Historically, primary hyperparathyroidism has been defined as the presence of increased parathyroid hormone (PTH) concentration or PTH in the reference range, in the face of increased ionized serum calcium, in the absence of azotemia, and with one or two enlarged parathyroid glands visualized on ultrasonography or at surgery (Feldman et al. 2005; Gear et al. 2005; Rasor et al. 2007). Primary hyperparathyroidism is rare in cats. There have only been 13 cases described to date (Kallet et al. 1991; Marquez et al. 1995; den Hertog et al. 1997; Reimer et al. 2005; Garrett et al. 2007; Sellon et al. 2009). Prognosis in cats is good if all autonomously secreting tissue is removed.

Anatomy

The parathyroid glands in dogs and cats are tan-colored ovoid structures closely associated with each thyroid gland. The external parathyroid is cranially located, sitting on the ventral aspect of the thyroid capsule (Hullinger 1993), sometimes even a few millimeters from the capsule in loose fascia. The internal parathyroid is more caudally located, often two-thirds of the distance towards the caudal pole. It can be within the thyroid parenchyma, but is also occasionally found protruding through the parenchyma on the dorsal surface, especially when enlarged. Ultrasound of enlarged glands normally shows them to be located in either the cranial or caudal pole, although in 10% of dogs the gland is present in the mid-body of the thyroid (Wisner et al. 1997). A normal parathyroid is approximately 1 mm thick and 5 mm long (Flanders 1993). Dogs and cats have four parathyroid glands and ectopic parathyroid tissue is rare. Embryologically, the glands arise from the third and fourth pharyngeal pouches and remain associated with the thyroid glands. Theoretically, parathyroid tissue can migrate anywhere within the neck down to the heart base and reportedly ectopic parathyroid tissue is present in 35–50% of cats and 6–100% of dogs (Nicholas & Swingle 1925; Reed et al. 1928).

The majority of the blood supply to the thyroid and parathyroid glands comes from the cranial thyroid artery, a branch of the carotid artery (Hullinger 1993). The caudal thyroid artery is a branch of the brachiocephalic artery and is present in most dogs, but this artery is absent in cats (Nicholas & Swingle 1925). The venous drainage of the thyroid and parathyroid is similar to that of the arterial supply, by way of the cranial and caudal thyroid veins. The cranial vein drains into the internal jugular vein, and the caudal vein enters the brachiocephalic vein. Lymphatic drainage is by way of the cranial and caudal deep cervical lymph nodes. Efferent lymphatics reach the venous system by way of the right lymphatic duct and left tracheal duct (Hullinger 1993; Radlinsky 2007).

Physiology

PTH release is controlled by calcium receptors on the chief cells in the parathyroid glands in response to hypocalcemia. PTH has a short half-life (3–5 min) in serum and so a steady rate of secretion is necessary to maintain serum PTH concentrations (Schenck et al. 2006). Natural variations in PTH concentration occur in healthy dogs. Aging is associated with increased concentrations of plasma PTH in dogs (Aguilera-Tejero et al. 1998), and a diurnal rhythm in PTH secretion has been identified in dogs, with an early morning peak in PTH observed (Lopez et al. 2005).
PTH directly elevates plasma calcium concentration directly by mobilizing calcium from the bone and increasing urinary phosphate excretion (Ganong 2001), and indirectly through its actions on the intestine mediated through vitamin D₃ (Sutton & Dirks 1986). Serum calcium exists in three fractions: protein bound (40%), complexed to phosphate, citrate, sulfate, lactate or bicarbonate (10%), and ionized. Ionized calcium (iCa) comprises approximately 50% of serum total calcium and is the most biologically active fraction. It is fluctuations in iCa that directly affect PTH release (Forman & Lorenzo 1991; Ganong 2001).

Almost all (99%) of total body calcium is stored with phosphorus in the bone and PTH mobilizes calcium rapidly from the bone by acting on osteoblasts, and then in a sustained fashion through action on osteocytes. The action of PTH on osteoblasts causes release of osteoclast-stimulating factor, resulting in a rapid degradation of bone by osteoclasts and subsequent increase in serum calcium and phosphorus. PTH also increases differentiation of macrophage precursors into more osteoclasts (Bocznynski 2007). The more sustained osteocyte activity is again in direct response to PTH and it results in calcium and phosphorus being released from the bone matrix crystals hydroxyapatite and calcium phosphate. The action of PTH on osteocytes is potentiated synergistically by 1,25-dihydroxy-vitamin D₃ (Reeve & Zanelli 1986; Sutton & Dirks 1986; Flanders 1993).

