). Later, the parathyroid gland is replaced completely by lymphocytes, fibroblasts, and neocapillaries with only an occasional viable chief cell. The lymphocytic parathyroiditis may develop by means of an immune-mediated mechanism, since a similar destruction of secretory parenchyma and lymphocytic infiltration has been produced experimentally in dogs by repeated injections of parathyroid tissue emulsions. (120)

Other possible causes of hypoparathyroidism include invasion and destruction of parathyroids by primary or metastatic neoplasms in the anterior cervical area and trophic atrophy of parathyroids associated with long-term hypercalcemia. The presence of numerous distemper virus particles in chief cells of the parathyroid gland may contribute to the low blood calcium levels in certain dogs with this disease. (201) Agenesis of both pairs of parathyroids is a rare cause of congenital hypoparathyroidism in pups. Certain cases of idiopathic hypoparathyroidism with histologically normal parathyroids in both animals and humans may be due to a lack of the specific enzyme in chief cells that converts the proPTH molecule to the biologically active PTH secreted by the gland (Fig. 59-80).

Pseudohypoparathyroidism is a variant of the syndrome of hypoparathyroidism that has been reported in humans in which target cells in kidney and bone are unable to respond to the secretion of normal amounts of PTH (13,55,58). This is due to a lack of the nucleotide regulatory (N-) protein that couples the hormonereceptor complex to the catalytic subunit of adenylate cyclase in the plasma membrane, resulting in an inability to form cAMP in target cells (see Fig. 59-17). (58) Severe hypocalcemia develops in patients with pseudohypoparathyroidism even though parathyroid glands are hyperplastic (170) and iPTH levels are elevated. (13)

Tetany should be stopped initially by returning blood calcium levels to near normal through the intravenous administration of organic calcium solutions. Long-term maintenance of blood calcium levels in the absence of normal PTH secretion should be attempted by feeding diets that are high in calcium and low in phosphorus and that are supplemented with calcium (gluconate or lactate) and vitamin D3.
Large doses of vitamin D3 (25,000-50,000 or more units/day depending upon the size of the dog) may be required initially to elevate the blood calcium level in hypoparathyroid patients, since the lack of PTH diminishes the rate of formation of the biologically active vitamin D metabolite by the la-hydroxylase system in the kidney (see Fig. 59-28). In order to prevent the development of hypercalcemia and extensive soft tissue mineralization, the clinician should carefully adjust the dosage of vitamin D by frequently determining the serum calcium levels. After adjusting the dose of vitamin D, a 4-to 5-day interval should precede the next blood calcium determination in order to fully assess the effects of the change in vitamin D.

Once the blood calcium level has been returned to the normal range, substantially lower doses of vitamin D may be required for long-term maintenance of blood electrolyte levels. In some dogs only dietary calcium supplementation is required for long-term stabilization of the blood calcium level.(179)

Replacement therapy with either parathyroid extract or PTH derived from heterologous species (such as bovine) is expensive and ineffective on a long-term basis because of the development of antibodies. Synthetic PTH, especially the biologically active amino terminal (1-34) end of the molecule, and the active metabolite of vitamin D 1,25-DiOH-CC may be useful in the treatment of hypoparathyroidism of animals in the near future as has been reported in human patients.(85,95,147)

HYPOCALCEMIC SYNDROMES ASSOCIATED WITH PARTURITION

Considerably less is known about the pathogenesis of hypocalcemic syndromes in the dog and cat than is known about their development in the cow.(119,174) Puerperal tetany is encountered most frequently in the small, hyperexcitable breeds of dogs and occasionally in the cat.(56) The clinical course is rapid and the bitch may proceed from premonitory signs of restlessness, panting, and nervousness to ataxia, trembling, muscular tetany, and convulsive seizures in 8 to 12 hours. (106,166) Hyperthermia frequently is associated with the increased muscular activity, and elevations of body temperature to 107°F are not uncommon.

There is little evidence to suggest that puerperal tetany (eclampsia) in heavily lactating bitches is the result of an interference in PTH secretion. Severe hypocalcemia and often hypophosphatemia develop near the time of peak lactation (approximately 1-3 weeks postpartum), probably as the result of an imbalance between the rates of inflow and outflow from the extracellular calcium pool (Fig. 59-82). It is well known that feeding high-calcium diets to dairy cows in the prepartum period has a provocative effect on the development of hypocalcemic disorders following parturition because of diminished responsiveness of PTH-mediated bone resorption.(14,15) The reduced availability of calcium from skeletal sources leads to an excessive reliance on intestinal calcium absorption.

Functional disturbances associated with hypocalcemia in the bitch are the result primarily of neuromuscular tetany (Fig. 59-83), in contrast with those in the cow in which the principal clinical sign is paresis. Excitation-secretion coupling is maintained at the neuromuscular junction in the bitch with hypocalcemia. Tetany occurs as a result of spontaneous repetitive firing of motor nerve fibers. As a result of the loss of stabilizing membrane-bound calcium, nerve membranes become more permeable to ions and require a stimulus of lesser magnitude to depolarize.

