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In health, homeostatic control mechanisms maintain serum total calcium (TCa) and ionized calcium (iCa) concentrations within narrow ranges. In addition to providing skeletal support, calcium is a necessary component of numerous vital intra- and extracellular functions. Ionized calcium is required for bone formation and resorption, cell growth and division, membrane transport and stability, enzymatic reactions, nerve conduction, muscle contraction, hormone secretion, hepatic glycogen metabolism, blood coagulation, and numerous other activities. Ionized calcium in the extracellular fluid (ECF) contributes to regulation of cell function by binding to cell membrane calcium-sensing receptors (Brown et al, 1995). Intracellular calcium ions aid in cellular response to agonists by serving as messengers to transport signals received at cell surfaces to the interior (Rasmussen, 1989). Identification of abnormal serum calcium concentrations may help explain clinical signs and may aid in determining cause of illness. Ability to accurately assess concentrations of serum TCa, iCa, parathyroid hormone (PTH), parathyroid hormone–related protein (PTHrP), and vitamin D metabolites has enhanced our capacity to determine the cause of hypocalcemia in most patients.

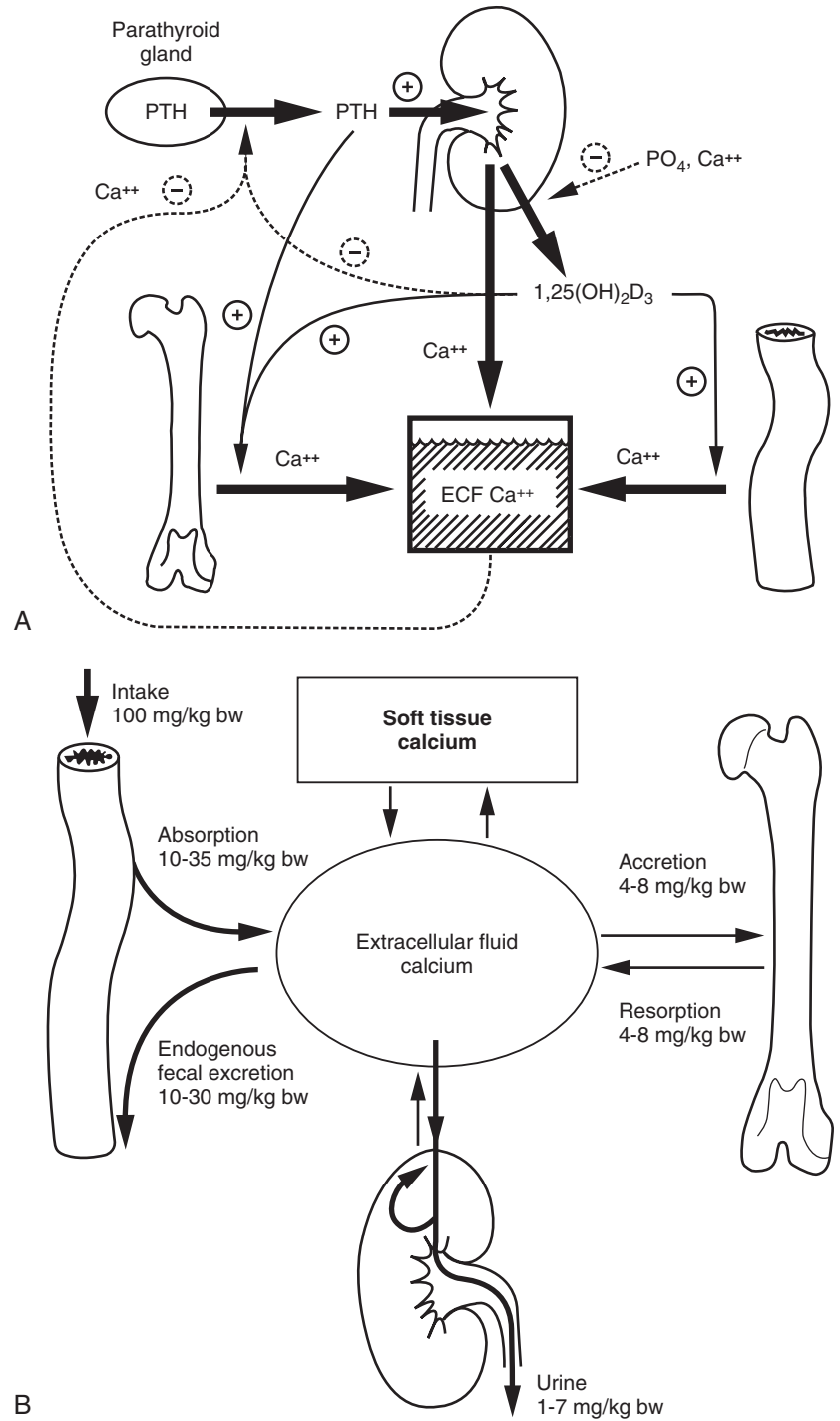
Several historical landmarks in the understanding of parathyroid physiology and maintenance of calcium homeostasis are significant regarding current knowledge of hypocalcemia. Rickets (hypovitaminosis D) was first described in 1645. More than 200 years later (1884), an association was made between thyroidectomy in dogs and cats and the development of clinical hypocalcemia (tetany). In 1891, Gley proved that the parathyroid glands must be removed with the thyroids to produce tetany and that administration of calcium salts following parathyroidectomy successfully prevented tetany. Almost a century later, the amino acid sequence of PTH was determined (Tepperman, 1980). Soon thereafter, the amino acid sequence of a PTHrP, produced by some cancers, was described in both humans and dogs (Broadus et al, 1988; Weir et al, 1988; Yates et al, 1988).



## PHYSIOLOGY OF SYSTEMIC HYPOCALCEMIA

## Maintenance of a Normal Serum Calcium Concentration

The parathyroid glands are exquisitely sensitive to small changes in the serum iCa concentration. The integrated actions of PTH on calcium resorption from bone, distal renal tubular calcium reabsorption, and 1,25-dihydroxyvitamin D<sub>3</sub> (1,25[OH]<sub>2</sub>D<sub>3</sub>) (calcitriol)–mediated intestinal calcium absorption are responsible for the fine regulation of serum iCa concentration. Precision in control is such that plasma iCa concentrations may fluctuate day-to-day by no more than 0.1 mmol/L from their “set” normal value. The “acute” phases of bone resorption and distal renal tubular calcium reabsorption are important components of minute-to-minute calcium homeostasis.



**FIGURE 16-1** **A**, Regulation of extracellular fluid (ECF) calcium concentration by the effects of parathyroid hormone (PTH) and 1,25-dihydroxyvitamin D<sub>3</sub> (1,25[OH]<sub>2</sub>D<sub>3</sub>; calcitriol) on gut, kidney, bone, and parathyroid gland. The principal effect of PTH is to increase the ECF calcium concentration by mobilizing calcium from bone, increasing tubular calcium reabsorption, and, indirectly on the gut, by increasing calcitriol synthesis. The principal effect of calcitriol is to increase intestinal absorption of calcium, but it also exerts negative regulatory control of PTH synthesis and further calcitriol synthesis. **B**, Normal calcium balance showing the major organs that supply or remove calcium from ECF: bone, gut, and kidney. Total calcium (TCa) input into ECF equals TCa leaving the extracellular space. *bw*, Body weight, *Ca<sup>++</sup>*, ionized calcium; *PO<sub>4</sub>*, phosphate. (From Rosol et al.: Disorders of calcium. In DiBartola SP, editor: *Fluid therapy in small animal practice*, ed 2, Philadelphia, 2000, WB Saunders, p 108.)

The effect of PTH on distal renal tubules is quantitatively most important. Adjustments in the rate of intestinal calcium absorption via the calcium-PTH-vitamin D axis require about 24 to 48 hours to become maximal (see full discussion in Chapter 15).

**Defense Against Hypocalcemia**

Physiologic responses to hypocalcemia have been characterized (Fig. 16-1). The three classic challenges to maintaining serum calcium concentrations within the narrow reference range include (1) minor transient challenges, (2) moderate challenges, and (3) severe, prolonged challenges. Hypocalcemia elicits corrective homeostatic responses that are mediated by PTH and vitamin

D. Acute effects occur in seconds to minutes, subacute or moderate effects occur over several hours and may last a few days, and chronic effects occur over days to weeks and even months (Rosol and Capen, 1997; Rosol et al, 2000).

**Minor Transient Hypocalcemia Challenges**

A 12- to 15-hour fast (or consumption of a diet completely deficient in calcium) in a normal mammal requires only subtle hormonal adjustments. If there are slight decreases in serum calcium concentration, slight increases in secretion of preformed PTH quickly take place. With increases in PTH secretion, renal calcium reabsorption and phosphorus excretion are enhanced within minutes, whereas bone mobilization of calcium and phosphorus occurs over

a period of hours (Rosol et al, 2000). Hypocalcemia also decreases the proportion of PTH that is degraded in the parathyroid chief cells, making more hormone available for secretion. By 12 hours, only minor increases in vitamin D synthesis have occurred.

### Moderate Hypocalcemia Challenges

Moderate reductions in dietary calcium intake, or other causes of hypocalcemia, initiate a series of adjustments in calcium metabolism beyond those documented with minor decreases. The result is a new steady state of PTH and vitamin D (calcitriol) synthesis and secretion. Moderate increases in the secretion rate of PTH result in (1) increased calcium reabsorption from distal renal tubules, (2) increased mobilization of calcium and phosphorus from bone, and (3) increased synthesis of  $1,25(\text{OH})_2\text{D}_3$  (calcitriol). Calcitriol teams with PTH in bone resorption and increases the efficiency of calcium and phosphorus absorption from the intestine (see Fig. 16-1). The increased concentrations of circulating PTH enhance renal excretion of phosphorus, thereby compensating for the increased amounts of phosphorus mobilized from bone and absorbed from the intestine. In this new steady state, the serum calcium concentration returns to normal, the serum phosphorus concentration is unchanged or slightly reduced, and a state of mild secondary hyperparathyroidism with enhanced intestinal mineral absorption exists. Initial requirement of calcium mobilization from skeleton is largely replaced by the enhanced absorption of calcium from intestine.

### Severe and Prolonged Hypocalcemia Challenges

Lactation and chronic kidney disease (CKD) with decreasing ability to excrete phosphorus represent two common examples of severe challenges to calcium homeostasis. These issues cannot be corrected by processes known to occur within minutes or hours. Assuming the four parathyroid glands are intact and functional, the previously described sequence of events resulting from “minor” and “moderate” challenges caused by hypocalcemia ensue. However, continuing losses of calcium into milk associated with lactation (for example) prevents complete compensation by the usual calcium-PTH-vitamin D absorption axis. Physiologic compensation in this setting includes (1) a maximal PTH secretion rate of approximately five times normal, (2) a maximal rate of vitamin D synthesis, and (3) initiation of maximal “rapid” and “late” phases of bone resorption in response to the combined effects of PTH and vitamin D.

Over days, weeks, or even longer periods of hypocalcemia, increases in PTH secretion (beyond those already described) are achieved largely via hyperplasia of parathyroid gland chief cells (Roth and Capen, 1974; Rosol et al, 2000). Hypocalcemia directly stimulates the growth of parathyroid cells. This effect occurs regardless of vitamin D metabolite concentrations (Li et al, 1998; Malloy et al, 1999, Marx, 2000). With hyperplasia of parathyroid chief cells, PTH secretion rates approach 10 to 50 times normal. These circulating concentrations of PTH result in recruitment of an increasing osteoclast population and the incorporation of substantial bone surfaces into the resorption process. In the final steady state, serum calcium concentrations are maintained at the expense of the skeleton, and significant bone losses ensue. Thus, the integrity of skeletal mineral homeostasis is sacrificed in an attempt to compensate for systemic mineral deficits (Broadus, 1981).

## Physiology of Hypocalcemia Caused by Hypoparathyroidism

### Definition

A pair of parathyroid glands is located in close proximity to each thyroid lobe in healthy individuals. Hypoparathyroidism, an

### BOX 16-1 Signs Noted by Owners of Dogs and Cats with Primary Hypoparathyroidism\*

#### Common

Muscle tremors, twitching, fasciculations  
 May be focal or diffuse; often worse with activity or excitement  
 Facial rubbing (possible paresthesia)  
 Intense biting or licking their paws (possible paresthesia)  
 Oral “chomping” (possible paresthesia)  
 Generalized seizures (convulsions, “fits”)  
 Rear leg muscle cramping, pain, or stiff gait  
 Can occur in forelegs, but rear leg signs are more common  
 Behavior changes  
 Restless, nervous, anxious  
 Aggressive, biting  
 Hypersensitive (reluctant to be petted, touched, or handled)  
 Poor appetite, weight loss  
 Less active, listless

#### Uncommon

Weakness  
 Anorexia, vomiting, diarrhea  
 Ataxia  
 Pyrexia  
 Prolapsed third eyelid and/or ptialism (cats)

#### Rare

No signs observed  
 Circling  
 Respiratory arrest or death

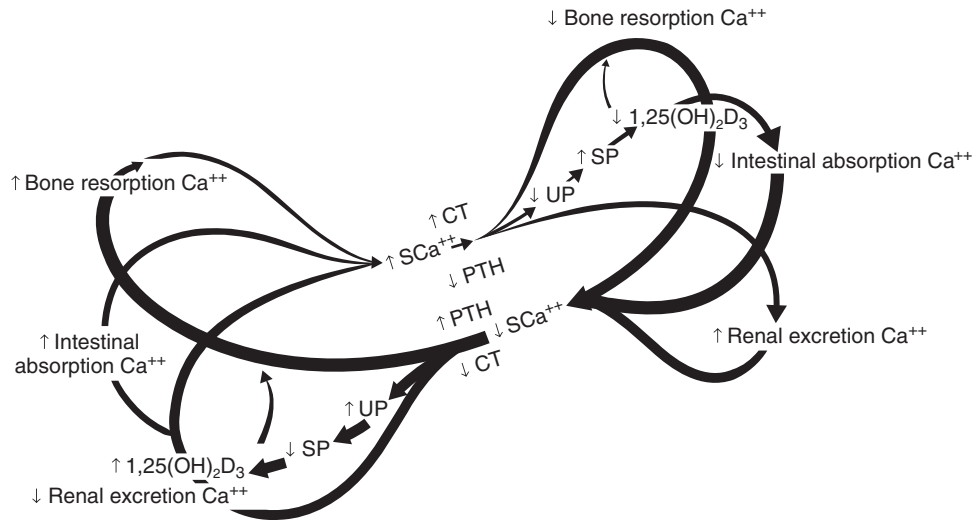
\*Note: Most signs are seen episodically.

uncommon endocrine disorder, develops as a result of an absolute or relative deficiency in synthesis and secretion of PTH, the sole product of the parathyroid glands. PTH deficiency invariably leads to hypocalcemia, usually defined as a serum TCa concentration less than about 9 mg/dL and/or an iCa less than about 1.0 mmol/L in dogs. Values defining hypocalcemia in cats are slightly lower. In dogs, the serum TCa concentration tends to underestimate the iCa. In cats, the serum TCa concentration tends to overestimate the iCa concentration (Schenck and Chew, 2005; Schenck et al, 2012). Signs of hypocalcemia are similar, regardless of cause (Box 16-1). Once hypocalcemia is identified, clinicians are encouraged to determine cause in order to formulate appropriate short- and long-term treatment strategies and a prognosis.

### Initial Physiologic Alterations

The pathologic and biochemical consequences of parathyroid gland removal or loss of a critical number of parathyroid chief cells secondary to immune-mediated destruction (a less common condition) can be appreciated by referring to the “butterfly” diagram (Fig. 16-2). In this condition, the right limbs of the three feedback loops predominate with (1) decreased bone resorption; (2) decreased renal phosphate excretion, increased serum phosphate, decreased calcitriol and intestinal absorption of calcium; and (3) excess renal excretion of calcium relative to the prevailing circulating concentration. Typically, there is hypocalcemia and hyperphosphatemia if dietary phosphate intake has been normal.

All changes discussed can be explained by a PTH deficiency. The processes that are *not* taking place include (1) mobilization of calcium and phosphate from the skeleton via increased



**FIGURE 16-2** Regulation of calcium homeostasis. Three overlapping control loops interlock and relate to one another through the level of blood concentrations of ionic calcium, parathyroid hormone (PTH), and calcitonin (CT). Each loop involves a calciotropic hormone target organ (bone, intestine, or kidney). The limbs on the left depict physiologic events that increase the blood serum concentration of ionic calcium ( $\text{SCa}^{++}$ ), and the limbs on the right depict physiologic events that decrease this concentration.  $1,25(\text{OH})_2\text{D}_3$ , 1,25-dihydroxyvitamin D<sub>3</sub> (calcitriol); SP, serum phosphorus; UP, urine phosphorus. (Modified and reproduced with permission from Arnaud and Kolb, 1991.)

osteoclast activity on bony surfaces, (2) retention of calcium and enhanced excretion of phosphate by kidneys as a direct effect that PTH has on the distal convoluted tubule and its indirect effects on the thin ascending loop of Henle, (3) increased absorption of calcium and phosphate from the intestine, and (4) accelerating the formation of the active metabolite of vitamin D in the kidney by both inducing synthesis and by activating  $1\alpha$ -hydroxylase in mitochondria of renal epithelial cells of proximal convoluted tubules (Skelly, 2012). Activation of vitamin D, under the control of PTH, increases intestinal absorption of calcium and phosphate, a process diminished without PTH (Skelly, 2012).

PTH also stimulates release of magnesium from bone, enhances magnesium uptake through the intestinal wall, and supports renal tubular magnesium resorption. An initial magnesium diuresis without significant change in plasma magnesium concentration has also been observed in hypoparathyroidism. In spite of dramatic changes in the concentrations of serum calcium and phosphate secondary to PTH deficiency, bone mineralization is normal, bone resorption rates decline, and bone formation declines only slightly. Ultimately, bones are slightly more dense than normal in humans with hypoparathyroidism and, in long-standing cases, osteosclerosis may be seen.