Vitamin D exists in two forms: cholecalciferol (vitamin D₃) in animals, and ergocalciferol (vitamin D₂) predominantly in plants. Cholecalciferol can be produced in the skin of most mammals from the activation of the provitamin 7-dehydrocholesterol by ultraviolet light, although dogs and cats can synthesize less cholecalciferol in the skin than many other mammals (Gross et al. 2000; Mellanby et al. 2005; Schenck et al. 2006). Dietary vitamin D is transported to the liver and metabolized to 25-hydroxyvitamin D₃ (cholecalciferol) by the liver. PTH then potentiates hydroxylation of 25-hydroxyvitamin D₃ in the kidneys to 1,25-dihydroxyvitamin D₃ (calcitriol). Calcitriol is the most active metabolite and causes a 100-fold increase in bone calcium resorption, enhances intestinal calcium and phosphorus absorption threefold compared with cholecalciferol, and increases calcium resorption in the kidney (Gross et al. 2000; Flanders 2003). Hydroxylation of cholecalciferol to calcitriol is inhibited by hypercalcemia, hyperphosphatemia, excess calcitriol, and absence of PTH (Flanders 2003).

The increase in calcium absorption across the small intestinal mucosa is affected by a combination of actions, mediated by vitamin D₃; increased permeability of cell membranes to calcium, production of intracellular calcium-binding proteins in the enterocytes of the duodenum and jejunum, and increased activity of a membrane-bound calcium/magnesium pump which transports calcium out of the cell and into the blood (Sutton & Dirks 1986; Flanders 1993).

PTH directly increases serum calcium concentration by increasing the rate of calcium reabsorption in the distal renal tubules. PTH has no effect on the proximal tubules where calcium is reabsorbed by diffusion. However, PTH does inhibit reabsorption of phosphorus in the proximal renal tubules, leading to increased phosphorus excretion (Morrow & Volmer 2002; Flanders 2003; Schenck et al. 2006).

Calcitonin antagonizes PTH and is secreted by the C cells of the thyroid gland in response to hypercalcemia. It reduces plasma calcium concentration by reducing its absorption from the bone by inhibiting osteoclasts (Ganong 2001; Schenck et al. 2006). Calcitonin will also inhibit renal phosphorus reabsorption and increase calcium reabsorption (Flanders 2003). PTH synthesis and secretion is also inhibited in the face of elevated serum calcium by a negative feedback loop to the parathyroid glands.

**History and clinical signs**

Dogs with primary hyperparathyroidism have a median age of 9.3 years (Gear et al. 2005) and a mean age of 10.5–11.8 years (Feldman & Nelson 2004; Feldman et al. 2005; Ham et al. 2009). Mean body weight is 18–22.2 kg (Feldman et al. 2005; Ham et al. 2009). Reportedly Labrador retrievers, golden retrievers, and German shepherd dogs are at increased risk (Feldman et al. 2005) and a familial predisposition in Keeshonden has been described (DeVries et al. 1993), with this breed comprising 19–40% of affected animals in several studies (Feldman et al. 2005; Goldstein et al. 2007; Rasor et al. 2007). Primary hyperparathyroidism is an autosomal dominant, genetically transmitted disease in Keeshonden, although the gene mutations responsible have yet to be identified (Goldstein et al. 2007; Skelly & Franklin 2007). In one study, 14% were German shepherd dogs and 14% Keeshonden, the latter being closely related dogs (Gear et al. 2005). No sex predisposition is seen (Feldman et al. 2005; Gear et al. 2005).

All clinical signs associated with primary hyperparathyroidism are related to the hypercalcemia secondary to the elevation in PTH. With an increasing number of ‘wellness’ examinations being performed in an ever-aging population of pets, asymptomatic hypercalcemic patients are being diagnosed more commonly and reportedly 21–42% of cases are incidental findings (Feldman et al. 2005; Gear et al. 2005; Rasor et al. 2007; Ham et al. 2009).

If symptomatic, clinical signs are normally vague and nonspecific (Wisner et al. 1997), the majority of cases
having an insidious onset (Gear et al. 2005). Polyuria and polydipsia are well-recognized clinical signs, the former caused by hypercalcemia reducing expression of aquaporin-2 (a vasopressin-regulated water channel) in the renal collecting ducts (Earm et al. 1998). Lethargy, weakness, vomiting, diarrhea, inappetance, weight loss, tremors, and stiffness are common (Berger & Feldman 1987; Gear et al. 2005), and in up to 50% of dogs, signs consistent with urolithiasis or urinary tract infections had been observed for days or months (DeVries et al. 1993; Feldman et al. 2005; Gear et al. 2005). Occasionally dogs present with pathologic fractures, presumably due to osteolysis from chronically elevated PTH, but with earlier detection this is becoming increasingly rare (Gear et al. 2005).

The masses themselves are typically less than 10 mm in diameter and thus symptoms due to the physical presence of the mass in the neck are rare (Berger & Feldman 1987; DeVries et al. 1993; Feldman et al. 1997). In fact 71% of dogs with primary hyperparathyroidism have no obvious abnormalities observed on clinical examination (Feldman et al. 2005).