Clinical diagnosis is based on history, clinical signs, and response to therapy in most cases. If laboratory facilities are readily available, demonstration of hypocalcemia with serum calcium levels less than 7 mg/dl confirms the clinical diagnosis. The serum phosphorus level often is lowered to a comparable degree. The blood glucose determination is in the low normal range or decreased as a result of the intense muscular activity associated with tetany.

The slow intravenous administration of an organic calcium solution such as calcium gluconate should result in rapid clinical
improvement and cessation of tetanic spasms within 15 minutes. For most bitches weighing between 5 kg and 10 kg, 5 ml to 10 ml of 10% calcium gluconate will provide sufficient calcium. Intravenous administration should proceed slowly to avoid inducing ventricular fibrillation and cardiac arrest.

Puppies should be removed from the bitch for 24 hours to reduce the lactational drain of calcium. During this period the puppies should be fed a milk substitute or other appropriate diet. If the puppies are mature enough it is advisable to wean them; otherwise, they should be returned to the bitch after the 24-hour period. Although some clinicians advocate the use of corticosteroids in addition to calcium and vitamin D to prevent relapses after the original therapy, there is no logical basis for use of these drugs in such treatment regimens. Since corticosteroids may lower serum calcium levels by interfering with intestinal calcium transport, their real value in the treatment of eclampsia is questionable.

During gestation a good-quality, balanced diet with a calcium:phosphorus ratio of 1:1 or less that provides the required (but not excessive) amounts of calcium may result in a more responsive calcium homeostatic mechanism to meet the markedly increased demands of lactation.

Calcium homeostasis in animals fed balanced or relatively low-calcium diets during gestation appears to be under better control by PTH secretion with the approach of parturition and initiation of the lactational drain (Fig. 59-84). The higher levels of PTH secreted during the prepartal period by an expanded population of actively synthesizing chief cells results in a larger pool of active boneresorbing cells to fulfill the increased needs for calcium mobilization at the critical time near parturition and initiation of lactation.(209) These animals appear to be less susceptible to the influence of decreased calcium absorption and flow into the extracellular pool, which can occur in the immediate postpartum period and during early lactation.

Calcium homeostasis in animals fed a high-calcium diet during gestation appears to be maintained principally by intestinal calcium absorption (Fig. 59-85). This greater reliance on intestinal absorption rather than on PTH stimulated bone resorption probably is a significant factor in the more frequent development of hypocalcemia near parturition in animals fed high-calcium diets prepartum. (14,15)
HYPERCALCITONINISM

Clinical syndromes associated with abnormalities in the secretion of CT are recognized much less frequently than disorders of PTH in both animals and humans. A hypersecretion of CT has been reported in humans, (89,181) bulls, (16,26,28) and laboratory rats (22,47) with medullary (ultimobranchial) thyroid neoplasms derived from C cells. In humans the syndrome often is familial with involvement of many persons in a kindred.

A medullary thyroid carcinoma that contained CT was reported by Leav and co-workers (117) in a dog with a firm mass in the anterior cervical region and chronic watery diarrhea. CT activity was localized to the cytoplasm of tumor cells by immunoenzymatic techniques. Medullary (C-cell) carcinomas may secrete humoral substances other than CT, such as prostaglandins, serotonin, and bradykinin, that result in a wide spectrum of clinical manifestations. (126)

The incidence of C-cell tumors of the thyroid in dogs is uncertain, but it appears to be greater than previously expected. Zarrin (212) reported that 7 of 200 thyroid gland tumors in dogs were derived from C cells. They often are firm on palpation owing to the presence of large amounts of amyloid in the stroma (Fig. 59-86). Thyroid neoplasms of C-cell origin can be readily differentiated ultrastructurally by the presence of numerous membrane-limited secretory granules in the cytoplasm (Fig. 59-87). (26) Small granules of this type are not present in thyroid tumors derived from follicular cells. C-cell tumors in both humans and animals may be associated with the simultaneous occurrence of pheochromocytoma in the adrenal medulla and neoplasms in other endocrine organs. (181,208)

Serum calcium and phosphorus levels in adults with a chronic excessive secretion of CT either remain in the low normal range owing to the relatively slow turnover rate of bone and compensatory increase in PTH secretion or are significantly decreased below normal. Osteosclerotic changes have been reported in animals with this syndrome, but the relationship of long-term excessive CT secretion to the pathogenesis of the skeletal lesions and their occurrence in other animal species is uncertain. Histomorphometric analysis of iliac crest biopsies from human patients with hypercalcitoninemia revealed normal
trabecular bone volume but significant increase in fractional formation and labeled surfaces. The bone formation rate at tissue level was high normal.

HYPOCALCITONISM

Specific disease syndromes resulting from a lack of CT secretion have not been recognized in either humans or animals. However, experimentally thyroidectomized animals are less able than normal animals to handle a high calcium meal and may develop postprandial hypercalcemia (Fig. 59-88). (187)

FIG. 59-88 Hyperealremic response to an oral calcium load in a thyroidectomized animal without an endogenous source of calcitonin compared with that of controls with an intact thyroid gland. (Barlet JP Calcium homeostasis in the normal and thyroidectomized bovine Horm Metab Res 4:300, 1972)

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