### Peripheral Neuromuscular Observations

Although all cells are affected by deficiencies in  $\text{iCa}$ , clinical signs are typically associated with the neuromuscular system, simply because alteration in the function of these cells results in obvious visible abnormalities. Ionized calcium is involved in the release of acetylcholine during neuromuscular transmission and is essential for muscle contraction. Ionized calcium stabilizes nerve cell membranes by decreasing their permeability to sodium.

When the ECF concentration of  $\text{iCa}$  progressively declines below normal, the nervous system, in a parallel manner, becomes progressively more excitable, a result of increases in neuronal membrane permeability. This increased excitability occurs both in the central nervous system (CNS) and in peripheral nerves. With severe hypocalcemia, nerve fibers begin to discharge spontaneously, initiating

nerve impulses that pass to the peripheral skeletal muscles, where they elicit tetanic contractions (“cramps” or “tetany”).

*Tetany* is defined as a random stiffening or tightening of various muscle groups. It is reasonable to assume that nerve fibers are particularly sensitive to decreases in calcium in part because signs associated with the nervous system precede others, and because those signs are so acute, dramatic, and obvious. Dogs with tetany that had previously undergone spinal cord transection had signs above but not below the transection site, suggesting that tetany is primarily initiated in the CNS (Arnaud and Kolb, 1991). Acute hypocalcemia can be fatal secondary to respiratory muscle paralysis, decreased myocardial contractility, hypotension, or from persistent seizure activity.

Hypocalcemia, based on the serum TCa concentration, is a relatively “common” laboratory abnormality, being observed on more than 13% of serum biochemical profiles in dogs in one report (Chew and Meuten, 1982). If the diagnosis of hypocalcemia is based on the serum  $\text{iCa}$  concentration, the prevalence was 31% (Schenck and Chew, 2005). Severe hypocalcemia and/or clinical tetany are rarely observed unless the decreases in serum calcium concentration are severe. For example, tetany is likely present when the serum TCa concentration declines to or below 6 to 7 mg/dL, or the serum  $\text{iCa}$  concentration declines to less than about 0.7 mmol/L. Concentrations slightly higher than these may be worrisome but are usually clinically silent. Serum TCa concentrations below 4 mg/dL for any length of time are frequently fatal.

Although dogs with untreated hypoparathyroidism consistently have obvious decreases in serum TCa concentrations, the onset of *clinical* tetany is not entirely predictable. We tend to associate clinical signs with serum TCa concentrations below 6 to 7 mg/dL and serum  $\text{iCa}$  concentrations below about 0.7 mmol/L. It is possible for a dog to have clinical signs with serum concentrations slightly above these values, whereas others have no discernible signs despite extremely low calcium concentrations. Physical activity and/or excitement have a role in development of clinical tetany. A quiet dog is less likely than an active dog to exhibit signs. Individual variation, however, is the only consistent feature of this condition. Calcium concentrations within cerebrospinal

fluid (CSF) do not decrease as rapidly as serum concentrations in parathyroidectomized dogs. Although the serum TCa concentration decreases as much as 27% (iCa, 28%) within 24 hours of surgery, decreases in CSF TCa concentration are less than 5% and in iCa less than 10% (Wysolmerski and Insogna, 2012). Rapid equilibrium does not occur between plasma and CSF iCa. Thus the concentration of calcium ions in the CSF is relatively constant despite large fluctuations in plasma. Conversely, relatively small decreases in CSF calcium concentration may result in dramatic clinical abnormalities.

When serum calcium concentrations decline to subnormal levels but not low enough to cause obvious clinical tetany, a physical state of “latent tetany” may exist. This condition is described as one in which an individual can progress from appearing clinically normal to becoming “tetanic” with minimal stimulation. Such a condition can be demonstrated to be present in people by weakly stimulating a nerve and observing an abnormal response (see Physical Examination). Another example of tetany lurking under the surface (being “latent”) can be demonstrated when a human with latent tetany hyperventilates. The resulting subtle alkalization of the body fluids can decrease the iCa concentration with increased nerve irritability, causing overt signs of tetany. It is assumed that similar situations develop in hypocalcemic dogs or cats. Some owners have described that sudden excitement, activity, or petting may unpredictably cause muscle cramping, lameness, facial rubbing, pain, irritability, or aggressive behavior. These signs usually disappear quickly, only to recur sporadically. In addition, the non-tetanic severely hypocalcemic pet is usually described by the owner as having a change in personality. Such dogs are often observed to have a poor appetite and to be irritable, non-playful, and slow-moving. Frequently, owners report that their dog “seems to be in pain.” Such signs are vague, but after hypocalcemia is diagnosed, the clinical signs are most consistent with those of “latent” tetany.

### The Heart

Calcium has both positive inotropic and chronotropic cardiac effects (Milnor, 1980). Hypocalcemia prolongs action potential duration in cardiac cells. This may result in decreased force of myocardial contraction (negative inotropic effect) and, in severe cases, bradycardia (negative chronotropic effect).

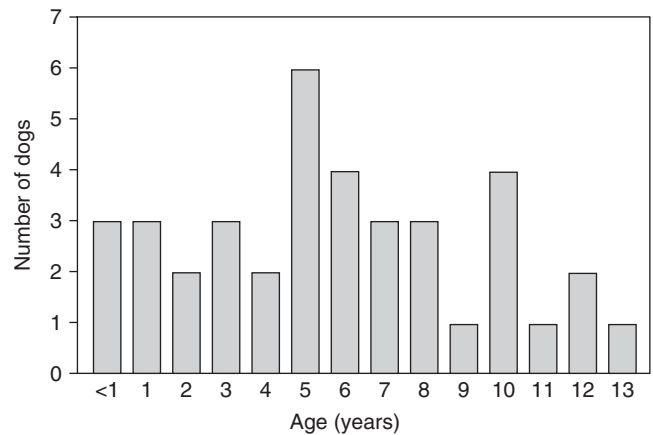
### Miscellaneous Physiologic Effects of Hypocalcemia

Because calcium serves as a cofactor in both the intrinsic and extrinsic blood clotting systems, coagulopathies are theoretically possible in hypocalcemia. In hypocalcemic humans, disorders less common and less dramatic than tetany may be encountered, including (1) basal ganglia calcification and occasional extrapyramidal neurologic syndromes; (2) papilledema and increased intracranial pressure; (3) psychiatric disorders; (4) skin, hair, and fingernail abnormalities; (5) candidal infections; (6) inhibition of normal dental development; (7) lenticular cataracts; (8) intestinal malabsorption; and (9) increased serum concentrations of creatine phosphokinase and lactic dehydrogenase (Arnaud and Kolb, 1991; Wysolmerski and Insogna, 2012).

## CLINICAL FEATURES: NATURALLY OCCURRING HYPOPARATHYROIDISM IN DOGS

### Signalment

The records from 57 dogs seen at University of California, Davis (UC Davis) with naturally occurring primary hypoparathyroidism (includes Bruyette and Feldman, 1988) and from an additional



**FIGURE 16-3** The ages of 38 dogs at the time of primary hypoparathyroidism diagnosis. These include 25 dogs in our series, as well as 4 dogs from Kornegay and colleagues (1980), 1 dog from Crawford and Dunstan (1985), 6 dogs from Sherding and colleagues (1980), 1 dog from Meyer and Tyrrell (1976), and 1 dog from Burk and Schaubhut (1975).

BREED	NUMBER OF DOGS (TOTAL = 87)*
Toy Poodle	13
German Shepherd dog	9
Labrador Retriever	8
Miniature Schnauzer	8
Terrier breeds	8
St. Bernard	4
Beagle	4
Dachshund	4
Golden Retriever	3
Chihuahua	2
Boxer	2
Breeds represented once each	12
Mixed breed	10

\*Includes 57 dogs from our UC Davis series, 17 dogs from Russell and colleagues (2006), 6 dogs from Sherding and colleagues (1980), 4 dogs from Kornegay and colleagues (1980), 1 dog each from Burk and Schaubhut (1975), Meyer and Tyrrell (1976), and Crawford and Dunstan (1985).

30 dogs with hypoparathyroidism in the veterinary literature were reviewed. Hypoparathyroidism can be recognized in dogs of any age; the youngest dog being 6 weeks and the oldest being 14 years (Fig. 16-3). The average age was 5.4 years. Of 57 dogs in the ongoing UC Davis series, about half were female; and in a published series of 735 hypoparathyroid dogs, 62% were female (Refsal et al, 2001; Skelly, 2012). The breeds most frequently identified as having primary hypoparathyroidism were Toy Poodles, Labrador Retrievers, Miniature Schnauzers, German Shepherd dogs, various terrier breeds, and mixed breed dogs (Table 16-1). In a report on 17 dogs from Australia with naturally occurring hypoparathyroidism, St. Bernards, Chihuahuas, Jack Russell Terriers, and West Highland White Terriers were each represented more than

once (Russell et al, 2006). As anticipated from the various breeds described, body weights vary greatly.

## History

### *Duration of Illness*

As described by their owners, the 57 dogs in the UC Davis series commonly developed an abrupt onset of intermittent neurologic or neuromuscular disturbances (see Box 16-1). About half of the owners noted that signs were initiated or worsened by excitement, exercise, or petting. The hypocalcemia-related signs had been observed for periods of only about 24 hours in some dogs to as long as 12 months in others. Only a minority of the 57 dogs had signs for longer than 14 days before veterinary care was sought. Some dogs with prolonged histories had been symptomatic for 1 to 12 months, but some of these had been diagnosed and treated for nonspecific seizure disorders. The dogs with signs for more than several days invariably had neuromuscular disturbances that became progressively more frequent and violent despite administration of anticonvulsant medication.

### *Early Signs*

Clinical signs observed by owners that resulted in their seeking veterinary care varied (see Box 16-1). The most common reason for seeking veterinary care was apparent grand mal convulsions (discussed in the next section). Owners also sought veterinary care after seeing apparent muscle cramping, tonic spasm of leg muscles, or pain. Focal muscle twitching, tremors, fasciculations, or trembling were commonly seen as were stiff, hunched, or rigid gait. One of the first owner observations (retrospectively) was that their pet appeared abnormally “nervous” or “anxious.” Owners also commonly described their pets as having poor appetites or as being “slow,” “less playful,” or “not as friendly.” A few were noted to have had episodes of vomiting or diarrhea. Aggressive behavior was seen in a majority of affected dogs and is assumed to be caused by pain associated with muscle cramping. The muscle cramping could be elicited by petting, possibly explaining why dogs that previously suffered acute pain from such a mild stimulus are reluctant to be handled. This likely also explains the observations of dogs appearing to be less friendly or for their change in behavior or personality. Also retrospectively, owners noted that their dogs would intensely use their paws or the ground to rub their muzzles (discussed later) or they would intensely lick or chew their paws. Although common, such signs were usually not mentioned by owners until specifically questioned or were noted as having disappeared after treatment had been instituted. In one study, “mandibular champing,” possibly a reflection of masticatory muscle cramping or facial paresthesias, was observed by almost half the owners (Russell et al, 2006).

### *Seizures*

Grand mal convulsions were observed by owners of 49 out of 57 dogs with naturally occurring primary hypoparathyroidism. As previously reported, most of these dogs had typical-appearing grand mal convulsions. However, some dogs had atypical seizures in that the dogs either did not appear to lose consciousness or were neither urinary nor fecal incontinent during the episode. Of interest was the incidence of seizure activity seen by veterinarians. Of the 57 dogs in our series, 45 were observed by a veterinarian to have seizures. This frequency of observing seizure-like episodes represents a much higher incidence of veterinarian-witnessed neuromuscular disorders than expected with idiopathic epilepsy. Also, as noted by other investigators (Sherding et al, 1980; Russell et al, 2006; Skelly, 2012), muscle tremors during some episodes began in one limb and gradually became generalized and more violent, finally culminating

in a generalized seizure. In some dogs, seizure episodes were as brief as 30 to 90 seconds; in others, they lasted for more than 30 minutes. Most, but not all, of the generalized seizures lasted less than 3 minutes and spontaneously abated.

### *Miscellaneous Signs*

As can be seen in Box 16-1, many owners observed overlapping neurologic and neuromuscular signs. Retrospectively, each dog suffered bouts of significant hypocalcemic tetany as a part of their initial signs. Some vague signs included panting, ataxia, circling, episodic weakness, complete anorexia, vomiting, diarrhea, and weight loss. Veterinarians occasionally noted an increase in body temperature. All owners observed some clinical signs. Although hypocalcemia was almost always considered a serendipitous finding on laboratory testing, it remains an abnormality that “made sense” after being demonstrated. Death remains a potential sequela of untreated hypocalcemia.

### *Facial Rubbing*

Thirty-five out of 57 dogs in our series were observed to paw their muzzles, eyes, and ears and/or to rub their muzzles on the ground. Additionally, most owners noted their dogs intensely licking or chewing at their paws. These signs of pain are thought to be associated with masseter and temporal muscle cramping caused by hypocalcemia, or they could result from a “tingling” sensation around the mouth or at the distal extremities. Classic signs of hypocalcemia in humans include “paresthesias,” which are defined as numbness and tingling that often occur around the mouth, fingers, and/or toes (Arnaud and Kolb, 1991).

### *Hyperventilation*

Because of the acute anxiety or pain associated with tetany, hypoparathyroid humans (and presumably dogs) may episodically hyperventilate and secrete increased amounts of epinephrine. Hyperventilation may lead to hypocapnia and alkalosis, either of which can worsen hypocalcemia by causing increased binding of ionic calcium to plasma proteins. Hyperventilation in healthy people can decrease serum iCa concentration (Arnaud and Kolb, 1991).

### *Episodic Nature of the Illness*

All neurologic and neuromuscular signs in hypocalcemic dogs tend to be episodic, often followed by asymptomatic periods. The periods of clinical well-being lasts minutes to days or even weeks. Tetany was rather unpredictable, although retrospectively, these signs were more frequent or inducible with exercise (even slow or short “leash” walks), excitement, petting (possible latent tetany), or stress (being taken to the veterinarian).

All of the dogs were persistently hypocalcemic but displayed tetany only episodically. This illustrates some adaptation in each to hypocalcemia, suggesting that minor alterations in calcium concentration could result in profound clinical signs. One dog in our series had been diagnosed as having primary hypoparathyroidism but remained untreated for almost a year. This dog was persistently hypocalcemic but had only one or two clinically obvious hypocalcemic episodes monthly. In spite of this tragic history, the dog was relatively well, suffering primarily from a poor appetite and weight loss.

## Physical Examination

### *General Observations*

Other than signs related to hypocalcemia, dogs with primary hypoparathyroidism usually do not have additional physical examination abnormalities. Physical examination findings on hypoparathyroid dogs varied (Table 16-2). Retrospectively, most

TABLE 16-2 INITIAL PHYSICAL EXAMINATION FINDINGS IN 57 DOGS WITH NATURALLY OCCURRING PRIMARY HYPOPARATHYROIDISM

SIGN	NUMBER OF DOGS	%
Seizure or “in tetany”		
Initial examination	23	40
Total: First 4 days of hospitalization	41	72
Intense rubbing or pawing at face	35	61
Intense biting or licking at paws	34	60
Fever	31	54
Tense, splinted abdomen	30	53
Stiff gait	29	51
Thin	25	44
Generalized muscle fasciculations	24	42
Growling	23	40
Cardiac abnormalities		
Tachyarrhythmia	14	25
Muffled heart sounds/weak pulse	4	7
Neurologic examination difficult to complete and/or interpret	37	65
Cataracts	14	25
No abnormality	6	10

dogs were “in tetany” on presentation, an observation made after review of serum biochemical results. Forty-eight of the 57 dogs were referred for evaluation of hypocalcemia. Thus, the veterinarian examining such a dog was “primed” to observe tetany. Observations (almost all of which are noted in Table 16-2), although impressive to the uninitiated, may not have been made if the history not alerted the clinician to the underlying condition.

A minority of dogs appeared healthy, despite their previous history of neurologic or neuromuscular disorders. A number of dogs were thin and/or growled when examined. It is accepted that the growling dogs were in pain or were anticipating that handling would cause them pain, because almost all of them became friendly after resolution of their hypocalcemia. Cardiac abnormalities were suspected in 18 dogs on initial examination. These abnormalities consisted of paroxysmal tachyarrhythmias suspected in 14 dogs and muffled heart sounds with weak pulses suspected in four dogs.

#### Spontaneous Neurologic and Neuromuscular Signs

On initial examination, 51 of the 57 dogs with primary hypoparathyroidism had at least one abnormality that could be attributed to hypocalcemia. Most of these dogs had a convulsion or were considered to be “in tetany.” Others growled, were extremely tense or “rigid,” or had “splinted” abdomens, stiff gaits, and/or muscle fasciculations. Virtually every time that a dog growled, the owner would comment that this “new behavior” had been noticed at home as well. Fever was noted in 31 of the 57 dogs.

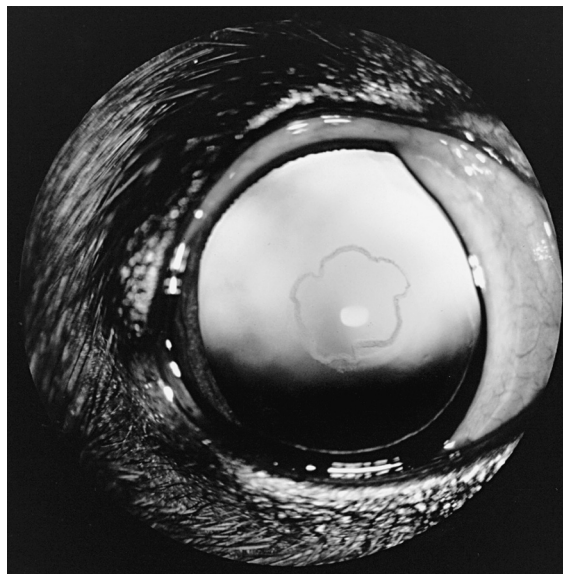


FIGURE 16-4 Lenticular cataract in the lens of a hypoparathyroid dog.