Information about the animal’s diet should be part of the history as calcium can be increased if the animal is on calcium supplements, calcium-rich phosphate binders, or vitamin D supplements (Bonczynski 2007). Some commercial dogfoods have also been found to contain vitamin D concentrations over 100 times higher than that stated on the manufacturer’s data sheet (Mellanby et al. 2005).

Diagnosis

Hematology

In most cases this is unremarkable. Mild anemia and mild polycythemia are seen only rarely (Feldman et al. 2005; Gear et al. 2005).

Serum chemistry

An elevation in iCa concentration is the most sensitive means of detecting hypercalcemia. One recent study defined hypercalcemia as iCa above 1.33 mmol/L (reference range 1.13–1.33 mmol/L) (Messinger et al. 2009), and in dogs with primary hyperparathyroidism the reported range is 1.48–2.55 mmol/L, with a median of 1.89 mmol/L (Gear et al. 2005; Ham et al. 2009) and a mean of 1.67–1.71 mmol/L (Feldman et al. 2005; Ham et al. 2009). An elevated reading should always be validated by a second sample and it has been suggested that sampling should be at least 30 days apart (Feldman et al. 2005). Most routine serum chemistry profiles report total calcium, which also includes protein-bound and complexed forms (Messinger et al. 2009). Total calcium and iCa may be poorly correlated in a patient. Equations using the dog’s serum albumin to ‘correct’ total protein to more accurately estimate iCa have proven inaccurate (Meuten et al. 1982a; Finco 1983; Messinger et al. 2009).

Hyperggammaglobulinemia secondary to inflammatory conditions will also affect total calcium (LeBlanc et al. 2008). The calcium ion binds to the increased number of negatively charged globulins resulting in an increased total calcium concentration but an iCa concentration within the reference range (Stockham & Scott 2002). A monoclonal β-gammopathy in association with primary hyperparathyroidism and hypercalcemia has also been reported, which decreased following the removal of a parathyroid adenoma (Benchekroun et al. 2009).

A diagnosis of hypercalcemia using total calcium is made if the concentration is 12 mg/dL or more (reference range 9.9–11.4 mg/dL) (Feldman et al. 2005). Total calcium elevation is often 2.97–5.83 mmol/L, median 3.47 mmol/L (Gear et al. 2005), or 12.1–23.4 mg/dL, mean 14.5 mg/dL; 48% of dogs had calcium greater than 14 mg/dL (Feldman et al. 2005).

Primary hyperparathyroidism comprises only 13% of cases of ionized hypercalcemia, with 58% being neoplasia (predominantly lymphoma and various carcinomas) and 17% being chronic or acute renal failure (Messinger et al. 2009). The magnitude of ionized hypercalcemia cannot be used to predict specific disease states (Messinger et al. 2009). In studies with total serum calcium, dogs with primary hyperparathyroidism had significantly lower concentrations than dogs with neoplasia (Kruger et al. 1996), and dogs with primary hyperparathyroidism, lymphoma and anal sac adenocarcinoma had higher serum total calcium than dogs with chronic renal failure or vitamin D toxicosis (Feldman et al. 2005).

Serum inorganic phosphorus should be evaluated as an elevation in both calcium and phosphorus is suggestive of renal failure or vitamin D toxicosis (Feldman et al. 2005). However, in primary hyperparathyroidism, phosphate concentration is more likely to be normal or decreased (Gear et al. 2005). A concomitant hypophosphatemia is seen in up to 65% of cases, with 98% of dogs being below the lower half of the reference limit (Feldman et al. 2005). Alkaline phosphatase is increased in 48–50% of dogs, urea is elevated in 37–47%, creatinine is elevated in 3–36%, and cholesterol elevated in 41% (DeVries et al. 1993; Feldman et al. 2005; Gear et al. 2005). These values must be taken in the context that some dogs were pretreated with glucocorticoids or were subsequently diagnosed with hyperadrenocorticism.

Urinalysis

The mean urine specific gravity is 1.012 (range 1.006–1.017) (DeVries et al. 1993) and is significantly more dilute than in ‘normal’ control dogs. Urine culture can be
positive in 29% of dogs, often in association with cystic calculi (Feldman et al. 2005).

**Parathyroid hormone assays**

Intact PTH concentration is best determined using the two-site immunoradiometric assay, which has been validated for use in dogs (Torrance & Nachreiner 1989a,b). The test typically takes several days before results are available and a ‘point-of-care’ assay has recently been described in dogs (Ham et al. 2009), although this is expensive and currently poorly available to veterinary patients. However, accurate results are available 10–20 min after blood sampling (Ham et al. 2009).

The upper limit of the PTH reference range is 13–17 pmol/L (Feldman et al. 2005; Ham et al. 2009). In order to diagnose primary hyperparathyroidism in the face of hypercalcemia, one study required PTH to be in the upper half of the reference range or higher (Messinger et al. 2009), although in one study of 210 dogs, 73% had a serum PTH concentration within the reference range (Feldman et al. 2005). In this study mean PTH concentration was 11.3 pmol/L (range 2.3–121 pmol/L).