Twenty-three dogs were observed to have a convulsion during their initial examination, and an additional 18 had at least one convulsion observed within the first 96 hours of hospitalization. Complete neurologic examinations were attempted on 37 dogs revealing a variety of problems—the most common of which was that “the dog was too tense and nervous to complete a thorough evaluation.” Retrospectively, these dogs were recognized to have been in tetany. Other findings included brisk reflexes, absent reflexes, clonus, and/or pain. Because these dogs were in latent or active tetany, their neurologic examinations were difficult to interpret until hypocalcemia was identified.

#### Induced Neurologic or Neuromuscular Signs

Two physical tests are used in humans as aids in diagnosing latent tetany (hypocalcemia). *Chvostek's sign* is elicited by tapping the facial nerve just anterior to the ear lobe. A positive sign is one of extensive facial muscle twitching or muscle contraction. *Trousseau's sign* is induced with a blood pressure cuff inflated above systolic blood pressure for at least 2 minutes. A positive response consists of carpal spasm, at least 5 to 10 seconds in duration, after release of the cuff or while the cuff is inflated (Arnaud and Kolb, 1991; Meininger and Kendler, 2000). Although such tests are not described for dogs suspected of being hypocalcemic, episodes of intense muscle spasm have been stimulated when testing reflexes.

#### Cataracts

Posterior lenticular cataract formation is the most common permanent sequela of hypoparathyroidism in humans (Arnaud and Kolb, 1991). Such cataracts are thought to require 5 to 10 years before visual impairment occurs. Successful treatment of hypocalcemia generally halts their progression (Arnaud and Kolb, 1991). Cataracts were first described in two hypoparathyroid dogs (Kornegay et al, 1980) and have been seen in 14 of the 57 dogs in our series. No dog was blind. Opacities are randomly distributed along the lens fibers and are separated from the capsule by an intervening zone of normal thin cortex (Fig. 16-4). Other ocular signs not yet reported in dogs include papilledema, optic neuritis, conjunctivitis, keratitis, blepharospasm, loss of lashes, strabismus, nystagmus, and anisocoria.



**CLINICAL FEATURES: NATURALLY OCCURRING HYPOPARATHYROIDISM IN CATS**

Hypocalcemia in cats, like dogs, is seen with hypoalbuminemia, although iCa concentrations are typically within reference limits. Hypocalcemia in cats has also been associated with renal failure, intestinal malabsorption, acute pancreatitis, lactation, and ethylene glycol toxicity. The most common iatrogenic cause of hypocalcemia is removal of all parathyroid glands as a complication of cervical surgery, such as bilateral thyroidectomy for hyperthyroidism. Surgical techniques have improved, and this complication is now uncommon. However, parathyroid damage or removal is a risk with any cervical surgery involving both sides of the trachea. Less frequently, hypocalcemia may occur after administration of phosphate containing enemas.

Naturally occurring primary hypoparathyroidism in cats is encountered less often than in dogs. Nine cats with naturally occurring primary hypoparathyroidism have been reported in the veterinary literature, and an additional seven have been seen at UC Davis. These 16 cats, 6 months to 11 years of age and of various breeds, include 11 males. The clinical course of each cat was characterized by an abrupt or gradual onset of intermittent neurologic or neuromuscular disturbances, which included focal or generalized muscle tremors, seizures, ataxia, stilted gait, disorientation, and weakness. Other concerns included lethargy, anorexia, panting, and raised nictitating membranes. Less commonly, dysphagia, pruritus, and ptyalism were observed. Physical examination findings included depression, weakness, fever, hypothermia, bradycardia, and mild to severe dehydration. Lenticular cataracts were detected in several of these cats (Forbes et al, 1990; Parker, 1991; Peterson et al, 1991; Bassett, 1998; Ruopp, 2001; Gunn-Moore, 2005; Skelly, 2012).



**DIAGNOSTIC EVALUATION: ROUTINE STUDIES**

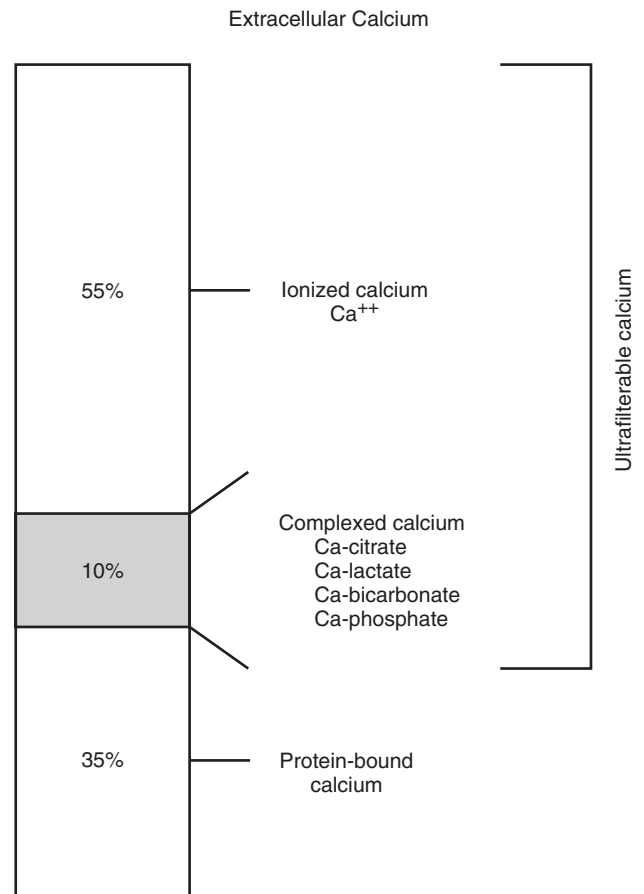
**Calcium**

Hypocalcemia was a serendipitous finding in each of our 57 dogs with primary, naturally occurring, hypoparathyroidism. All had a history consistent with a behavioral, neurologic, muscular, or neuromuscular disorder. A complete blood count, urinalysis, and serum chemistry profile were considered necessary aids in attempting to determine the cause of abnormalities noted by owners and the veterinarian. Severe hypocalcemia was suspected in few but noted in all (Table 16-3). Because severe hypocalcemia (serum calcium concentration < 7.0 mg/dL) is an unusual finding in our clinic population, this parameter was invariably rechecked with a separate blood sample. Actually, each dog had its serum calcium concentration monitored three to five times during the first 72 hours of hospitalization as therapy was begun. Persistent hypocalcemia was

uniform. No dog had a serum calcium concentration greater than 6.1 mg/dL on any assessment until therapy began to have an effect. After serum iCa concentrations became routinely available, each of these results was also profoundly low (see Table 16-3).

**“Corrected” Serum Calcium Values**

Calcium in plasma or serum exists in three fractions: ionized (free calcium), complexed or chelated (bound to phosphate, bicarbonate, sulfate, citrate, and lactate), and protein-bound (Fig. 16-5). In general, between 50% and 60% of TCa is in the “ionized” form in normal animals. In clinically normal dogs, protein-bound, complexed, and iCa account for approximately 34%, 10%, and 56% of the serum TCa, respectively (Schenck et al, 1996). Laboratories generally measure these components together and report them as



**FIGURE 16-5** Serum total calcium (TCa) concentration consists of ionized (free), complexed, and protein-bound fractions. Ca, Calcium; Ca<sup>++</sup>, ionized calcium.

**TABLE 16-3 PERTINENT FINDINGS IN 57 DOGS (30 FEMALE, 27 MALE) WITH PRIMARY HYPOPARATHYROIDISM**

	AGE (YEARS)	DURATION OF SIGNS (DAYS)	TOTAL CALCIUM (mg/dL)	IONIZED CALCIUM (mm/L)	SERUM PHOSPHATE (mg/dL)	PLASMA MAGNESIUM (mg/dL)	BLOOD UREA NITROGEN (mg/dL)	PARATHYROID HORMONE (pmol/L)
Result ranges	0.5-14	1-360	3.4-6.1	0.2-0.6	4.9-10.2	1.2-2.3	8-51	0.05-3.4
Mean values	5.4	26	4.6	0.3	7.7	1.9	15	0.5
Median values	4.0	3	4.3	0.3	7.9	1.8	17	0.6
Reference ranges	—	—	8.9-11.4	1.1-1.4	3.0-4.7	1.8-2.4	12-28	2-13



a TCa value. Ionized calcium is the biologically active component, and protein-bound calcium serves as a “reservoir” or storage pool for the ionized fraction. However, changes in serum concentration of albumin and globulins may alter the measured serum TCa concentration without altering iCa levels. Despite an alteration in the total amount of serum calcium resulting from hyperproteinemia or hypoproteinemia, the biologically active iCa concentration remains stable because of homeostatic mechanisms. Any dog or cat with hypocalcemia should also have its serum albumin assessed (Chew and Meuten, 1982).

Two formulas were developed for use in dogs to account for changes in the reported serum calcium value attributed to changes in serum protein values (Meuten et al, 1982). The formulas were thought to be of significant value prior to routine availability of iCa assays. These formulas are:

$$\text{corrected TCa (mg/dL)} = \text{measured TCa (mg/dL)} - \text{albumin (g/dL)} + 3.5$$

or

$$\text{corrected TCa (mg/dL)} = \text{measured TCa (mg/dL)} - [0.4 \times \text{total protein (g/dL)}] + 3.3$$

Hypoalbuminemia is a common explanation for apparent hypocalcemia. However, it is the least important, causes no hypocalcemia-related clinical signs, and is associated with only mild changes from reference ranges. Although correction to normal limits implies that the ionized fraction is “normal,” the ionized fraction may yet be low. These formulas, developed more than three decades ago, were derived from serum albumin concentrations obtained with analytical methods no longer employed by modern automated analyzers. The reference range for serum albumin concentration reported then (Meuten et al, 1982) was considerably lower than those reported now. At the time, a positive correlation was noted, but only 33% of the variability in serum TCa concentration could be attributed to serum albumin concentration, and only 17% of the variability could be attributed to serum total protein. There was no association in cats between serum total protein and serum calcium concentrations, and only 18% of the variability in TCa concentration could be attributed to albumin concentration (Flanders et al, 1989). In another study, only 17% and 29% of the variability in serum TCa concentration in dogs and cats, respectively, could be attributed to serum albumin concentration (Bienzle et al, 1993). For these reasons, plus the availability of serum iCa results via commercial laboratories, these correction formulas are no longer used (Rosol et al, 2000).

### Serum Phosphorus

The most consistent laboratory findings among the dogs with primary hypoparathyroidism in our series were the presence of both hypocalcemia and hyperphosphatemia. Most dogs with primary hypoparathyroidism have a serum phosphorus concentration higher than the TCa concentration on the same sample. All had had blood urea nitrogen (BUN), total protein, and serum albumin concentrations within the reference range. The absence of an absolute hyperphosphatemia in some of the dogs can be explained in part by the wide variation in what is considered “normal” by veterinary laboratories. Such reference ranges may include results of all ages, and readers are reminded that immature pets typically have a relative hyperphosphatemia. Their serum phosphorus concentrations gradually decline until puberty, at which time the levels remain relatively constant. Inappetent hypoparathyroid dogs were noted to have higher mean phosphate concentrations than those with adequate food intake (Russell et al, 2006).

### Remainder of the Serum Chemistry Profile

The diagnosis of primary hypoparathyroidism in the dog is usually made “by exclusion.” In other words, clinicians develop a complete differential diagnosis for hypocalcemia and then attempt to rule each condition in or out. In this context, a complete database is invaluable when assessing any nonlactating hypocalcemic animal. It has been suggested that hypoparathyroidism is the only possible diagnosis when one encounters a combination of low serum calcium concentration, increased serum phosphorous concentration, normal renal function, and a decreased (relative or absolute) serum PTH concentration (Rosol et al, 2000).

There are three potential causes of hypoparathyroidism: suppressed secretion of PTH without parathyroid gland destruction (Dhupa and Proulx, 1998); sudden correction of chronic hypercalcemia in which the remaining parathyroid glands are severely atrophied; and absence or destruction of the parathyroid glands. In reviewing the additional routine laboratory tests performed on hypoparathyroid dogs, abnormalities were not seen. Therefore the only significant alterations were hypocalcemia in all patients and hyperphosphatemia in most.

### Laboratory Testing of Cats with Primary Hypoparathyroidism

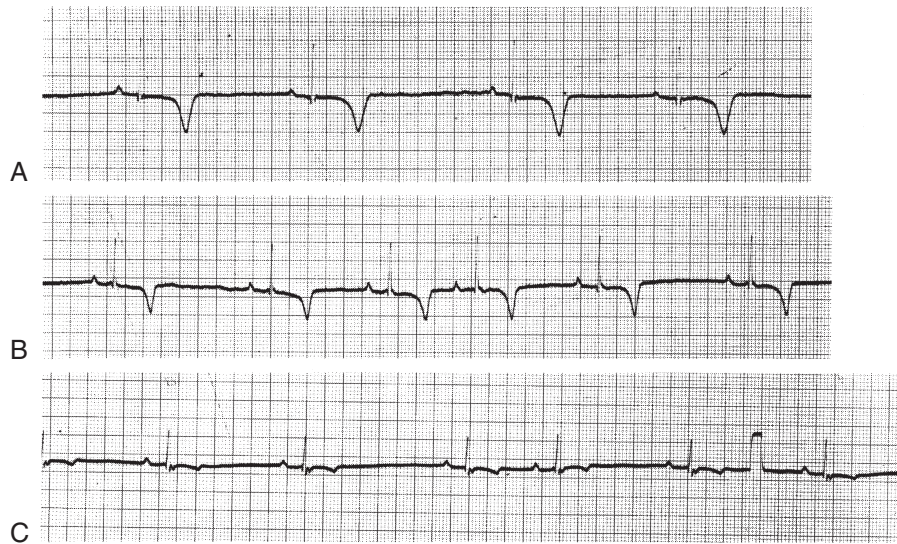
Laboratory testing in 16 cats (nine reported cases and seven in our series) with naturally occurring primary hypoparathyroidism demonstrated severe hypocalcemia in each cat (range, 2.5 to 4.4 mg/dL). Serum phosphate concentrations were inappropriately increased in each cat (range, 5.2 to 19 mg/dL). Serum protein, albumin, urea nitrogen, creatinine, and magnesium concentrations were within reference limits in each cat tested (Forbes et al, 1990; Parker, 1991; Peterson et al, 1991; Bassett, 1998; Ruopp, 2001; Gunn-Moore, 2005).

### Electrocardiogram

A good correlation exists between severity of hypocalcemia and duration of the electrocardiogram (ECG)-demonstrated S-T segment. Most hypoparathyroid dogs in our series had no clinical evidence of cardiovascular disease and were not assessed with an ECG. When an ECG was taken, changes observed that were consistent with hypocalcemia included (1) deep and wide T waves, (2) prolonged Q-T or S-T intervals (also noted in four out of four dogs in a separate study [Russell et al, 2006]), and (3) bradycardia (Kornegay et al, 1980; Sherding et al, 1980; Russell, et al, 2006). When the ECGs obtained during hypocalcemia were compared with those taken following restoration of normal calcium concentrations, the R waves appeared taller during hypocalcemia (Fig. 16-6). No obvious ECG explanation could be found for the arrhythmias, weak pulses, or muffled heart sounds that were suspected on several physical examinations.

### Magnesium

Magnesium is an important cofactor for PTH secretion because it is required for release of stored hormone from secretory granules. In conditions of severe magnesium deficiency, suppressed parathyroid secretion with concurrent hypocalcemia and hyperphosphatemia has been documented. Another contributor to the hypocalcemia seen with hypomagnesemia is a reversible resistance



**FIGURE 16-6** Electrocardiogram (ECG) illustrating various stages in the treatment of a dog with hypocalcemia secondary to primary hypoparathyroidism. **A**, The serum calcium level was 4.0 mg/dL. On this ECG, prolonged S-T and Q-T segments are obvious. The T wave itself is prolonged and deep. At this time the serum potassium (4.3 mEq/L), sodium (147 mEq/L), and chloride (103 mEq/L) levels were normal. The inorganic phosphorus level was 4.9 mg/dL. **B**, ECG taken when the serum calcium level was 6.2 mg/dL. The S-T, Q-T, and T wave durations are diminished, as is the T wave amplitude. **C**, ECG taken of a dog with a normal serum calcium level of 9.7 mg/dL. The S-T, Q-T, and T waves are normal. The three ECGs also suggest a diminishing R wave amplitude as the serum calcium level rises to normal.

#### BOX 16-2 Causes of Hypomagnesemia and Magnesium Depletion in Humans

##### Decreased Intake and/or Absorption

Protein-calorie malnutrition  
Magnesium-free fluid therapy  
Magnesium-free total parenteral nutrition

##### Gastrointestinal Disorders

Prolonged nasogastric suction  
Chronic diarrhea  
Malabsorption syndromes  
Extensive bowel resection, intestinal fistulas

##### Renal Losses

Chronic parenteral fluid therapy without magnesium  
Nonazotemic renal tubular dysfunction (see text)  
Loop and osmotic diuretics  
Hypercalcemia  
Hypokalemia  
Alcohol

##### Metabolic

Hypercalcemia  
Hypophosphatemia

##### Endocrine

Diabetes mellitus, insulin therapy  
Hyperthyroidism  
Primary hyperparathyroidism  
Primary and secondary hyperaldosteronism  
Hyperadrenocorticism  
Syndrome of inappropriate secretion of antidiuretic hormone

##### Redistribution

Pancreatitis  
Hyperadrenergic states  
Massive blood transfusion  
Hypothermia  
Acute respiratory alkalosis  
Sepsis

##### Other

Burns  
Excessive lactation  
Excessive sweating

to the actions of PTH at the level of both bone and kidney (Wysolmerski and Insogna, 2012).

In humans, there are a variety of causes for severe (serum concentration < 1.2 mg/dL) magnesium deficiency (Box 16-2; Yu, 2012). People with various intestinal disorders associated with small bowel malabsorption and/or steatorrhea are at risk for magnesium depletion. Responsible mechanisms include formation of magnesium soaps with unabsorbed fatty acids in addition to simple loss of magnesium into intestinal contents. Decreased renal tubular magnesium

reabsorption and hypomagnesemia has been reported in people during the diuretic phase of acute renal tubular necrosis, renal tubular acidosis, pyelonephritis, and hydronephrosis. Impaired magnesium reabsorption and hypomagnesemia has been documented with gentamicin nephrotoxicity and is recognized as a potential adverse reaction to cisplatin chemotherapy. Virtually all diuretics increase magnesium excretion and symptomatic hypomagnesemia has been documented with primary and secondary states of hyperaldosteronism (Yu, 2012). The osmotic diuresis associated with diabetic

ketoacidosis (DKA) can be associated with significant urinary losses of magnesium. The time course for the development of hypomagnesemia in response to treatment of ketoacidosis is similar to that for decreasing serum potassium and phosphorus concentrations. Normal pretreatment magnesium concentrations may decrease to less than 1 mg/dL during the first 24 hours of intensive therapy for DKA unless anticipated and treated. Hyperthyroidism is sometimes associated with negative magnesium balance and hypomagnesemia due to bone resorption and altered distribution of magnesium into soft tissues (Yu, 2012). Primary infantile hypomagnesemia is a rare autosomal recessive disorder in people that appears to be caused by a specific abnormality in intestinal magnesium absorption (Wysolmerski and Insogna, 2012).

Hypoparathyroidism secondary to hypomagnesemia in dogs with protein-losing enteropathies and in dogs with eclampsia have been reported (Aroch et al, 1999; Kimmel et al, 2000; Bush et al, 2001). Serum magnesium concentrations were determined in 38 of the 57 hypoparathyroid dogs included in Table 16-3. Eight of these dogs were hypomagnesemic. Hypocalcemia in people with concurrent hypomagnesemia is often refractory to calcium therapy unless magnesium is administered first (Hansen, 2000). In humans, symptoms of hypomagnesemia do not usually occur at serum levels of magnesium above 1.5 mg/dL, and obvious signs are not always seen, even at serum magnesium levels below 1.0 mg/dL (Wysolmerski and Insogna, 2012).

Poor quantitative relationships between testing and clinical relevance are limitations created by having only 0.3% of total body magnesium in plasma or serum (Elin, 1994). Serum magnesium concentrations may be normal or high in the presence of intracellular depletion. Although serum testing is the least expensive and most convenient, most authorities recognize inaccuracies associated with such assessments. Furthermore, interest in measuring serum ionized magnesium concentration has involved expensive equipment or facilities not widely available (Wysolmerski and Insogna, 2012).

It is unclear whether mild/asymptomatic hypomagnesemia needs to be treated. In humans, magnesium repletion is recommended if a patient is symptomatic, has concurrent severe hypocalcemia, hypokalemia, or an underlying cardiac arrhythmia or seizure disorder. Intravenous (IV) magnesium sulfate can be used for repletion, and its redistribution from extracellular to intracellular space is relatively slow. Normalization of serum concentrations usually precedes achievement of total magnesium replacement needs. It is recommended, therefore, that humans receiving IV supplementation continue to be treated for 24 to 48 hours beyond the time that serum concentrations normalize. In people with normal renal function, excess supplementation should be excreted. Symptoms of hypermagnesemia in people include hypotension and flaccid paralysis (Yu, 2012).



### DIAGNOSTIC EVALUATION: PARATHYROID HORMONE CONCENTRATIONS

#### Clinical Usefulness in Humans

Measurement of serum PTH concentration is an important aid to the diagnosis of parathyroid gland disorders in people (Arnaud and Kolb, 1991; Wysolmerski and Insogna, 2012). Decreases in serum PTH concentration are consistent with primary parathyroid gland failure in hypocalcemic individuals. Increases in serum PTH concentration (an appropriate physiologic response to hypocalcemia) rules out hypoparathyroidism in individuals whose hypocalcemia is unexplained, suggesting end-organ resistance to PTH (pseudohypoparathyroidism or vitamin D deficiency) or secondary hyperparathyroidism due

to conditions such as dietary calcium deficiency or intestinal malabsorption.

#### Clinical Usefulness in Dogs and Cats

Undetectable serum PTH concentration in a severely hypocalcemic animal confirms the diagnosis of primary hypoparathyroidism. Reliable and validated PTH assays are commercially available for cats and dogs. Serum PTH concentrations may be detectable or “low-normal” in pets with hypoparathyroidism. A serum PTH concentration within the reference range is not a healthy response to hypocalcemia (see Figs. 15-5, 15-22, and 15-23). Low-normal to extremely low serum PTH concentrations were obtained from each of 44 dogs with primary hypoparathyroidism we tested (see Table 16-3 and Figs. 15-22 and 15-23).

Response to therapy, coupled with ruling out each differential diagnosis for hypocalcemia, has served as a relatively reliable and logical method for supporting a diagnosis of primary hypoparathyroidism. This approach allows assessment of serum PTH concentration to serve in a “confirmatory” role. Because naturally occurring primary hypoparathyroidism is a permanent condition requiring lifelong therapy, assaying serum PTH concentrations is warranted and serves to aid both veterinarian and client (Torrance, 1998). Despite inevitable changes in methodologies over the years, PTH assays for both dogs and cats have provided excellent and reliable information (Feldman and Krutzik, 1981; Torrance and Nachreiner, 1989; Flanders and Reimers, 1991; Flanders et al, 1991; Barber et al, 1993; Chew et al, 1995; see Chapter 15). The most important differential diagnoses for hypocalcemia are laboratory error, hypoalbuminemia, surgical removal of the parathyroids, use of phosphate enemas, acute or chronic kidney failure, eclampsia, malabsorption, and severe pancreatitis (Schenck and Chew, 2012).



### DIFFERENTIAL DIAGNOSIS OF EPISODIC WEAKNESS

Because the clinical signs of hypocalcemia occur episodically, clinicians may consider a variety of potential causes for “episodic weakness” or paroxysmal neurologic and/or neuromuscular disorders. The differential diagnosis for episodic weakness presented in Chapter 9 is worth reviewing because those clinical signs are somewhat similar to those of hypocalcemia. Several of the dogs in this series were initially believed to have idiopathic epilepsy. Toxins were also commonly suspected (e.g., strychnine, metaldehyde, and/or lead). Other tentative diagnoses after initial examination of hypocalcemic dogs included tetanus, trauma, cardiac disease, myasthenia gravis, hepatic disease, and hypoglycemia.



### DIFFERENTIAL DIAGNOSIS FOR HYPOCALCEMIA

The differential diagnosis for hypocalcemia is listed in Box 16-3 and the diagnostic algorithm is in Fig. 16-7.

#### Parathyroid-Related Hypocalcemia

##### *Naturally Occurring Primary Hypoparathyroidism in Dogs and Cats*

Naturally occurring hypoparathyroidism is an uncommon condition in dogs and cats. The onset of signs typically seem abrupt to owners and may be severe (e.g., tetany and/or seizures). Although the onset of signs almost always seems sudden, the condition is likely insidious with mild subclinical hypocalcemia present for some period. Surprisingly, some dogs and cats with naturally occurring disease have had signs for months at

**BOX 16-3 Differential Diagnosis of Hypocalcemia**

**Parathyroid-related hypocalcemia**

- Naturally occurring primary hypoparathyroidism
- Rare disorders in people
- Iatrogenic (surgically removed or damaged glands)
- Acute resolution of chronic hypercalcemia
- Pseudohypoparathyroidism

**Pseudopseudohypoparathyroidism**

- Hypomagnesemia
- Chronic Kidney Disease (CKD)
- Hypoalbuminemia
- Acute pancreatitis
- Critically ill patients
- Diabetes mellitus
- Puerperal tetany (eclampsia)
- Malabsorption syndromes

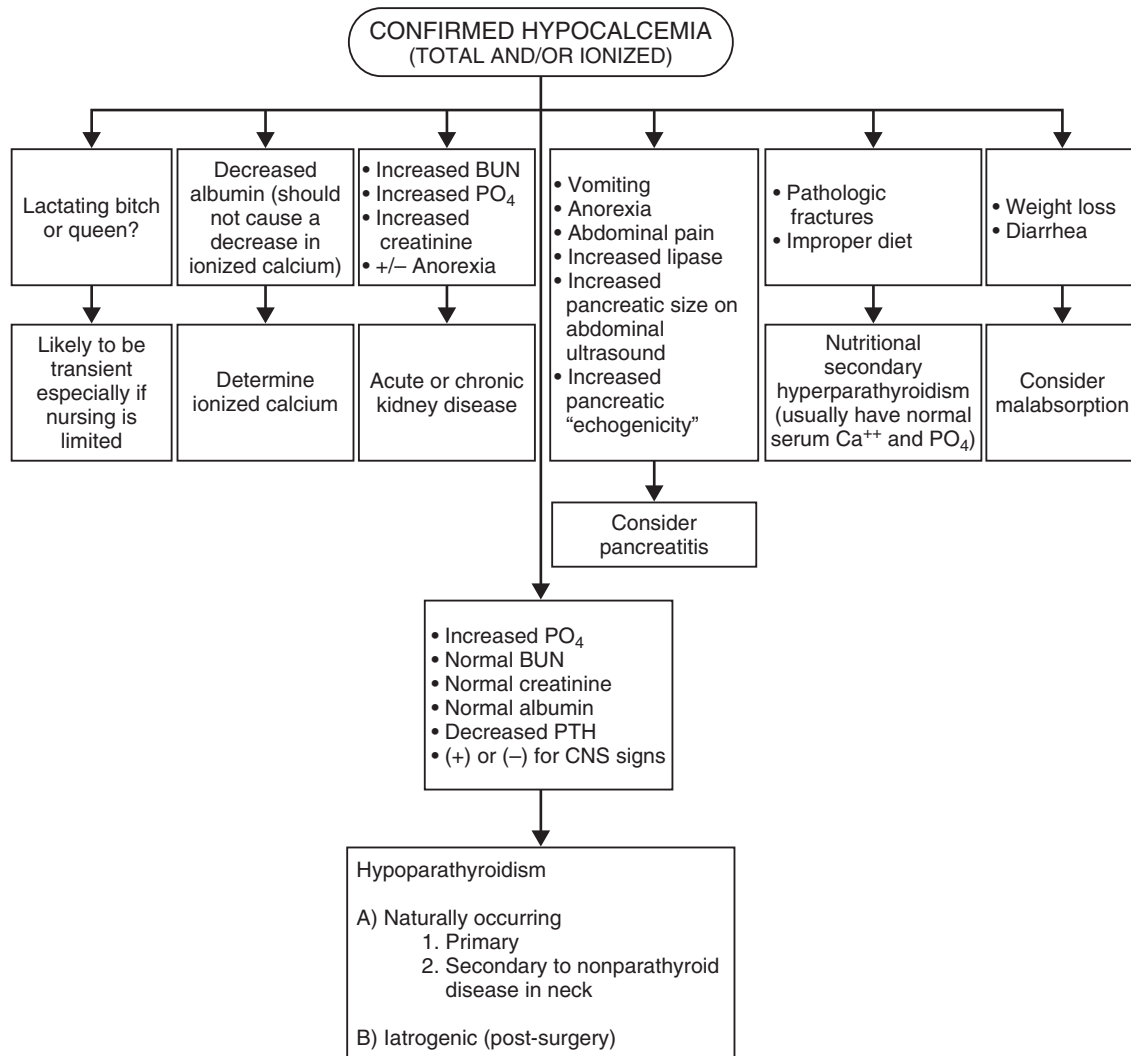
**Nutritional secondary hyperparathyroidism**

- Acute kidney injury (AKI) and ethylene glycol toxicity
- Urinary tract obstruction

**Phosphate-containing enemas**

**Miscellaneous causes of hypocalcemia**

- Laboratory error
- Anticonvulsant therapy
- Hyperthyroidism
- Vitamin D deficiency
- Transfusion using citrated blood
- Use of EDTA-coagulated blood
- Trauma to the neck area
- Medullary carcinoma of the thyroid
- Primary and metastatic bone cancer
- Side-effect to some cancer chemotherapies



**FIGURE 16-7** Algorithm for diagnosing the various causes of hypocalcemia. *BUN*, Blood urea nitrogen; *Ca*, calcium; *Ca<sup>++</sup>*, ionized calcium; *CNS*, central nervous system; *PO<sub>4</sub>*, phosphorus; *PTH*, parathyroid hormone.

the time of diagnosis (one, in our series, for about a year) and survive without appropriate treatment. Signs are not usually recognized until there has been a decline in the TCa concentration below some critical level (approximately 6 to 7 mg/dL). At such serum calcium concentrations, relatively small decreases in calcium concentration may result in obvious clinical problems. For example, a serum TCa decline of 0.3 mg/dL in a dog or cat with a serum concentration of 10.5 mg/dL has no effect and remains “normal,” but the same decrease when the serum calcium concentration is 5.7 mg/dL could result in convulsions.

Diffuse lymphocytic “parathyroiditis” was described in seven dogs with hypoparathyroidism (Kornegay, 1982). Our series includes an additional 19 dogs with similar histologic findings, and a few others had their parathyroid tissue replaced by fibrous tissue. It is possible that fibrous tissue is an “end result” following lymphocytic/plasmacytic inflammation. Therefore the finding of either inflammatory infiltrates or scar tissue is most likely dependent on when tissue is obtained relative to the time course of the condition. Interestingly, two dogs with primary hypoparathyroidism from Australia had no histologic abnormalities (Russell et al, 2006). Detection of antibodies against parathyroid tissue in people with idiopathic hypoparathyroidism has confirmed presence of an autoimmune disease. An immune-mediated mechanism may explain the condition in some dogs and cats.

#### **Rare Disorders in Humans Causing Hypoparathyroidism**

The DiGeorge syndrome in humans consists of parathyroid gland absence and thymic aplasia (Rasmussen, 1981; Marx, 2000; Yu, 2012). This disorder presumably results from abnormal development of the third pharyngeal pouch during embryogenesis. Parathyroid agenesis has also been reported in dogs (Meuten and Armstrong, 1989). Another form of idiopathic hypoparathyroidism in humans is a familial immune-mediated endocrine syndrome that includes hypofunction of the adrenal cortex, ovarian failure, pernicious anemia, thyroiditis, diabetes mellitus, candidiasis, and occasionally malabsorption. Those patients who manifest disease before 6 months of age conform to an X-linked recessive inheritance pattern, and older individuals likely have an autosomal recessive inherited condition (Arnaud and Kolb, 1991; Wysolmerski and Insogna, 2012). Calcium-sensing receptor mutations have also been identified (Pearce et al, 1996).

#### **Surgically Induced Hypoparathyroidism**

An uncommon cause for primary hypoparathyroidism in dogs and cats, but relatively common in people, is surgical removal, damage, or interruption of blood supply to the glands (Marx, 2000). Hypoparathyroidism is a risk of thyroid, parathyroid, or other neck surgeries. Because the incidence of hyperthyroidism in cats is high and because canine thyroid tumors are often malignant, thyroid surgery is common in both species. One group estimated that as many as 10% of hyperthyroid cats undergoing surgery suffer from transient or permanent hypoparathyroidism (Peterson, 1986). Of 41 hyperthyroid cats that had bilateral thyroidectomy, postoperative hypocalcemia (not always associated with clinical signs) developed in 82% undergoing an extracapsular surgical technique, 36% with an intracapsular technique, and 11% with two separate thyroidectomies performed 3 to 4 weeks apart (Flanders et al, 1987). Of 106 cats studied in a subsequent report, postoperative hypocalcemia developed in 22% to 33% of cats, depending on the surgical technique (Welches et al, 1989). Clinical signs were observed only in severely hypocalcemic cats (TCa < 7.0 mg/dL). The incidence of surgically-related hypoparathyroidism is now much lower, because surgeons are more

aware of this complication and because techniques have improved (Henderson et al, 1991; Flanders, 1994; Graves, 1995; Klein et al, 1995). Because this complication is recognized as possible, autotransplantation of removed parathyroid tissue has been successfully employed in humans and has excellent veterinary potential (Padgett et al, 1998).

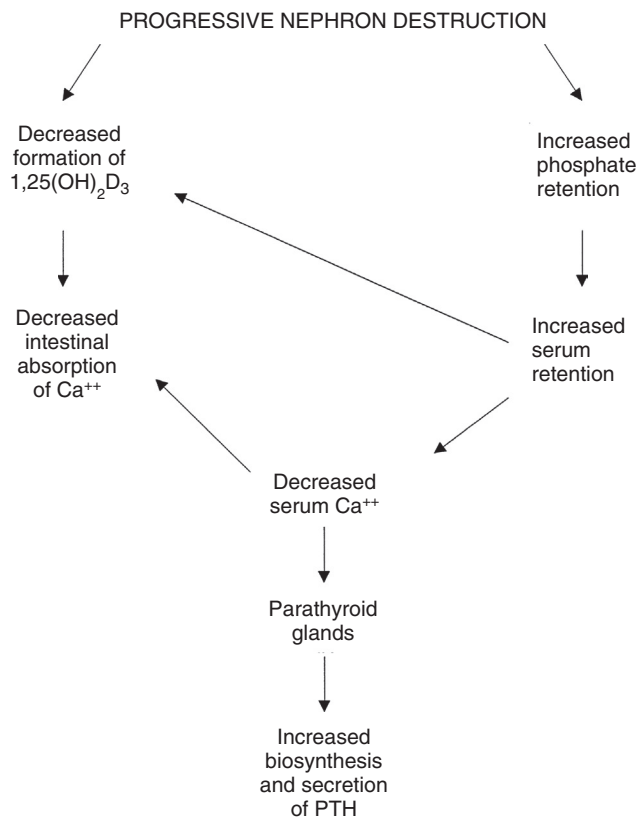
The transient nature of hypoparathyroidism following thyroid surgery in many cats is not well understood. The physiology of this complication may be related to the hyperphosphatemia and secondary hyperparathyroidism documented in 18% and 77%, respectively, of untreated hyperthyroid cats (Barber and Elliott, 1996). It has been postulated that this may be the result of thyroxine (T<sub>4</sub>)-mediated alterations in bone metabolism and increased phosphate absorption (Barber and Elliott, 1996). One group of cats had significantly reduced serum PTH concentrations after thyroparathyroidectomy. During the 12 weeks following surgery, serum PTH concentrations did not recover, but the serum calcium concentration did slowly increase. The increases in serum calcium concentration in these thyroparathyroidectomized cats, it was theorized, were an “accommodation” of existing calcium-regulating systems that operate at suboptimal levels in the absence of PTH. One example of such an “accommodation” might involve changes in vitamin D metabolism, allowing continued calcium absorption from the intestine despite the PTH deficiency (Flanders et al, 1991). The onset of biochemical or clinical signs suggestive of parathyroid failure after neck surgery in dogs and cats can begin within days or take as long as several weeks. Other potential but rare destructive disorders of the parathyroids include neck injury, neoplastic conditions within the neck, irradiation, and aminoglycoside intoxication. We have not observed iodine<sup>131</sup>-induced parathyroid damage in any so-treated hyperthyroid cat.