In one study of 29 dogs with primary hyperparathyroidism, PTH values ranged from 57 to 680 pg/mL (median 167.5 pg/mL). No correlation could be detected between PTH and total or ionized calcium (Gear et al. 2005). If ionized calcium is high and the phosphate is low, renal secondary hyperparathyroidism cannot be ruled out (Feldman 2000). Elevated PTH has also been identified in up to 92–95% of dogs with hyperadrenocorticism, but these cases are not hypercalcemic (Ramsey 2001; Ramsey et al. 2005; Tebb et al. 2005). The term ‘adrenal secondary hyperparathyroidism’ has been suggested for these dogs (Ramsey et al. 2005).

Feldman et al. (1997) investigated whether comparing the level of intact PTH from each jugular vein could be used to accurately localize the primary parathyroid tumour. In only 8% of dogs was the serum PTH from the jugular vein ipsilateral to the parathyroid tumour greater than that from the contralateral vein. In 92% the concentrations were similar and not helpful in localizing abnormal parathyroid tissue. A more recent study using a ‘point-of-care’ analyzer in dogs with unilateral disease found PTH concentration on the affected side was much higher than that on the unaffected side in only 43% dogs (Ham et al. 2009), again suggesting this was not a useful differentiating test.

Reference range for PTH in cats is lower than dogs at 0–4 pmol/L (Reimer et al. 2005).

**Diagnostic imaging**

Normal parathyroid glands in healthy dogs range from 2 to 4.6 mm in diameter when imaged ultrasonographically, with a strong positive correlation between diameter and body weight (Wisner et al. 1997; Wisner & Nyland 1998; Reusch et al. 2000; Benchekroun et al. 2009). In a study of 23 normal dogs, the largest parathyroid gland measured 3 mm in dogs weighing less than 10 kg, 3.5 mm in dogs weighing 10–19 kg, 4 mm in dogs weighing 20–29 kg, and 4.6 mm in dogs weighing over 30 kg. Two to four glands are normally visible, with all four glands normally visible in dogs over 30 kg (Reusch et al. 2000). Ultrasound examination is normally performed with a 10 MHz sector scanning transducer or a 7.5–10 MHz linear array transducer and abnormal parathyroid tissue is typically round or oval and anechoic or hypoechoic compared with surrounding thyroid parenchyma (Wisner & Nyland 1998) (Figure 1-1). They are typically well-defined structures and this becomes more apparent with increasing size. In a study of 142 parathyroid masses, the median greatest diameter was 6 mm (range 3–23 mm) (Feldman et al. 2005) and neoplastic lesions (median diameter 6 mm, range 4–20 mm) typically are significantly larger than hyperplastic glands (median 2 mm, range 2–6 mm), regardless of whether the hyperplasia is primary or secondary (Wisner et al. 1997). In 87–100% of dogs, a solitary parathyroid nodule is identified, with up to 13% of dogs having two abnormally large glands (Feldman et al. 2005; Gear et al. 2005; Rasor et al. 2007; Ham et al. 2009). The side identified correlates to surgical findings in up to 93% of dogs (Gear et al. 2005). However, ultrasonography is operator dependent and the skill of the individual performing the examination is a major factor in the value of this test (Feldman et al. 1997). Parathyroid masses can be up to 12 mm in diameter in cats (Reimer et al. 2005).

Up to 47% of dogs in one study had concurrent renal abnormalities on ultrasound, including renal calculi, hyperechogenic cortices, and pyelectasia (Gear et al. 2005). The only consistent abnormality identified during abdominal radiography and ultrasonography in 210 dogs was cystic calculi in 24% (Feldman et al. 2005).

![Figure 1-1 Ultrasound image showing oval hypoechoic parathyroid gland at the cranial end of the thyroid gland.](image-url)
One dog was diagnosed with primary hyperparathyroidism following a thyroid technetium scan which demonstrated a defect in the posterior pole of the left thyroid, subsequently confirmed by surgery (van Vonderen et al. 2003).

Double-phase parathyroid scinitigraphy using $^{99m}$Tc-sestamibi, although successful in humans for preoperative localization of hyperfunctioning parathyroid tissue, has proven to be disappointing in dogs. Parathyroid scintigraphy correctly identified the presence and location of hyperfunctioning parathyroid tissue in only one of six dogs with a parathyroid adenoma, with many false-negative results (Matwichuk et al. 2000).

In humans, magnetic resonance imaging (MRI) is used in patients with persistent or recurrent hyperparathyroidism, in whom it has been shown to be effective in locating remaining abnormal parathyroid tissue. In instances in which no neck lesion is identified or an ectopic parathyroid gland is suspected, ECG-gated axial images of the mediastinum can be effective (Johnson et al. 2007). In most cases, abnormal parathyroid tissue demonstrates isointense to low signal intensity relative to muscle on T1-weighted images, with increased signal intensity typically present on T2-weighted images. Intense contrast enhancement is frequently observed (Gotway et al. 2001). The role of MRI in veterinary patients has yet to be fully elucidated.