#### **Pseudohypoparathyroidism**

Pseudohypoparathyroidism is a rare familial disorder in humans characterized by target tissue resistance to PTH. These individuals have hypocalcemia, increased serum concentrations of PTH, and a variety of congenital developmental growth and skeletal defects. Increases in serum PTH concentration represent an appropriate physiologic response to hypocalcemia. If the serum calcium concentration is transiently normalized by an infusion of calcium, the concentration of circulating PTH decreases. Therefore diagnosis of end-organ unresponsiveness involves (1) the inability of PTH to increase cyclic adenosine 3',5'-monophosphate (cAMP) excretion and (2) elevated circulating PTH concentrations. The hormone secreted by patients with pseudohypoparathyroidism is presumably normal in structure. Some of these patients have no developmental abnormalities (Wysolmerski and Insogna, 2012). A deficiency in renal PTH-sensitive cAMP results in renal tubular resistance to PTH and diminished phosphaturia. Deficits in active vitamin D and/or bone cAMP have also been claimed to be the inciting factor leading to pseudohypoparathyroidism. One dog with apparent hypoparathyroidism had an increased serum PTH concentration, urine cAMP, and plasma cAMP (Kornegay et al, 1980). Another dog with hypoparathyroidism had Fanconi syndrome, which was thought to occur secondary to a 1,25-vitamin D deficiency (Freeman et al, 1994).

#### **Pseudopseudohypoparathyroidism**

Humans with this disorder have typical developmental defects (growth and skeletal abnormalities) associated with pseudohypoparathyroidism, but they are not hypocalcemic or hyperphosphatemic, nor do they have abnormalities in serum PTH concentration (Marx, 2000).



**FIGURE 16-8** Pathogenesis of parathyroid hyperplasia during progressive destruction of nephrons.  $1,25(\text{OH})_2\text{D}_3$ , 1,25-dihydroxyvitamin  $\text{D}_3$  (calcitriol);  $\text{Ca}$ , calcium;  $\text{Ca}^{++}$ , ionized calcium;  $\text{PTH}$ , parathyroid hormone.

### Hypomagnesemia

Magnesium deficiency can result in hypocalcemia (see earlier Magnesium section).

### Chronic Kidney Disease (CKD)

Dogs and cats with CKD usually have (in addition to abnormal BUN and serum creatinine concentrations) increased serum phosphate and normal serum calcium concentrations. Despite hypocalcemia being uncommon in dogs and cats with CKD, the prevalence of CKD makes this condition one of the more frequent causes of low calcium. Low serum TCa was detected in about 10% of dogs with CKD, and the iCa concentration was low in about 30% (Schenck and Chew, 2012). In cats, as CKD progresses, the incidence of hypocalcemia increases. About 15% of cats with “moderate CKD” had low iCa, and the percentage rises to 50% if the condition is “advanced” (Schenck and Chew, 2010). In CKD patients, hypocalcemia is a biochemical problem and rarely clinically significant.

When present in CKD, hypocalcemia is the result of decreased vitamin D synthesis by diseased kidneys and mass law interactions of calcium with the sometimes markedly increased phosphate. Early stages of progressive CKD are associated with a decreased capacity to excrete phosphate. Even mild hyperphosphatemia induces subclinical ionized hypocalcemia which, in turn, stimulates PTH synthesis and secretion. This ionized hypocalcemia is the classically described genesis of renal secondary hyperparathyroidism (Fig. 16-8). In dogs with nonazotemic kidney disease (IRIS stage I; International Renal Interest Society; [www.iris-kidney.com](http://www.iris-kidney.com)), 36% had secondary hyperparathyroidism. The hyperparathyroidism

should augment phosphate excretion, but with time, secondary hyperparathyroidism can no longer compensate for the alterations of CKD; hyperphosphatemia develops and it becomes progressively worse (Chew and Nagode, 1990). Because progressive renal disease leads to reduced capacity to form active vitamin D, intestinal absorption of calcium is limited, enhancing the potential for hypocalcemia. Also, increased urinary calcium excretion may contribute to the hypocalcemia sometimes seen in CKD.

### Hypoalbuminemia

Reductions in total serum protein and/or albumin concentrations are encountered in a variety of disorders. Hypoalbuminemia is the most common and clinically least important cause of hypocalcemia. As previously described, reductions in circulating albumin concentration cause a decrease in the protein-bound fraction of circulating calcium. However, since iCa concentrations remain normal, these animals rarely have clinical signs of hypocalcemia.

### Acute Pancreatitis

Hypocalcemia, when it occurs in dogs with acute pancreatitis, is usually mild and subclinical. Coexisting acidosis, which is commonly present, increases the ionized fraction of TCa and further reduces the likelihood of clinical signs related to hypocalcemia (Hess et al, 1998). The incidence of hypocalcemia may be higher in cats with pancreatitis than in dogs. Results of one study suggest that low TCa and iCa concentrations are common in cats with acute pancreatitis (41% and 61%, respectively). Furthermore, cats with ionized hypocalcemia, even though none had clinical signs related to this complication, had a poorer prognosis than those with normal concentrations. A grave prognosis and aggressive medical therapy was recommended for cats with both acute pancreatitis and a plasma iCa concentration less than 1.00 mmol/L (Kimmel et al, 2001).

The traditional theory for development of hypocalcemia in pancreatitis is that calcium precipitates into insoluble soaps via saponification of peripancreatic fatty acids formed subsequent to release of pancreatic lipase. Despite general agreement that this occurs, it is not clear whether it is sufficient to account for hypocalcemia in view of the large quantity of calcium that potentially can be mobilized from skeletal reserves. Other contributors to hypocalcemia may include hypomagnesemia, decreased secretion of or resistance to PTH secondary to magnesium deficiency, hypoproteinemia, and glucagon-stimulated calcitonin secretion (Ryzen and Rude, 1990; Dhupa and Proulx, 1998; Schenck and Chew, 2012).

### Critically Ill Patients

Hypocalcemia due to decreases in TCa and/or iCa concentrations is common among critically ill people, dogs, and cats, especially those with sepsis. Magnitude of the decreases appears to correlate with severity of illness. In addition to sepsis, causes of hypocalcemia include systemic inflammatory response syndrome, hypomagnesemia, blood transfusions, and acute kidney disease (Zivin et al, 2001; Schenck and Chew, 2012).

### Diabetes Mellitus

Almost 50% of diabetic dogs have ionized hypocalcemia. Because pancreatitis was diagnosed in less than 15% of these dogs, it is unlikely for pancreatitis to be the sole explanation for the hypocalcemia (Hess et al, 2000). In a study on more than 100 dogs in DKA, slightly more than 50% had ionized hypocalcemia, the

severity of which correlated with mortality (Schenck and Chew, 2012).

### Puerperal Tetany (Eclampsia)

Eclampsia is an acute life-threatening condition that develops secondary to extreme hypocalcemia in lactating bitches and queens (Fascetti and Hickman, 1999; Drobatz and Casey, 2000). Dogs and cats with clinical signs of eclampsia are usually severely hypocalcemic (< 6 to 7 mg/dL). Eclampsia is most common in small dogs and less common in cats and large dogs. Signs seen by veterinarians usually depend on how quickly the owner recognizes the problem and seeks professional care. Most bitches and queens are affected during the first 21 days of nursing, although eclampsia has been diagnosed as early as during the last 2 weeks of gestation and as late as 45 days after whelping. Diagnosis of eclampsia is usually based on the presence of neuromuscular signs (tetany) in a lactating bitch or queen. In most situations, the diagnosis is so obvious that the serum calcium concentration is never assessed. However, three cats with preparturient eclampsia had hypothermia rather than the expected hyperthermia, and four cats had clinical signs that included flaccid paralysis, rather than the more typical tonic-clonic muscle fasciculations noted in dogs (Fascetti and Hickman, 1999).

Hypocalcemia typically arises as a consequence of lactation and its attendant calcium loss into milk. Other possible contributors include poor use of dietary calcium and loss of calcium to fetal skeletal development. Sometimes the stress of nursing reduces a bitch's (or queen's) appetite or interferes with her ability to eat. Another predisposing factor is the parathyroid gland atrophy that can be caused by improper diet or dietary supplements. In one study, 44% of bitches with eclampsia had hypomagnesemia. Decreased magnesium-to-calcium ratios at the neuromuscular junctions can promote tetany. Magnesium therapy may be beneficial for treatment of eclampsia (Aroch et al, 1999).

### Malabsorption Syndromes

Many patients with protein losing enteropathies have hypoalbuminemia and typical decreases in serum TCa concentrations but serum iCa concentrations that are within reference intervals. True enteropathy-associated vitamin D deficiency leading to hypocalcemia is uncommon but possible. Malabsorption conditions, such as inflammatory bowel disease (IBD) or intestinal lymphoma, in dogs, cats, and people are frequently associated with derangements in fat soluble vitamin metabolism (Gow et al, 2011; Wysolmerski and Insogna, 2012; Lalor et al, 2014). Various explanations have been proposed for enteropathy-associated hypocalcemia, including decreased intestinal absorption or increased intestinal loss of both albumin and vitamin D bound to vitamin D-binding protein (Lalor et al, 2014). Decreased appetite in patients with significant enteropathies may contribute to vitamin D deficiency. Serum vitamin D concentrations were significantly lower in dogs with IBD and moderate to severe decreases in appetite as compared with dogs that had similar bowel disease but normal appetites (Gow et al, 2011). A majority of 10 IBD cats and six with intestinal small cell lymphoma had low vitamin D concentrations, but only two were hypocalcemic (Lalor et al, 2014). There is also evidence from experimental models suggesting that IBD may be due to hypovitaminosis D rather than caused by it (Mora et al, 2008).

Hypocalcemia may be caused by or worsened by excess fecal calcium excretion due to decreased resorption of calcium in disorders

such as lymphangiectasia. The degree of calcium malabsorption and the poor absorption of vitamin D appear to correlate with the extent of small bowel disease (Mellanby et al, 2005). Hypomagnesemia may also play a role in the physiology resulting in hypocalcemia. In two studies, it was suggested that hypomagnesemia and hypocalcemia may have a related pathogenesis involving intestinal loss, malabsorption, and abnormalities of vitamin D and PTH metabolism. Magnesium supplementation was demonstrated to normalize serum magnesium and PTH concentrations, improve plasma iCa concentrations, and alleviate clinical signs of paresis (Kimmel et al, 2000; Bush et al, 2001).

### Nutritional Secondary Hyperparathyroidism

It would be rare for a pet being fed commercially available nutritionally complete and balanced diet to ever develop this condition. However, dogs or cats exclusively fed diets containing a low calcium-to-phosphorus ratio (the classical examples are beef heart and liver) can develop severe mineral deficiencies. BARF ("biologically appropriate raw food" or "bones and raw food") diets have also been implicated (DeLay and Laing, 2002). Severe gastrointestinal disease may also result in this condition by directly impairing calcium absorption or, indirectly, by interfering with vitamin D absorption (Mellanby et al, 2005; Skelly, 2012). If either a dietary deficiency or an inability to absorb calcium from intestinal content results in decreased circulating calcium concentration, a cascade of events begins. Those events include increased PTH secretion, reduction in bone mass as calcium is removed from bone to replace that not available in the diet, diffuse skeletal osteopenia, and, if persistent, "nutritional secondary hyperparathyroidism." Although renal secondary hyperparathyroidism seems to target bones of the face (fibrous osteodystrophy), nutritional hyperparathyroidism appears to target long bones and vertebrae. This process can cause bone pain and pathologic fractures. Because the skeletal disturbances are the result of physiologic processes placing the serum calcium concentrations as highest priority, affected dogs and cats usually have normal serum concentrations of TCa, iCa, and phosphorus. A minority of affected dogs and cats have had mild to severe hypocalcemia (Tomsa et al, 1999). Treatment involves providing balanced diets and restricting activity until skeletal remodeling is complete. Diagnosis is based on recognizing skeletal disorders in a dog or cat receiving an improper diet.

### Acute Kidney Injury (AKI) and Ethylene Glycol Toxicity

Acute kidney injury (such as that which occurs with ethylene glycol poisoning) and postrenal failure (such as that which occurs with urinary tract obstruction) may result in abrupt and severe increases in serum phosphate concentration. Mass law effects cause a secondary reduction in serum calcium concentrations. Hypocalcemia may be exaggerated in acute failure because rapid onset of these disturbances blunts compensatory mechanisms. Dogs with acute intrinsic renal failure had a mean serum TCa concentration of 9.8 mg/dL (Vaden et al, 1997). Ethylene glycol intoxication can cause severe renal failure, acidosis, hypocalcemia, tetany, and death.

### Urinary Tract Obstruction

Male cats with long-standing (more than 12 to 24 hours) urethral obstruction and severe hyperphosphatemia often have associated

hypocalcemia, hyperkalemia, azotemia, and sometimes experience seizures (Chew and Meuten, 1982). Hypocalcemia was diagnosed in 26% of male cats with urethral obstruction at initial presentation, based on serum TCa assessment. On the basis of iCa concentrations, however, 75% were hypocalcemic. The hypocalcemia was defined as mild in 37.5%, moderate in 25%, and severe in 12.5% of affected cats. These abnormalities may contribute to cardiac dysfunction in severely affected cats. Although effects of IV administration of calcium were not evaluated, results in this study support their use in cats with urethral obstruction (Drobatz and Hughes, 1997).

### Phosphate-Containing Enemas

Phosphate-containing enemas may result in acute and severe hyperphosphatemia following colonic absorption, especially when administered to dehydrated cats with colonic atony and mucosal disruption. Colonic absorption of sodium and phosphate from the enema solution as well as transfer of intravascular water to the colonic lumen (because of hypertonicity of the enema solution) can cause hypernatremia and hyperphosphatemia. Acute increases in serum phosphate may cause reciprocal significant declines in serum calcium concentration (Atkins et al, 1985; Jorgensen et al, 1985). Therefore use of phosphate-containing enemas is not recommended in animals predisposed to hyperphosphatemia, such as with severe obstipation, marginal renal function, or abnormal serum calcium-to-phosphorus ratios. Clinical signs of phosphate enema toxicosis (shock and neuromuscular irritability) result from hypocalcemia and hypernatremia. Treatment may require plasma volume expansion and calcium. Diagnosis is based on the history (Peterson, 1992).

### Miscellaneous Causes

#### Laboratory Error

An uncommon cause of reported hypocalcemia is laboratory error. Incorrect reporting of the serum calcium concentration can reflect a simple mistake or artifact due to samples submitted in tubes containing ethylenediaminetetraacetic acid (EDTA) as an anticoagulant, because EDTA chelates calcium. Mixing of serum with air can significantly decrease iCa concentrations. Freshly obtained plasma for iCa determination should be transported to reference laboratories with a cold pack. If a delay in processing lasting days seems likely, plasma should be sent frozen (Schenck et al, 1995). Caution should be exercised in the interpretation of iCa measured with portable analyzers, because results for dogs and cats are lower than those obtained with standard methodology. The use of dry heparin syringes for sample collection may negate this difference (Grosenbaugh et al, 1998). Whenever the reported serum calcium concentration is unexpectedly high or low, it should be rechecked.

#### Anticonvulsant Therapy

Surveys of humans receiving long-term anticonvulsant therapy (principally phenobarbital and phenytoin) have shown a tendency to develop hypocalcemia, hypophosphatemia, and abnormal serum alkaline phosphatase activities. Studies of these subjects reveal a state similar to vitamin D deficiency. Bone biopsies and radiographs suggest osteomalacia without evidence of malabsorption or renal disease. Serum PTH concentrations are increased but remain normally suppressible with calcium infusions. Severity of the altered calcium metabolism is directly related to dosage (Arnold and Kolb, 1991).

Although this problem has not been recognized in the dog, it is described here to remind practitioners that a variety of drugs have the potential to cause unexpected endocrine problems. Furthermore, several of our hypoparathyroid dogs were referred because of failure to respond to anticonvulsant therapy. The finding of hypocalcemia in dogs on relatively high doses of anticonvulsants may be mistakenly interpreted as iatrogenic.

#### Hyperthyroid Cats

Cats with untreated hyperthyroidism have significantly lower iCa concentrations than do control cats, although none had decreases in TCa concentration, and only 4 of 15 had iCa concentrations below the reference range. Hyperthyroid cats also had significantly increased serum PTH concentrations. These changes are likely associated with the hyperphosphatemia often noted in hyperthyroid cats. The importance of these findings is not known (Barber and Elliott, 1996).

#### Vitamin D Deficiency

Vitamin D deficiency is an unlikely clinical cause of hypocalcemia (Henik et al, 1999). Dogs and cats with a significant and diffuse intestinal malabsorption syndrome may lose the ability to absorb vitamin D.

#### Use of Citrated Blood

Blood for transfusion that contains citrates as anticoagulant may induce hypocalcemia, particularly if the volume of donor blood is small compared with the volume of anticoagulant.

#### Trauma

Trauma, especially soft tissue trauma, has been reported as a cause of hypocalcemia (Chew and Meuten, 1982), but this is rare.

#### Medullary Carcinoma of the Thyroid

Medullary carcinoma of the thyroid has been reported to cause severe hypocalcemia and tetany in one dog and represents an unusual cause of hypocalcemia in humans.

#### Primary and Metastatic Bone Cancer

Primary and metastatic bone tumors are common in small animal practice. Humans, dogs, and cats with tumors that have metastasized to bone usually have normal serum calcium concentrations. Hypercalcemia is occasionally associated with primary bone neoplasia and with metastasis of certain cancers to bone. However, hypocalcemia and hypophosphatemia rarely occur in humans. When osteoblastic metastases are present in humans, the incorporation of calcium into those lesions may be sufficient to result in measurable hypocalcemia and even clinical signs. This has not been reported in dogs or cats.

#### Chemotherapy and the "Tumor Lysis Syndrome"

The tumor lysis syndrome can follow acute release of intracellular potassium and phosphate during chemotherapy for highly sensitive neoplasms, such as lymphoid or bone marrow tumors (Persons et al, 1998). Among the multiple metabolic abnormalities that can occur in this setting is hypocalcemia due to mass law interactions induced by acute and severe hyperphosphatemia (Calia et al, 1996; Piek and Teske, 1996). Further, calcium salts can be deposited into soft tissues. Acute kidney injury may also result (Schenck and Chew, 2012). In addition to hypocalcemia, transient PTH deficiency may occur (Horn and Irwin, 2000). One salicylate-intoxicated cat developed hypocalcemia associated with sodium bicarbonate therapy (Abrams, 1987).





## THERAPY FOR HYPOCALCEMIA AND HYPOPARATHYROIDISM

### General Approach

Primary hypoparathyroidism can be permanent, requiring acute and then lifelong management to alleviate and prevent clinical signs. Hypoparathyroidism following surgical removal or ablation of a parathyroid adenoma that caused hyperparathyroidism may require short-term therapy but, as remaining normal-but-atrophied parathyroid cells return to function, one should be able to taper and discontinue medications. Similarly, eclampsia (puerperal tetany) is a classic condition due to hypocalcemia in which specific and acute correction of the calcium deficiency is necessary but chronic treatment is not. In contrast to these examples, no treatment is indicated for animals with hypocalcemia attributable entirely to hypoalbuminemia, assuming the *i*Ca fraction is normal.

Treatment of hypocalcemia virtually always requires that a protocol be tailored to the individual needs of a dog or cat. Management will be effected by the magnitude of the hypocalcemia and the rate of decline in calcium concentration. The trend in serum concentrations (fluctuating, remaining stable, or quickly falling) will influence decision processes. Aggressive approaches are needed for dogs and cats with obvious clinical signs, for those with significant decreases in TCa or *i*Ca concentrations, or when severe hypocalcemia can be anticipated (e.g., with therapy for primary hyperparathyroid dogs who have endured chronically increased serum TCa concentrations; see Chapter 15). Veterinarians should not delay treatment for hypocalcemia until clinical signs are obvious. Such an approach, at best, exposes the pet to an extremely painful condition. At worst, it places the pet at risk for developing a life-threatening event.

The goal of therapy, one that may be difficult to achieve, is to increase serum calcium concentrations smoothly above the threshold responsible for clinical signs. That threshold is usually a TCa concentration of about 6.0 mg/dL, or above a plasma *i*Ca concentration of about 0.6 to 0.7 mmol/L. Individual differences can be significant, however. Clinical signs typically improve with slight increases in measurable calcium. Veterinarians should raise measured calcium concentrations conservatively, because values that increase into reference ranges increase risk for hypercalcemia, associated hyperphosphatemia, tissue mineralization, and stone formation. For anticipated or known postsurgical hypocalcemia that will be transient, as in pets being treated for primary hyperparathyroidism, it is physiologically ideal to maintain calcium concentrations above the threshold for tetany but below established reference ranges, because “below normal” values should enhance functional recovery of atrophied parathyroid glands.

### Emergency Therapy for Tetany—Diagnosis Not Apparent

In the event that a practitioner is treating a seizing animal without a specific diagnosis, anti-convulsants are usually utilized. This approach is usually beneficial, even in hypocalcemic pets. However, if treatment fails or if a diagnosis is still not obvious, blood should be drawn for glucose, calcium, and any other parameter that may lead to a diagnosis. In the meantime, IV glucose and/or calcium can be administered.

#### *Hypocalcemic Tetany: Intravenous Calcium*

When possible, hypocalcemic tetany should immediately be treated with calcium salts. Ten percent calcium gluconate, readily available and not as caustic as calcium chloride, is recommended and should be slowly administered intravenously, usually over a 10 to 30 minute period, or to effect. ECG monitoring is advisable and, if not possible, one should listen to the heart and have a finger on the pulse during the calcium infusion. If bradycardia, pulse deficits, arrhythmias, S-T segment elevation, shortened Q-T intervals, and/or premature complexes are recognized, the IV infusion should be slowed or temporarily discontinued (Peterson, 1992). This emergency therapy is usually successful and cessation of seizures, for example, is typically noted within a minute or minutes of initiating the infusion. The total dose needed to control tetany is not predictable. Furthermore, some clinical signs may be slower to respond. Nervousness, panting, and behavioral changes may persist for as long as 30 to 60 minutes after return of eucalcemia, perhaps reflecting a lag in equilibrium between CSF and circulating calcium.

#### *Calcium Dose and Salt Choices*

The calcium content of different salts varies considerably. For example, both calcium gluconate and calcium chloride supplements are available as 10% solutions in 10-mL ampules, and each ampule provides 1 g of the parent compound. However, calcium chloride provides approximately 27 mg/mL of elemental calcium, and calcium gluconate provides approximately 9 mg/mL. The 200 mg/mL calcium borogluconate solution contains the equivalent of about 15 mg/mL of elemental calcium. Calcium borogluconate is 1.6 times more concentrated and calcium chloride is 3 times more concentrated than the 10% calcium gluconate solution. Thus, guideline doses for calcium gluconate (0.5 to 1.5 mL/kg), calcium borogluconate (0.3 to 0.9 mL/kg), and calcium chloride (0.15 to 0.5 mL/kg) reflect these different concentrations (Table 16-4). It may be easiest to achieve a slow infusion by first calculating the estimated required dose and then diluting that amount in a larger volume of 0.9% saline. Recommended doses should be used as guidelines, and patient response should be the definitive factor in determining the volume administered (Skelly, 2012). Remember that extravasation of calcium chloride outside

TABLE 16-4 SOME AVAILABLE PARENTERAL CALCIUM PREPARATIONS

PREPARATIONS	APPROXIMATE CALCIUM CONTENT	DOSE	COMMENT
10% Calcium gluconate (IV)	9.3 mg Ca/mL	0.5-1.5 mL/kg	Administer slowly “to effect” Stop if bradycardia or shortened Q-T interval
		2.5-3.75 mg/kg/hr	Infusion to maintain safe serum Ca level
10% Calcium gluconate (SC)	9.3 mg Ca/mL	Dilute 2, 3, 4:1	SC to support serum calcium without IV (see text)
10% Calcium borogluconate (IV)	15.0 mg Ca/mL	0.3-0.9 mL/kg	Same as for Ca gluconate
10% Calcium chloride (IV)	27.2 mg Ca/mL	Do not use	Do not use

Ca, Calcium; IV, intravenous; Q-T, interval on an electrocardiogram (ECG); SC, subcutaneous.

a vein is caustic, potentially causing large areas of tissue death and sloughing. Extravasation may also cause calcinosis cutis (Schick et al, 1987). In our opinion, calcium chloride should never be stocked by small animal practitioners, thus eliminating any possibility of its use.

### **Hyperphosphatemia**

Infusion of calcium-rich fluids should be performed with caution in any hyperphosphatemic dog or cat. Hyperphosphatemia, however, is common among hypocalcemic animals due to mass law effects. Therefore, although a concern, as calcium increases with treatment, the phosphate concentrations should decrease. However, in conditions like CKD, the combination of calcium administration and hyperphosphatemia could cause soft tissue mineralization and further renal damage to the kidneys (Chew and Meuten, 1982).

### **Fever**

Fever, sometimes greater than 105° F, commonly accompanies tetany. Veterinarians may be tempted to treat both hypocalcemia and fever (using ice or alcohol baths and/or parenteral drugs). However, with administration of calcium, fever should be monitored but not treated. Fever usually dissipates rapidly with control of tetany. Additional measures to lower body temperature may result in hypothermia and the development of shock. Further, three of four cats reported to have had preparturient eclampsia were hypothermic (Fascetti and Hickman, 1999).

## **Subacute Management of Hypocalcemia: Post-Tetany Maintenance Therapy**

**The Issue.** Once signs of hypocalcemic tetany are controlled with an IV calcium infusion, its effects usually only last minutes to an hour or so. On the other hand, long-term maintenance therapy with oral vitamin D and oral calcium supplementation usually requires 24 to 96 hours before effect is achieved. Therefore, parenteral calcium support during the initial post-tetany period is necessary.

**The Alternatives. Repeated Intravenous Boluses.** One method for managing hypocalcemia in the immediate post-tetany period is repeated IV calcium boluses. This procedure is not recommended except in emergencies, because wide fluctuations in circulating calcium concentrations result.

**Continuous Intravenous Infusion.** Continuous IV infusion of calcium can be utilized at doses of 60 to 90 mg/kg/day elemental calcium (2.5 to 3.75 mg/kg/hr) until oral medications provide control of serum calcium concentration. Initial doses in the high end of this protocol are recommended for dogs and cats with severe hypocalcemia. The dose should be decreased according to the serum calcium concentration achieved and as oral calcium and vitamin D become effective.

Using 10% calcium gluconate solutions, 10 mL provides 93 mg of elemental calcium. A convenient protocol for infusing calcium assumes that the IV fluids are being administered at a typical maintenance rate of about 60 mL/kg/day (2.5 mL/kg/hr). Approximately 1, 2, or 3 mg/kg/hr of elemental calcium is provided by adding 40, 80, or 120 mL of 10% calcium gluconate, respectively, to each liter of fluid solution, equivalent to 6.5 to 10 mL/kg/day. Calcium salts may precipitate if added to solutions containing lactate, acetate, bicarbonate, or phosphates. Additionally, IV solutions containing sodium bicarbonate should be avoided because systemic alkalinization can decrease circulating iCa concentrations, precipitating clinical signs in dogs or cats with borderline hypocalcemia (Rosol et al, 2000).

**Subcutaneous Calcium.** Once tetany has been controlled with IV calcium gluconate, administration of subcutaneous (SC) calcium has been effective, simple, and inexpensive. Continuous IV administration of fluids is expensive and requires hospitalization. However, one can utilize the dose of calcium gluconate required to control tetany initially and administer that dose SC every 6 to 8 hours. Alternatively, a calcium dose of 60 to 90 mg/kg/day, divided, can be given. The calcium gluconate should be diluted as one part of calcium to two, three, or four parts of saline. This protocol has effectively supported serum calcium concentrations and has not caused inflammation or sloughing of skin. This is true even in dogs treated subcutaneously for months. The SC regimen is an efficacious method of supporting circulating calcium while waiting for atrophied parathyroid glands to regain function, or while waiting for oral vitamin D and calcium to have effect. The procedure is easily taught to owners, further decreasing expense.

Remember, calcium chloride should never be administered subcutaneously, but calcium gluconate is usually safe. Several cases of calcinosis cutis following SC administration of calcium gluconate have been reported (Ruopp, 2001; Schaer et al, 2001; Skelly, 2012). However, our experience with repeated SC injections of diluted 10% calcium gluconate, without problems, suggests that such terrible side effects are quite uncommon.

After normal or near-normal serum calcium concentrations have been maintained for 48 hours, the frequency of SC injections should be decreased from every 6 to every 8 hours. If serum calcium concentrations remain stable for the ensuing 48 to 72 hours, the calcium can be tapered to twice daily. This protocol is continued until parenteral calcium has been completely discontinued. Obviously, the tapering process in each patient may not be this smooth, because response to oral therapy is variable. Ideally, the serum TCa concentration should be maintained above 8 mg/dL. Concentrations below 8 mg/dL indicate a need to increase the dose or frequency of parenteral calcium. Serum calcium concentrations of 8 to 9 mg/dL suggest maintaining the current parenteral dose. Concentrations greater than 9 mg/dL may indicate need for reducing the dose. The frequency and/or dosage of parenteral calcium are often increased before the therapy can be safely decreased and then discontinued. This is true regardless of the calcium supplementation protocol used.

## **Maintenance (Chronic) Therapy for Hypoparathyroidism**

### **General**

The most appropriate therapy for hypoparathyroidism would be some form of PTH given to maintain normal physiologic concentrations, likely determined on an individual basis. However, no long-acting commercially available PTH preparation is available at the time of writing this comment, although such a product is currently being evaluated. Parenteral PTH is available on a limited basis but lasts only hours. Thus, oral administration of both a vitamin D product and a calcium product, especially in the early phases of therapy, remains the most successful means of treating hypoparathyroidism. It is emphasized that oral calcium should be a component of any early treatment plan, especially if the animal is not eating. Active intestinal calcium uptake transport mechanisms are under control of vitamin D when calcium intake is low, but vitamin D-independent passive intestinal absorption of calcium occurs when intake is high. One can take advantage of this passive-but-enhanced calcium absorption process while administered vitamin D has time to become effective (Chew et al, 2009).

Because most commercially available pet food contains adequate calcium for daily needs, once a dog is home and stable, we typically slowly taper oral calcium therapy over a period of 12 to 16 weeks. Recurrent hypocalcemia and worrisome hypercalcemia represent potential complications of treatment if adequate calcium and phosphorus monitoring is neglected. On the other hand, we have successfully helped monitor and manage a number of primary hypoparathyroid dogs for years and encourage clients to treat their pet.

### Vitamin D

**General.** Maintenance therapy for hypoparathyroidism consists of oral vitamin D and calcium supplementation. The need for vitamin D therapy is usually permanent in dogs and cats with primary, naturally occurring, parathyroid gland failure. Calcium supplementation, however, can often be tapered and even stopped after several months of administration, because dietary calcium is sufficient for maintaining the needs of the animal. Conservative doses of supplemental calcium given chronically, however, ensure that vitamin D, which raises serum calcium by promoting its intestinal absorption, has substrate upon which to function. Iatrogenic hypoparathyroidism in dogs and cats treated for primary hyperparathyroidism is often transient and lifelong therapy is not always needed.

In contrast to tetany, for which the immediate goal of treatment is to avoid recurrence of neuromuscular signs, the aim of long-term therapy is to maintain serum TCa concentrations at mildly low to low-normal concentrations (8.0 to 9.5 mg/dL). Such calcium concentrations are well above the risk threshold for clinical hypocalcemia and well below concentrations (even with day-to-day fluctuations) that might be associated with hypercalcemia and hyperphosphatemia, which would place the patient at risk for renal damage due to nephrocalcinosis. Maintaining the serum calcium concentration at the low end or just below the reference range also reduces risk of hypercalciuria and associated calculi formation. Mild hypocalcemia should also serve to promote return to function of atrophied parathyroid glands

**Vitamin D<sub>2</sub> (Ergocalciferol).** Vitamin D<sub>2</sub> is a widely available and relatively inexpensive drug (40,000 USP U/mg; Table 16-5).

Initially, large doses are required to induce normocalcemia. Dogs and cats often require 4000 to 6000 U/kg daily doses to offset the decreased biologic potency of this product in hypoparathyroid patients. Additionally, large doses are required to saturate fat depots, which is important because vitamin D is a fat-soluble vitamin. Effect of the medication is usually obvious 5 to 14 days after beginning therapy. Parenteral calcium can usually be discontinued 1 to 5 days after starting oral vitamin D treatment. The serum calcium concentrations should be below the level that might be associated with hypercalciuria (risk for calculi formation) or severe hypercalcemia and hyperphosphatemia (risk for nephrocalcinosis and renal failure).

Dogs and cats receiving vitamin D<sub>2</sub> should remain hospitalized until the serum TCa concentration remains between 8 and 10 mg/dL without parenteral support and the pet is eating and drinking on its own. Once these goals are achieved, the pet can be returned to the owner, and the vitamin D<sub>2</sub> is usually given every other day. Serum calcium concentrations should be monitored weekly, with vitamin D<sub>2</sub> doses adjusted to maintain a serum calcium concentration of 8 to 9.5 mg/dL. The aim of therapy is to avoid hypocalcemic tetany on one hand, while also limiting hypercalcemia.

Even after a pet appears stable, monthly rechecks are strongly advised for 6 months and should be followed by rechecks every 2 to 3 months indefinitely. These animals cannot be rechecked too often. Underdose can place the pet at risk for tetany. Vitamin D-induced hypercalcemia can result in renal damage and failure, a problem minimized through proper monitoring. Vitamin D<sub>2</sub> has been used in cats and dogs with success and is relatively inexpensive. Some of our dogs and cats receive medication as infrequently as twice monthly, whereas others require daily supplementation.

The drawbacks of vitamin D<sub>2</sub> include the length of time to achieve maximal effect and the length of time it takes to reduce effects if an overdose is documented. If hypocalcemia is documented, it may take days to weeks before an increase in dose is reflected in the serum calcium concentration. Hypercalcemia, if it occurs, is not easily resolved because fat-soluble vitamin D may need to be discontinued for as long as 1 to 4 weeks before serum concentrations decline significantly. Hypercalcemia should be aggressively treated with IV fluids, especially if the product of

TABLE 16-5 SOME VITAMIN D PREPARATIONS

DRUG	DOSE*	TIME TO MAXIMUM EFFECT	TIME FOR TOXICITY TO RESOLVE
1,25-dihydroxyvitamin D <sub>3</sub> (1,25[OH] <sub>2</sub> D <sub>3</sub> ; calcitriol)	<i>Initial:</i> 20 to 30 ng/kg/day, divided b.i.d. <i>Maintenance:</i> 5 to 15 ng/kg/day	1 to 4 days	2 to 14 days
Vitamin D <sub>2</sub> (ergocalciferol)	<i>Initial:</i> 4000 to 6000 U/kg/day <i>Maintenance:</i> 1000 to 2000 U/kg/7 days	5 to 21 days	7 to 28 days
Alfacalcidol	<i>Initial:</i> 0.01 to 0.03 µg/kg/day <i>Maintenance:</i> May need to be increased or decreased	1 to 4 days	2 to 14 days
Dihydrotachysterol (DHT)	<i>Initial:</i> 0.02 to 0.03 mg/kg/day <i>Maintenance:</i> 0.01 to 0.02 mg/kg/24 to 48 hours	1 to 7 days	2 to 14 days

\*Note: Doses are listed as mg, µg, ng, and Units/kg of body weight.

the serum calcium multiplied by the serum phosphate is greater than 60 to 80. These factors make ergocalciferol the least attractive agent for long-term treatment of hypocalcemia. We restrict use of ergocalciferol to dogs whose owners have financial limitations that prevent use of calcitriol.