**Differential diagnosis**

Some of the disorders associated with hypercalcemia include lymphoma (Meuten et al. 1982a; Weir et al. 1986; Kubota et al. 2002), apocrine gland adenocarcinoma of the anal sac (Meuten et al. 1982b; Hobson et al. 2006), hypervitaminosis D (Gunther et al. 1988; Mellanby et al. 2005), acute and chronic renal failure, multiple myeloma, thymoma (Foley et al. 2000), melanoma (Pressler et al. 2002), hypoadrenocorticism (Willard et al. 1982), mycosis (Dow et al. 1986), and idiopathic hypercalcemia of cats (Midkiff et al. 2000).

**Hypercalcemia of malignancy: parathyroid hormone-related protein**

Dogs with neoplasms, especially lymphoma, apocrine gland adenocarcinoma of the anal sac, or multiple myeloma, comprise 58% of dogs with ionized hypercalcemia (Messinger et al. 2009) and are typically hypercalcemic due to the synthesis and secretion of parathyroid hormone-related protein (PTHrP) by the tumor. This has polypeptide segments that are homologous to native PTH and which cause hypercalcemia by increasing bone resorption and the renal tubular reabsorption of calcium (Rosol & Capen 1988; Strewler 2000).

PTHrP is measured by an immunoradiometric two-site assay and in normal healthy dogs lies within the reference range (0.3–1.0 pmol/L). Dogs with hypercalcemia due to lymphoma have an elevated PTHrP (median 5.05 pmol/L, range 0.5–16.0 pmol/L) and PTH below the reference range in most but not all cases (Mellanby et al. 2006). This is presumably due to suppression of PTH secretion by the negative feedback effects of high concentrations of calcium and PTHrP (Motellon et al. 2000). A similar relationship between ionized calcium, PTHrP, and PTH was seen in hypercalcemic dogs with adenocarcinoma of the apocrine gland of the anal sac.

PTHrP in seven hypercalcemic dogs with parathyroid adenoma was within the reference range. PTHrP in two hypercalcemic dogs with parathyroid carcinoma was greater than the reference range in both cases, at 1.8 and 8.1 pmol/L, all nine dogs also having the expected elevations in PTH (Mellanby et al. 2006).

Such elevations in both PTH and PTHrP in hypercalcemic dogs are rare. Other possibilities include a dog with primary hyperparathyroidism also having an additional malignancy secreting PTHrP. An association between primary hyperparathyroidism and a secondary malignancy is well recognized in people and has occasionally been described in dogs and cats (Strodel et al. 1988; Hutchesson et al. 1995; Walker et al. 2000; Reimer et al. 2005). Another possibility is the rare example of a tumor producing both PTH and PTHrP (Uchimura et al. 2002). Malignancies growing within the bone marrow and metastasis of solid tumors to the skeleton are other possible causes.

**Hypoadrenocorticism**

Hypercalcemia is seen in 18–30% of dogs with hypoadrenocorticism (Peterson et al. 1996; Adler et al. 2007). Furthermore, it is an important differential diagnosis for hypercalcemia, as it is the cause in 5–25% of hypercalcemic dogs (Elliott et al. 1991; Messinger et al. 2009). In a recent study of eight dogs with hypoadrenocorticism, four of five dogs with ionized hypercalcemia had a PTH concentration within the reference range (Gow et al. 2009) and it was concluded that hypercalcemia associated with spontaneous hypoadrenocorticism is independent of PTH. The exact pathogenesis of the hypercalcemia is not clear. Possibilities include decreased glomerular filtration, increased tubular calcium reabsorption, excessive intestinal absorption of calcium, and increased bone resorption (Walser et al. 1963; Hahn et al. 1981; Walker & Davies 1981).

**Hypervitaminosis D**

The parathyroid glands in healthy dogs are relatively inactive, possibly the result of the relatively large amount
of vitamin D in commercial dogfood (Kallfelz & Dzanis 1989) and cases of hypercalcemia through dietary oversupplementation have been reported (Mellanby et al. 2005). Hypervitaminosis D as a cause of ionized hypercalcemia is rare, comprising only 3% of dogs (Messinger et al. 2009), but is most commonly seen secondary to ingestion of either rodenticides containing cholecalciferol or antipsoriatic ointments that contain vitamin D analogues. Hypervitaminosis D has been reported following treatment of hypoparathyroidism.