**Calcidiol and Alfalcidol.** Alfalcidol has about twice the potency of ergocalciferol in binding capacity to natural calcitriol receptors. It is, however, 500 times less potent than calcitriol in this regard. It is a reasonable alternative to calcitriol. This form of vitamin D must undergo 25-hydroxylation by the liver before it is metabolically active. The process occurs rapidly and is unregulated; therefore the time required for effect is similar to that of calcitriol (Skelly, 2012). The drug is available in some countries as 0.25, 0.5, and 1  $\mu\text{g}$  capsules and in a liquid formulation of 2  $\mu\text{g}/\text{mL}$ . As available, the drug can be used in cats and small dogs. The recommended dose is 0.01 to 0.03  $\mu\text{g}/\text{kg}$ , once daily. The dose should be tailored to the needs of the individual (Skelly, 2012).

**Oral 1,25-Dihydroxyvitamin D<sub>3</sub>; Calcitriol.** Calcitriol is the most potent form of vitamin D in stimulating intestinal calcium transport and osteoblastic activity in the skeleton. It also has the most rapid onset of maximal action and the shortest biologic half-life (Chew and Nagode, 2000; Rosol et al, 2000). Oral calcitriol has a direct effect on intestinal receptors, stimulating intestinal calcium absorption to a greater degree than other forms of vitamin D, including parenteral administration (Coburn, 1990). Because calcitriol only programs undifferentiated cells in intestinal crypts and turnover of these cells takes place every 24 hours, calcitriol is given twice daily to ensure continuous effect (Chew et al, 2009).

The dose of calcitriol can be adjusted and changes take effect quickly because of its rapid onset of action and brief biologic effect. If hypercalcemia occurs, the effects of this drug abate quickly after stopping therapy or with dose reduction. The peak serum concentration of calcitriol is reached after 4 hours, the half-life is 4 to 6 hours, and the biologic half-life is 2 to 4 days. A loading dose of 20 to 30  $\text{ng}/\text{kg}/\text{day}$  can be administered for 2 to 4 days and then decreased to a maintenance dose of 5 to 15  $\text{ng}/\text{kg}/\text{day}$ , divided and given twice a day. (Note: This dose is in nanograms.) Calcitriol (250 and 500  $\text{ng}$  capsules as well as 1000  $\text{ng}/\text{mL}$  liquid formulation; Rocaltrol, Hoffman-LaRoche) is formulated for humans and may require reformulation for dogs and cats. The concerns we have regarding calcitriol only relate to expense and the need for reformulation. Although reformulation should be reliable, inconsistencies occur among pharmacies. Reformulation by specialty pharmacies of calcitriol into liquid or into capsule sizes tailored to the need of specific pets may not provide the same effectiveness to each patient.

We have had experience with one dog that did not respond to oral calcitriol at any dose. This dog was known to have liver “insufficiency” because a diagnosis of vascular anomaly had been made 10 years earlier. Although calcitriol is “active,” it is interesting to note lack of response in this setting. Although this dog was not tested, it is now understood that if a patient is documented to have concurrent hypomagnesemia, supplementation with the sulfate form should be considered at a dose of 1 to 2  $\text{mEq}/\text{kg}/\text{day}$ . In some cases, normalization of serum magnesium concentrations may lead to lower requirements of calcitriol and/or calcium.

**Parenteral Calcitriol.** In the event that oral medication cannot be administered or if oral calcitriol is ineffective, parenteral calcitriol can be given. Empirically, the same dose as that used for oral administration can be utilized (20 to 30  $\text{ng}/\text{kg}/\text{day}$ ). The drug is usually given IV to human dialysis patients, three times weekly, immediately after dialysis (Rolla et al, 1993; Selgas et al, 1993). The drug can also be given subcutaneously or intraperitoneally. We have used parenteral calcitriol successfully by administering it IV, t.i.d.

to effect and then progressively decreasing the dose. As with other forms of vitamin D, in-hospital monitoring is recommended until circulating calcium concentrations are stable. Owners can then administer the drug subcutaneously.

**Dihydrotachysterol.** DHT, although not available at the time of writing, is described here, because it may be marketed in the future. It is a synthetic vitamin D analogue. The advantages of DHT over vitamin D<sub>2</sub> are that it raises the serum calcium concentration more rapidly (1 to 7 days) and its effect dissipates faster when administration is discontinued. Veterinarians, therefore, have more control over therapy. DHT is more potent than vitamin D<sub>2</sub>; 1.0  $\text{mg}$  of DHT is equivalent to 120,000 U of vitamin D<sub>2</sub>. The rapid onset of action and the increased effectiveness of DHT are a result of its stereochemistry; the A ring of the sterol structure is rotated 180 degrees so that the hydroxyl group in the third position serves as a pseudo-1-hydroxyl group (Fig. 16-9). Therefore, after hepatic 25-hydroxylation, DHT has biologic activity that is greater than 25-hydroxyvitamin D (25[OH]D) and less than that of 1,25 dihydroxyvitamin D<sub>3</sub> (1,25[OH]<sub>2</sub>D<sub>3</sub>) (Peterson, 1982). The polarity and lower dose requirements of DHT limit its storage in fat compared with ergocalciferol.

DHT was initially given at a dose of 0.03  $\text{mg}/\text{kg}/\text{day}$  (divided and given twice a day) for 2 days or until effect is demonstrated, then 0.02  $\text{mg}/\text{kg}/\text{day}$  for several days, and finally 0.01  $\text{mg}/\text{kg}/\text{day}$  in divided dosages. As suggested with the less potent forms of vitamin D, significant individual variation in dose requirements dictate that pets remain hospitalized until the serum TCa concentration remains stable between 8 and 9.5  $\text{mg}/\text{dL}$  (or the iCa 1.0 to 1.2  $\text{mmol}/\text{L}$ ) for several days. We have seen cats and dogs that appeared to be resistant to the tablet and capsule forms of this drug (0.125, 0.25, 0.4  $\text{mg}$ ) but respond readily to the liquid (0.25  $\text{mg}/\text{mL}$ ). We have also seen dogs and cats fail to respond to any form of DHT but respond to calcitriol. Rechecks of the serum calcium concentration on a weekly basis allow dosage adjustment while avoiding prolonged hypercalcemia or hypocalcemia. As with vitamin D<sub>2</sub>, long-term rechecks at least every 2 to 3 months are strongly encouraged. Serum calcium concentrations higher than desired (> 10.5 to 11.0  $\text{mg}/\text{dL}$ ) should be treated by lowering or discontinuing vitamin D therapy and, depending on the severity of the clinical signs and biochemistry abnormalities, possibly initiating IV fluids (see Chapter 15). The lag period between stopping DHT and noting a fall in the serum calcium concentration has been 4 to 14 days, a longer period than is needed with calcitriol but a briefer period than with vitamin D<sub>2</sub>.

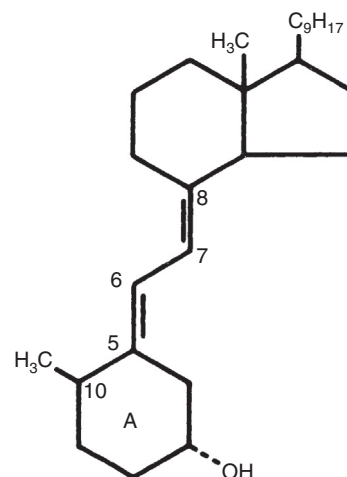


FIGURE 16-9 The chemical structure of dihydrotachysterol (DHT).

### Calcium Supplementation

**Initial Approach to Oral Calcium.** Once tetany is controlled with bolus IV calcium, serum calcium levels should be maintained with a slow IV infusion or SC injections. When the pet is able to eat without vomiting, oral calcium and vitamin D therapy should be initiated. Within 24 hours, parenteral calcium administration can begin to be tapered, and within 72 hours it is usually discontinued. Meanwhile, oral therapy is maintained. In this manner, smooth continuous control is achieved. Calcium available within intestinal content must be adequate when treating hypoparathyroidism, because long-term success depends on the action of administered vitamin D, which increases intestinal absorption of calcium. Commercial pet food typically contains sufficient calcium to supply the needs of hypoparathyroid dogs and cats. However, because symptomatic hypocalcemia can be fatal, such catastrophic consequences of severe hypocalcemia must be avoided. For this reason, especially early in the course of therapy, we continue oral calcium at low doses indefinitely.

**Calcium Supplements.** Supplements can be provided by administering calcium as the gluconate, lactate, chloride, or carbonate salt. Each has disadvantages. Calcium gluconate and lactate tablets contain relatively small quantities of elemental calcium, so relatively large numbers of tablets may need to be given. Calcium chloride and carbonate tablets contain large quantities of calcium but the chloride form tends to produce gastric irritation, whereas the carbonate form could contribute to alkalosis, which has the potential to worsen hypocalcemia. Calcium carbonate is 40% calcium. One gram yields 20 mEq of calcium, and gastric acid converts the calcium carbonate to calcium chloride. Calcium lactate is 13% calcium, and 1 g yields 6.5 mEq. Calcium gluconate contains 9% calcium, and 1 g yields 4.5 mEq.

Although there are numerous calcium preparations available (Table 16-6), calcium carbonate is the preparation of choice in treating hypoparathyroid humans because of its high percentage of calcium, low cost, lack of gastric irritation, and ready availability in stores in the form of antacids (Arnaud and Kolb, 1991). No specific research to support recommendations for use of this drug is available for dogs and cats, although our success with calcium carbonate has been excellent.

**Treatment Protocol.** In cats, the dosage of calcium is approximately 0.5 to 1.0 g/day in divided doses. In dogs, the dosage is usually 1.0 to 4.0 g/day in divided doses. Alternatively, the dose of elemental calcium can be determined as about 25 to 50 mg/kg/day, divided into two or three daily doses. Recommendations regarding calcium are always approximate, in part because the effectiveness of administered vitamin D, the oral preparation of calcium used, and the intestinal milieu are major contributors to the stability of serum calcium concentrations. As administered vitamin D reaches a steady level, the dose of oral calcium can be gradually tapered over a period of 2 to 4 months. This method of treatment avoids unnecessary therapy, considering that dietary calcium should be sufficient to supply the needs of the pet and should decrease the demands of treatment placed on the owner. In spite of this logical approach, we tend to continue low dose calcium supplementation to our patients.

### Summary of Keys to Long-Term Success

It is emphasized that the ideal serum calcium concentration in treated hypoparathyroid animals, long-term, is in the low-normal-to-slightly-low range. We attempt to achieve serum TCa concentrations of 9.0 to 10.5 mg/dL. Alternatively, one could utilize serum iCa concentrations with the goal of about 0.9 to 1.1 mmol/L. Serum TCa concentrations less than 8.0 mg/dL are a concern due to increased risk of symptomatic hypocalcemia, which can result in life-threatening convulsions or respiratory arrest. Serum TCa concentrations above 10 are unnecessarily high for avoiding tetany and increase risk of unwanted hypercalcemia, hyperphosphatemia, or a calcium-phosphorus product greater than 60 to 80. Each of these latter concerns could cause permanent renal damage and failure. Avoiding excess serum calcium concentrations also decreases calciuria (calcium in the urine) and risk of calculi within the urinary tract to which patients lacking PTH are predisposed.

It is quite valuable for the pet owner to understand as much as possible regarding hypoparathyroidism, hypocalcemia, and hypercalcemia. As owner knowledge increases, they gain a better understanding of how difficult it can be to achieve goals of therapy and

TABLE 16-6 SOME AVAILABLE ORAL CALCIUM PREPARATIONS\*†

FORMULATIONS	PREPARATIONS AVAILABLE	APPROXIMATE CALCIUM CONTENT	COMMENT
Calcium Carbonate	Tablets: many	1 mg of Ca/2.5 mg tablet	Commonly used
	500 mg	200 mg of Ca/tablet	
	750 mg	300 mg of Ca/tablet	
	1000 mg	400 mg of Ca/tablet	
	1250 mg	500 mg of Ca/tablet	
Calcium Gluconate	Tablets: many	1 mg of Ca/11.2 mg tablet	Less commonly used
	325 mg	30 mg of Ca/tablet	
	500 mg	45 mg of Ca/tablet	
	650 mg	60 mg of Ca/tablet	
	1000 mg	90 mg of Ca/tablet	
Calcium Lactate	Tablets: many	1 Ca/7.7 mg tablet	Less commonly used
	325 mg	42 mg of Ca/tablet	
	650 mg	85 mg of Ca/tablet	

From Schenck PA, Chew DJ: Investigation of hypercalcaemia and hypocalcaemia. In Mooney CT, Peterson ME, editors: *BSAVA manual of canine and feline endocrinology*, ed 4, British Small Animal Veterinary Association, 2012, p 221.

Ca, Calcium.

\*All are dosed at 25 to 50 mg/kg/day.

†Usually can be tapered to low doses or stopped once vitamin D reaches effective dose.

that one of the only means of improving of long-term success is frequent monitoring of calcium, phosphorus, and renal parameters. The importance of blood monitoring is underscored by realizing that one can never predict results. Remind clients that polydipsia, polyuria, decrease in appetite, vomiting, or depression may be indicative of hypercalcemia, and veterinary attention should be sought immediately should any of these signs be observed. Most clients need little reminder regarding the clinical signs of hypocalcemia because those were the signs in their pet that first necessitated veterinary care. Regardless, if an owner observes any signs of hypocalcemia (from restlessness to convulsions), veterinary care should be sought.

Occasional calcium assessments will reveal results higher or lower than desired, but catastrophic changes are quite uncommon when frequent monitoring, changing dose as predicted from test results, and luck are linked. The need for modifying doses of vitamin D can usually be explained by changes in diet, activity, and alterations in individual health. How often should these patients be monitored? Once returned to the owner, our uncomplicated patients have been checked twice the first week or two, weekly for 3 weeks, monthly for 3 months, and then every 2 to 3 months thereafter.

If a dose of calcitriol needs to be increased or decreased, changes should be small (10% to 20%). Increasing or decreasing the vitamin D dose should be followed by adequate time to determine if it had the anticipated result. The lag period varies because a dose decrease in ergocalciferol, for example, might take several weeks before change is documented on serum testing. Use of calcitriol shortens this lag period from weeks to days (see Table 16-5). Animals that develop worrisome iatrogenic hypercalcemia secondary to excess vitamin D administration would most likely benefit from hospitalization, IV fluid therapy, and, perhaps, furosemide, steroids, bisphosphonates, or calcitonin. Until the hypercalcemia is resolved, oral calcium and vitamin D should be discontinued.

Although studies evaluating long-term response to therapy have not been published, it is fair to state that many of our patients have done well for long time periods. Success has been achieved using all forms of vitamin D, because this is something determined in part by owners. As previously discussed, it is the monitoring, owner knowledge, and luck that have significant roles in long-term success. Whenever possible, we utilize calcitriol as the source of vitamin D because its relatively quick response to increasing or decreasing doses is easier to manage than the more long acting products. It has been pointed out that hypercalciuria, nephrocalcinosis, urolithiasis, and reduced renal function have been noted in people

being treated for primary hypoparathyroidism. As many as 80% of individuals treated for longer than 2 years have been reported to have decreases in creatinine clearance. All of these problems can be traced to occasional hypercalcemia due to excess vitamin D effect. Because these patients lack PTH action at the level of renal tubules, hypercalciuria occurs more readily, even if the serum calcium concentrations are within reference intervals. Therefore, as discussed, it is extremely important to maintain calcium concentrations below reference limits as much as possible while understanding that this alone may not be sufficient to avoid hypercalciuria.



### PARATHYROID HISTOLOGY IN HYPOPARATHYROIDISM

Animals have been classified as having idiopathic hypoparathyroidism when there is no evidence of trauma, cervical malignancy, surgical destruction, or other obvious damage to the neck or parathyroid glands. The glands from these dogs have been difficult to locate visually or via ultrasound and are microscopically atrophied. Approximately 60% to 80% of the glands are replaced by mature lymphocytes, occasional plasma cells, extensive degeneration of chief cells, and/or fibrous connective tissue. Chief cells are randomly isolated in multiple small areas or bands at the periphery. In the early stages of an immune-mediated attack, the gland is infiltrated with lymphocytes and plasma cells with nodular regenerative hyperplasia of remaining chief cells. Later, the parathyroid gland is completely replaced by lymphocytes, fibroblasts, and neocapillaries with only an occasional viable chief cell. The final interpretation is one of lymphocytic parathyroiditis (Sherding et al, 1980; Capen and Marten, 1983).



### PROGNOSIS

The prognosis in dogs and cats with primary hypoparathyroidism depends, for the most part, on the dedication of the owner, the attention of the veterinarian, and luck. With proper therapy, the prognosis is excellent. A large majority of the dogs we have treated have lived more than 5 years from the time of diagnosis and treatment. However, proper management requires close monitoring of the serum calcium concentration, ideally every 1 to 3 months once the pet is stabilized. The more frequent the rechecks, the better chance the pet has of avoiding extremes in serum calcium concentrations. The chance for a normal life expectancy is excellent with proper care.