**Renal failure**

Chronic renal failure is commonly associated with hyperparathyroidism through parathyroid gland hyperplasia (Flanders 2003). Increased serum phosphorus concentration, decreased 1,25-dihydroxyvitamin D₃ concentration (because of fewer functional nephrons to hydroxylate cholecalciferol to calitriol), greater skeletal resistance to the calcemic effects of PTH, and elevation of the serum calcium 'set point' for inhibition of PTH are all possible explanations for parathyroid hypersecretion (Feinfeld & Sherwood 1988; Flanders 2003). Most dogs and cats with renal failure have a normal or low concentration of serum calcium, but 10–20% of dogs have mild to moderate hypercalcemia (Feldman 1995) and they comprise 17% of dogs with ionized hypercalcemia (Messinger et al. 2009). The exact reason some chronic renal failure patients with secondary hyperparathyroidism become hypercalcemic is not known (Coburn & Slatopolsky 1986). The reason most cats and dogs are normocalcemic or hypocalcemic in the face of hyperparathyroidism may be due to low 1,25-dihydroxyvitamin D₃ decreasing intestinal calcium absorption, the calcemic effect of PTH on bone, a reduction in functional renal tubule cells to reabsorb calcium, and hyperphosphatemia (Feinfeld & Sherwood 1988; Flanders 2003).

Up to 77% of hyperthyroid cats have elevated PTH concentrations (Barber & Elliott 1996), and this can result in calcification of soft tissues, including the kidney, which may cause progression of chronic kidney disease. Dietary phosphate restriction, which decreases PTH concentration, has been shown to prolong the survival of cats with chronic kidney disease (Barber & Elliott 1996; Elliott et al. 2000).

**Granulomatous/inflammatory**

This was the final diagnosis in 4% of dogs with ionized hypercalcemia (Messinger et al. 2009). It is believed to be due to extrarenal synthesis of calcitriol (1,25-dihydroxyvitamin D₃) by activated macrophages (Sharma 2000; Mellanby et al. 2006; LeBlanc et al. 2008). Removal of the granulomatous or inflammatory process tends to result in rapid normocalcemia (LeBlanc et al. 2008). In one study of 38 dogs with blastomycosis, only 5% had ionized hypercalcemia and 95% were normocalcemic. When total calcium is measured, 2.5–6.4% of dogs are hypercalcemic (Legendre et al. 1981; Crews et al. 2007).

**Surgical therapy**

Exploratory surgery with parathyroidectomy in dogs with primary hyperparathyroidism serves as both a diagnostic test and definitive therapy (Wisner et al. 1997). Surgical exploration of the neck is warranted in a hypercalcemic dog with inappropriate levels of PTH and the absence of PTHrP, even with normal cervical ultrasound findings, as occasionally enlarged glands are identified at surgery that had not been detected by preoperative ultrasound (Ham et al. 2009). Surgery should be advocated to reduce the risk of urolithiasis and urinary tract infection (Devries et al. 1993), as well as improving the clinical signs seen with hypercalcemia such as polydipsia, polyuria, weakness, and decreased appetite (Feldman et al. 2005). Surgical time is reduced by accurate preoperative planning to localize the abnormal gland(s) and morbidity is reduced by familiarity with the local anatomy and an appropriate postoperative plan. With appropriate treatment the prognosis can be excellent (Berger & Feldman 1987).

**Preoperative considerations: hypercalcemia**

Preoperative treatment of hypercalcemia is contentious and there are no published standards (Bonczynski 2007). Recommendations exist in patients with serum calcium levels greater than 14 mg/dL, or if calcium-associated neurologic or cardiac signs exist, or if azotemia is present. If these conditions are present, then intravenous fluid therapy should be started 12–24 hours before surgery, ideally with 0.9% saline. During diuresis, care is taken not to overhydrate the patient and packed cell volume, total protein, weight, and respiratory rate are monitored twice daily. If hypercalcemia persists despite rehydration and diuresis, renal calcium excretion can be encouraged with furosemide at 2–4 mg/kg every 8–12 hours (Vasilopulos 2003; Schenck et al. 2006).

Calcitonin is effective for rapidly reducing serum calcium concentrations (Flanders 2003). Isolated case examples of its use to treat hypercalcemia exist in veterinary medicine; hypervitaminosis D has been treated with salmon calcitonin at a dose of 4.5 units/kg subcutaneously every 8 hours in a dog (Dougherty et al. 1990), and 4 units/kg intramuscularly was used successfully in a cat (Peterson et al. 1991).

Bisphosphonates are used as standard of care in human oncology to treat hypercalcemia of malignancy (Fan 2007). Their main mechanism of action is inhibition of bone resorption by reduction of osteoclast activites.
and induction of osteoclast apoptosis (programmed cell death) (Body 1998), thereby reducing serum calcium levels. However, bisphosphonates do not affect the increased renal tubular reabsorption seen with elevations in PTH and PTHrP (Rizzoli et al. 1992; Chisholm et al. 1996), and so dogs with primary hyperparathyroidism or with hypercalcemia and great elevations in PTHrP may respond less favorably to bisphosphonate therapy (Walls et al. 1994). The use of bisphosphonates to reduce serum calcium concentrations in tumor-bearing dogs and cats is poorly documented (Fan 2007). Published work has mostly concerned animals with hypercalcemia secondary to excessive PTHrP (not PTH) treated with intravenous saline diuresis and diuretics (Kadar et al. 2004; Fan et al. 2005; Hostutler et al. 2005). One study showed that clodronate could reduce hypercalcemia following experimental vitamin D toxicosis in dogs (Ulutas et al. 2006).

To prevent acute hypocalcemia after surgery, some authors have also recommended supplementing dogs preoperatively with vitamin D if total calcium is 14 mg/dL or higher, for example with dihydrotachysterol and calcium gluconate (Feldman et al. 2005), with alfalcaldol (0.05 μg/kg) the day before surgery with or without calcium gluconate (Gear et al. 2005), or with calcitriol (20 ng/kg per day orally starting 1–2 days before surgery) (Ham et al. 2009).

**Surgical technique**

Following a wide ventral neck clip, the patient is positioned in dorsal recumbency with the neck outstretched and a sandbag placed beneath it for further extension. The forelimbs are pulled caudally and tied in place. A ventral midline skin incision is made from the level of the larynx cranially midway to the manubrium caudally. The sphincter colli muscles are incised to expose the longitudinal fibres of the paired sternohyoideus muscles (Radlinsky 2007). Dissection is continued through the midline of sternohyoideus and sternothyroideus. The thyroid glands lie in the peritracheal fascia medial to the thyrohyoideus muscle. Locally, the recurrent laryngeal nerve and carotid sheath (containing vagus nerve and carotid artery and vein) should be identified. Each parathyroid–thyroid complex is inspected separately. If necessary a blunt-ended Gelpi retractor can be placed between the cranial trachea and neck muscles to help expose each thyroid. Preoperative ultrasound will guide the surgeon towards one side or the other, but it is imperative every parathyroid is gently palpated to ensure there is only one abnormal gland. Normal parathyroid tissue is soft and pale tan in color. When diseased, it becomes firmer, typically spherical, and often stands proud from the thyroid tissue. Parathyroid adenoma is usually a solitary disease, and if more than one gland is enlarged and firm, then hyperplasia should be suspected. When a dog has two parathyroid nodules, they can be either bilateral or ipsilateral (Rasor et al. 2007).

The abnormal parathyroid gland is removed through a combination of sharp and blunt dissection. Iris scissors, fine dissecting scissors, or bipolar cautery should be used to make a hole in the capsule between the parathyroid and thyroid gland (Figure 1-2), and then blunt dissection is used to ‘roll’ the gland out of the thyroid bed. Hemorrhage is typically minimal and easily controlled with cautery. If the parathyroid mass is clearly adherent to the thyroid parenchyma, then a partial thyroidectomy is indicated. This is most easily achieved by an encircling monofilament absorbable ligature at the thyroid gland mid body, or within palpably normal parenchyma away from the parathyroid nodule. Care should be taken to ensure that residual thyroid tissue has a visible blood supply. If in doubt (and the contralateral thyroid–parathyroid complex is normal), then a unilateral thyroidectomy is warranted.

Surgical decision-making involving a firm solitary parathyroid adenoma is straightforward. The primary parathyroid mass may be small but if one gland has a palpably firmer texture compared with its partners, the decision can be made to remove it. Problems arise during surgery when several glands appear enlarged or when no gland appears enlarged and none are noticeably firmer. All four glands may become enlarged due to renal secondary hyperparathyroidism and removal of one to three glands may decrease serum calcium levels sufficiently to ameliorate clinical signs (Flanders 2003). Parathyroid gland hyperplasia can present with one to four enlarged glands, with the other glands atrophied and unable to be found. In these dogs, all large parathyroid...
glands should be removed. Naturally, if all four are resected, the patient will likely need lifelong medical supplementation with vitamin D with or without dietary calcium and so removal of three may be sufficient to reduce the hypercalcemia (Flanders 2003).

If no gland appears asymmetrically enlarged or firm, possibilities include the following.

1. Explore the entire cervical region, among the loose peritracheal fascia, for evidence of ectopic parathyroid tissue. There has been one report of a mediastinal ectopic adenocarcinoma (Patnaik et al. 1978) and I have removed a similar tumor from a similar location (Figure 1-3).

2. Parathyroid hyperplasia is affecting all parathyroid glands symmetrically and there is no normal parathyroid tissue to use as a reference (Flanders 2003). One parathyroid gland (the largest or most prominent) can be removed for histological evaluation to rule out hyperplasia. If present and the dog is still hypercalcemic, the surgeon should consider second surgery, a percutaneous ablation technique, or long-term medical therapy. If hyperplasia is not demonstrated, it is possible a functional ectopic tumor exists.

3. Consider performing MRI postoperatively from the tongue base to the heart base to look for evidence of ectopic parathyroid tissue (see section on imaging below).