## REFERENCES

- Abrams KL: Hypocalcemia associated with administration of sodium bicarbonate for salicylate intoxication in a cat, *J Am Vet Med Assoc* 191:235, 1987.
- Arnaud CD, Kolb FO: The calciotropic hormones and metabolic bone disease. In Greenspan FS, Baxter JD, editors: *Basic and clinical endocrinology*, ed 5, Los Altos, CA, 1991, Lange Medical Publications, p 247.
- Aroch I, et al.: Serum electrolyte concentrations in bitches with eclampsia, *Vet Rec* 145:318, 1999.
- Atkins CE, et al.: Clinical, biochemical, acid-base, and electrolyte abnormalities in cats after hypertonic sodium phosphate enema administration, *Am J Vet Res* 46:980, 1985.
- Barber PJ, Elliott J: Study of calcium homeostasis in feline hyperthyroidism, *J Sm Anim Pract* 37:575, 1996.
- Barber PJ, et al.: Measurement of feline parathyroid hormone: assay validation and sample handling studies, *J Small Anim Pract* 34:614, 1993.
- Bassett JR: Hypocalcemia and hyperphosphatemia due to primary hypoparathyroidism in a six-month-old kitten, *J Am Anim Hosp Assoc* 34:503, 1998.
- Bienzie D, et al.: Relationship of serum total calcium to serum albumin in dogs, cats, horses, and cattle, *Can Vet J* 34:360, 1993.
- Broadus AE: Mineral metabolism. In Felig P, et al., editor: *Endocrinology and metabolism*, New York, 1981, McGraw-Hill, p 1056.
- Broadus AE, et al.: Humoral hypercalcemia of cancer: identification of a novel parathyroid hormone-like peptide, *N Engl J Med* 319:556, 1988.
- Brown EM, et al.: Calcium-ion-sensing cell-surface receptors, *N Engl J Med* 333:234, 1995.
- Bruyette DS, Feldman EC: Primary hypoparathyroidism in the dog: report of 15 cases and review of 13 previously reported cases, *J Vet Intern Med* 2:7, 1988.
- Burk RL, Schaubhut CW: Spontaneous primary hypoparathyroidism in a dog, *J Am Anim Hosp Assoc* 11:784, 1975.
- Bush WW, et al.: Secondary hypoparathyroidism attributed to hypomagnesemia in a dog with protein-losing enteropathy, *J Am Vet Med Assoc* 219:1732, 2001.

- Calia CM, et al.: Acute tumor lysis syndrome in a cat with lymphoma, *J Vet Intern Med* 10:409, 1996.
- Capen CC, Martin SL: Calcium-regulatory hormones and diseases of the parathyroid glands. In Ettinger SJ, editor: *Textbook of veterinary internal medicine*, Philadelphia, 1983, WB Saunders, p 1581.
- Chew DJ, Meuten DJ: Disorders of calcium and phosphorus metabolism, *Vet Clin North Am Small Anim Pract* 12:411, 1982.
- Chew DJ, Nagode LA: Renal secondary hyperparathyroidism, Proceedings of the 4th Annual Meeting of The Society for Comparative Endocrinology, 1990, p 17.
- Chew DJ, Nagode LA: Treatment of hypoparathyroidism. In Bonagura JD, editor: *Kirk's current veterinary therapy XIII*, Philadelphia, 2000, WB Saunders, p 340.
- Chew DJ, et al.: Utility of diagnostic assays in the evaluation of hypercalcemia and hypocalcemia: parathyroid hormone, vitamin D metabolites, parathyroid hormone-related peptide, and ionized calcium. In Bonagura JD, editor: *Kirk's current veterinary therapy XII*, Philadelphia, 1995, WB Saunders, p 378.
- Chew DJ, et al.: Treatment of hypoparathyroidism. In Bonagura JD, Twedt DC, editors: *Kirk's current veterinary therapy XIV*, St Louis, 2009, Saunders/Elsevier, p 241.
- Coburn JW: Use of oral and parenteral calcitriol in the treatment of renal osteodystrophy, *Kidney Int* 38(Suppl):S54, 1990.
- Crawford MA, Dunstan RW: Hypocalcemia secondary to primary hypoparathyroidism in a dog, *Calif Vet May/June*:21, 1985.
- DeLay J: Laing: Nutritional osteodystrophy in puppies fed a BARF diet, *AHL Newsletter* 6:23, 2002.
- Dhupa N, Proulx J: Hypocalcemia and hypomagnesemia, *Vet Clin North Am Small Anim Pract* 28:587, 1998.
- Drobatz KJ, Casey KK: Eclampsia in dogs: 31 cases (1995-1998), *J Am Vet Med Assoc* 217:216, 2000.
- Drobatz KJ, Hughes D: Concentration of ionized calcium in plasma from cats with urethral obstruction, *J Am Vet Med Assoc* 211:1392, 1997.
- Elin RJ: Magnesium: the fifth but forgotten electrolyte, *Clin Chem* 102:616, 1994.
- Fascetti AJ, Hickman MA: Preparturient hypocalcemia in four cats, *J Am Vet Med Assoc* 215:1127, 1999.
- Feldman EC, Krutzik S: Case reports of parathyroid hormone concentrations in spontaneous canine parathyroid disorders, *J Am Anim Hosp Assoc* 17:393, 1981.
- Flanders JA: Surgical therapy of the thyroid, *Vet Clin N Am Small Anim Pract* 24:607, 1994.
- Flanders JA, Reimers TJ: Radioimmunoassay of parathyroid hormone in cats, *Am J Vet Res* 52:422, 1991.
- Flanders JA, et al.: Feline thyroidectomy: a comparison of postoperative hypocalcemia associated with three different surgical techniques, *Vet Surg* 16:362, 1987.
- Flanders JA, et al.: Adjustment of total serum calcium concentration for binding to albumin and protein in cats: 291 cases (1986-1987), *J Am Vet Med Assoc* 194:1609, 1989.
- Flanders JA, et al.: Functional analysis of ectopic parathyroid activity in cats, *Am J Vet Res* 52:1336, 1991.
- Forbes S, et al.: Primary hypoparathyroidism in a cat, *J Am Vet Med Assoc* 196:1285, 1990.
- Freeman LM, et al.: Fanconi's syndrome in a dog with primary hypoparathyroidism, *J Vet Int Med* 8:349, 1994.
- Gow AG, et al.: Hypovitaminosis D in dogs with inflammatory bowel disease and hypoalbuminemia, *J Small Anim Pract* 52:411, 2011.
- Graves TK: Complications of treatment and concurrent illness associated with hyperthyroidism in cats. In Bonagura JD, editor: *Kirk's current veterinary therapy XII*, Philadelphia, 1995, WB Saunders, p 369.
- Grosenbaugh DA, et al.: Evaluation of a portable clinical analyzer in a veterinary hospital setting, *J Am Vet Med Assoc* 213:691, 1998.
- Gunn-Moore D: Feline endocrinopathies, *Vet Clinics North Amer Small Anim Pract* 35:171, 2005.
- Hansen B: Disorders of magnesium. In DiBartola SP, editor: *Fluid therapy in small animal practice*, ed 2, Philadelphia, 2000, WB Saunders, p 175.
- Henderson RA, et al.: Development of hypoparathyroidism after excision of laryngeal rhabdomyosarcoma in a dog, *J Am Vet Med Assoc* 198:639, 1991.
- Henik RA, et al.: Rickets caused by excessive renal phosphate loss and apparent abnormal vitamin D metabolism in a cat, *J Am Vet Med Assoc* 215:1644, 1999.
- Hess RS, et al.: Clinical, clinicopathologic, radiologic, and ultrasonographic abnormalities in dogs with fatal acute pancreatitis: 70 cases (1986-1995), *J Am Vet Med Assoc* 213:665, 1998.
- Hess RS, et al.: Concurrent disorders in dogs with diabetes mellitus: 221 cases (1993-1998), *J Am Vet Med Assoc* 217:1166, 2000.
- Horn B, Irwin PJ: Transient hypoparathyroidism following successful treatment of hypercalcemia of malignancy in a dog, *Aust Vet J* 78:690, 2000.
- Jorgensen LS, et al.: Electrolyte abnormalities induced by hypertonic phosphate enemas in two cats, *J Am Vet Med Assoc* 187:1367, 1985.
- Kimmel SE, et al.: Hypomagnesemia and hypocalcemia associated with protein-losing enteropathy in Yorkshire Terriers: five cases (1992-1998), *J Am Vet Med Assoc* 217:703, 2000.
- Kimmel SE, et al.: Incidence and prognostic value of low plasma ionized calcium concentration in cats with acute pancreatitis: 46 cases (1996-1998), *J Am Vet Med Assoc* 219:1105, 2001.
- Klein MK, et al.: Treatment of thyroid carcinoma in dogs by surgical resection alone: 20 cases (1981-1989), *J Am Vet Med Assoc* 206:1007, 1995.
- Kornegay JN: Hypocalcemia in dogs, *Comp Cont Ed Small Anim Pract* 4:103, 1982.
- Kornegay JN, et al.: Idiopathic hypocalcemia in four dogs, *J Am Anim Hosp Assoc* 16:723, 1980.
- Lalor AM, et al.: Cats with inflammatory bowel disease and intestinal small cell lymphoma have low serum concentrations of 25-hydroxyvitamin D, *J Vet Intern Med* 28:351, 2014.
- Li YC, et al.: Normalization of mineral ion homeostasis by dietary means prevents hyperparathyroidism, rickets, and osteomalacia, but not alopecia in vitamin D-receptor ablated mice, *Endocrinol* 139:4391, 1998.
- Malloy PJ, et al.: The vitamin D receptor and the syndrome of hereditary 1,25-dihydroxyvitamin D-resistant rickets, *Endocr Rev* 20:156, 1999.
- Marx SJ: Hyperparathyroid and hypoparathyroid disorders, *N Engl J Med* 343:1863, 2000.
- Meininger ME, Kendler JS: Trousseau's sign, *N Engl J Med* 343:1855, 2000.
- Mellanby RJ, et al.: Hypocalcemia associated with low serum vitamin D metabolite concentrations in two dogs with protein-losing enteropathies, *J Small Anim Pract* 46:345, 2005.
- Meuten DJ, Armstrong PJ: Parathyroid disease and calcium metabolism. In Ettinger SJ, editor: *Textbook of veterinary internal medicine*, ed 3, Philadelphia, 1989, WB Saunders, p 1610.
- Meuten DJ, et al.: Relationship of serum total calcium to albumin and total protein in dogs, *J Am Vet Med Assoc* 180:63, 1982.
- Meyer DJ, Tyrrell TG: Idiopathic hypoparathyroidism in a dog, *J Am Vet Med Assoc* 168:858, 1976.
- Milnor WR: Properties of cardiac tissues. In Mountcastle VB, editor: *Medical physiology*, St Louis, 1980, CV Mosby Co, p 980.
- Mora JR, et al.: Vitamin effects on the immune system: vitamins A and D take center stage, *Nat Rev Immunol* 8:685, 2008.
- Padgett SL, et al.: Efficacy of parathyroid gland autotransplantation in maintaining serum calcium concentrations after bilateral thyroparathyroidectomy in cats, *J Am Anim Hosp Assoc* 34:219, 1998.
- Parker JSL: A probable case of hypoparathyroidism in a cat, *J Small Anim Pract* 32:470, 1991.
- Pearce SHS, et al.: A familial syndrome of hypocalcemia with hypercalciuria due to mutations in the calcium-sensing receptor, *N Engl J Med* 335:1115, 1996.
- Persons DA, et al.: Tumor lysis syndrome and acute renal failure after treatment of non-small-cell lung carcinoma with combination irinotecan and cisplatin, *Am J Clin Oncol* 21:426, 1998.

- Peterson ME: Treatment of canine and feline hypoparathyroidism, *J Am Vet Med Assoc* 181:1434, 1982.
- Peterson ME: Hypoparathyroidism. In Kirk RW, editor: *Current veterinary therapy IX*, Philadelphia, 1986, WB Saunders, p 1039.
- Peterson ME: Hypoparathyroidism and other causes of hypocalcemia in cats. In Kirk RW, Bonagura JA, editors: *Current veterinary therapy XI*, Philadelphia, 1992, WB Saunders, p 376.
- Peterson ME, et al.: Idiopathic hypoparathyroidism in five cats, *J Vet Intern Med* 5:47, 1991.
- Piek CJ, Teske E: Tumor lysis syndrome in a dog, *Tijdschr Diergeneeskd* 121:64, 1996.
- Rasmussen H: Theoretical considerations in the treatment of osteoporosis. In De Luca HF, editor: *Osteoporosis: recent advances in pathogenesis and treatment*, Baltimore, 1981, University Park Press, p 383.
- Rasmussen H: The cycling of calcium as an intracellular messenger, *Sci Am* 261:66, 1989.
- Refsal KR, et al.: Update on the diagnosis and treatment of disorders of calcium regulation, *Vet Clinics N Amer Sm Anim Prac* 31:1043, 2001.
- Rolla D, et al.: Effects of subcutaneous calcitriol administration on plasma calcium and parathyroid hormone concentrations in continuous ambulatory peritoneal dialysis uremic patients, *Peritoneal Dialysis Int* 13:118, 1993.
- Rosol TJ, Capen CC: Calcium-regulating hormones and diseases of abnormal mineral (calcium, phosphorus, magnesium) metabolism. In Kaneko JJ, Harvey JW, Bruss ML, editors: *Clinical biochemistry of domestic animals*, San Diego, 1997, Academic Press, p 619.
- Rosol TJ, et al.: Disorders of calcium. In DiBartola SP, editor: *Fluid therapy in small animal practice*, ed 2, Philadelphia, 2000, WB Saunders, p 108.
- Roth SI, Capen CC: Ultrastructural and functional correlations of the parathyroid gland, *Int Rev Exp Pathol* 13:161, 1974.
- Ruopp JL: Primary hypoparathyroidism in a cat complicated by suspect iatrogenic calcinosis cutis, *J Am Anim Hosp Assoc* 37:370, 2001.
- Russell NJ, et al.: Primary hypoparathyroidism in dogs: a retrospective study of 17 cases, *Australian Vet J* 84:285, 2006.
- Ryzen E, Rude RK: Low intracellular magnesium in patients with acute pancreatitis and hypocalcemia, *West J Med* 152:145, 1990.
- Schaer M, et al.: Severe calcinosis cutis associated with treatment of hypoparathyroidism in a dog, *J Am Anim Hosp Assoc* 37:364, 2001.
- Schenck PA, Chew DJ: Prediction of serum ionized calcium concentration by serum total calcium measurement in dogs, *Am J Vet Res* 66:1330, 2005.
- Schenck PA, Chew DJ: Prediction of serum ionized calcium concentration by serum total calcium measurement in cats, *Can J Vet Res* 74:209, 2010.
- Schenck PA, Chew DJ: Investigation of hypercalcaemia and hypocalcaemia. In Mooney CT, Peterson ME, editors: *BSAVA manual of canine and feline endocrinology*, ed 4, British Small Animal Veterinary Association, 2012, p 221.
- Schenck PA, et al.: Effects of storage on normal canine serum ionized calcium and pH, *Am J Vet Res* 56:304, 1995.
- Schenck PA, et al.: Effects of storage on serum ionized calcium and pH from horses with normal and abnormal ionized calcium concentrations, *Vet Clin Pathol* 25:118, 1996.
- Schenck PA, et al.: Disorders of calcium: hypercalcemia and hypocalcemia. In DiBartola SP, editor: *Fluid, electrolyte, and acid-base disorders*, ed 4, St Louis, 2012, Elsevier/Saunders, p 120.
- Schick MP, et al.: Calcinosis cutis secondary to percutaneous penetration of calcium chloride in dogs, *J Am Vet Med Assoc* 191:207, 1987.
- Selgas R, et al.: The pharmacokinetics of a single dose of calcitriol administered subcutaneously in continuous ambulatory peritoneal dialysis patients, *Peritoneal Dialysis Int* 13:122, 1993.
- Sherding RG, et al.: Primary hypoparathyroidism in the dog, *J Am Vet Med Assoc* 176:439, 1980.
- Skelly BJ: Hypoparathyroidism. In Mooney CT, Peterson ME, editors: *BSAVA manual of canine and feline endocrinology*, ed 4, British Small Animal Veterinary Association, 2012, p 56.
- Tepperman J: *Metabolic and endocrine physiology*, Chicago, 1980, Year Book Medical Publishers, 297.
- Tomsa K, et al.: Nutritional secondary hyperparathyroidism in six cats, *J Sm Anim Pract* 40:533, 1999.
- Torrance AG: Disorders of calcium metabolism. In Torrance AG, Mooney CT, editors: *Manual of small animal endocrinology*, ed 2, British Small Animal Veterinary Association, 1998, p 129.
- Torrance AG, Nachreiner R: Intact parathyroid hormone assay and total calcium concentration in the diagnosis of disorders of calcium metabolism in dogs, *J Vet Intern Med* 3:86, 1989.
- Vaden SL, et al.: A retrospective case-control study of acute renal failure in 99 dogs, *J Vet Intern Med* 11:58, 1997.
- Weir EC, et al.: Isolation of 16,000-dalton parathyroid hormone like proteins from two animal tumors causing humoral hypercalcemia of malignancy, *Endocrinology* 123:2744, 1988.
- Welches CD, et al.: Occurrence of problems after three techniques of bilateral thyroidectomy in cats, *Vet Surg* 18:392, 1989.
- Wysolmerski JJ, Insogna KL: The parathyroid glands, hypercalcemia, and hypocalcemia. In Goldman L, Schafer AI, editors: *Goldman's Cecil medicine*, ed 24, Philadelphia, 2012, Elsevier/Saunders, p 1591.
- Yates AJ, et al.: Effects of a synthetic peptide of a parathyroid-related protein on calcium homeostasis, renal tubular calcium reabsorption and bone metabolism in vivo and in vitro in rodents, *J Clin Invest* 81:932, 1988.
- Yu ASL: Disorders of magnesium and phosphorus. In Goldman L, Schafer AI, editors: *Goldman's Cecil medicine*, ed 24, Philadelphia, 2012, Elsevier/Saunders, p 753.
- Zivin JR, et al.: Hypocalcemia: a pervasive metabolic abnormality in the critically ill, *Am J Kidney Dis* 37:689, 2001.