4. In patients with ionized hypercalcemia and PTH concentration within the reference range, consider atypical hypoadrenocorticism (Gow et al. 2009) and perform basal cortisol assay or adrenocorticotropic hormone (ACTH) stimulation test.

Closure of the wound is in three layers: the divided muscle, the subcutaneous tissue, and skin. Use of a drain is not routinely recommended.

Postoperative care

The greatest postoperative concern, reportedly occurring in 8–58% dogs (Berger & Feldman 1987; Ham et al. 2009), is hypocalcemia due to chronic suppression of the remaining parathyroid glands through negative feedback from the hypersecretory tumor. The suppressed glands require 2–3 weeks to begin secreting PTH (Flanders 2003). The parathyroid glands optimize their response to falling calcium levels by a phenomenon called hysteresis, a mechanism that allows the glands to increase PTH secretion in response to decreasing plasma calcium concentrations even though still exposed to hypercalcemia (Conlin et al. 1989; Domingo et al. 2007). However, atrophied glands cannot compensate for the rapid fall in calcium after parathyroidectomy and hypocalcemia can result. Clinical signs of hypocalcemia include seizures, muscle twitching, face rubbing, lethargy, and anorexia. Seizures and muscle twitching are due to neuronal hyperexcitability caused by sodium leaking into the neuron. The nerve cell membrane becomes more permeable to sodium in the face of low calcium concentrations and the altered membrane potential can result in spontaneous nerve depolarizations and muscle twitching.

After parathyroidectomy, total or ionized calcium should normalize within 1–6 days, with a median of 36 hours (Gear et al. 2005; Ham et al. 2009). Preoperative total calcium concentrations were significantly higher (median 4.2 mmol/L) in dogs which became hypocalcemic after surgery compared with dogs which remained normocalcemic (median 3.4 mmol/L) (Gear et al. 2005).

When faced with an acute onset of severe clinical signs, intravenous calcium gluconate (0.5 mL/kg of a 10% solution over 60 min) should be administered as a bolus and supported by a constant-rate infusion until vitamin D supplementation is at therapeutic levels (Schenck et al. 2006; Bonczynski 2007; Ham et al. 2009). An algorithm for treatment of postoperative hypocalcemia is shown in Figure 1-4. Vitamin D supplementation with or without calcium supplementation may be continued from a few weeks to indefinitely. Vitamin D supplementation should be tapered down 2 weeks after surgery while monitoring iCa.
Efforts to minimize postoperative hypocalcemia include supplementing dogs preoperatively with vitamin D (dihydrotachysterol or alfacalcidol), although this treatment has not been shown to be effective in preventing hypocalcemia. Also, it is important for the other parathyroid gland to be exposed to a normal calcium level to encourage PTH production. Therefore supplementation before normocalcemia has been reached may slow down the response from the remaining glands. Dihydrotachysterol has a long onset of action (3–5 days) and alfacalcidol is a hydroxylated vitamin D analogue with a shorter half-life (1–3 days). It has the advantage of reaching therapeutic levels quickly and is also eliminated from the body faster, allowing for tighter control of calcium (Gear et al. 2005).

**Histopathology**

In dogs with primary hyperparathyroidism, solitary adenoma is seen in approximately 74–90% of dogs, adenomatous hyperplasia in 5–24%, and carcinoma in 4–20% (DeVries et al. 1993; Feldman 1995; Wisner et al. 1997; Gear et al. 2005; Ham et al. 2009).

Parathyroid adenoma and hyperplasia are difficult to distinguish with hematoxylin and eosin staining (Feldman 1995; Feldman & Nelson 1996) and diagnosis is often based on size alone. Adenoma is arbitrarily defined as an encapsulated nodule with a diameter of at least 5 mm, and hyperplasia as a diffuse form affecting all glands or a (multi)nodular lesion with nodules less than 5 mm in diameter in one or more glands with the unaffected glands atrophied (DeVries et al. 1993). This leads to some disagreement between pathologists when classifying benign parathyroid disease. In one recent study three pathologists disagreed on the classification of 35% of submitted parathyroid glands (Ham et al. 2009). It has even been suggested there may not be a true distinction between parathyroid adenoma and nodular hyperplasia because there is no functional difference between them, and they simply represent a continuum of morphologic structures (van Vonderen et al. 2003). It is

**Figure 1-4** Algorithm for preoperative and postoperative management of calcium levels in primary hyperparathyroidism.
argued that since the success of surgery is dictated by removal of all abnormal parathyroid tissue and a return to normocalcemia, the relevance of classifying which of the two benign ‘cured’ processes is responsible may be academic (Ham et al. 2009).

**Nonsurgical therapy**

**Percutaneous ultrasound-guided ethanol ablation**

Dogs are anesthetized and under ultrasound guidance a 25 or 27G needle is inserted into the affected parathyroid gland. Ethanol (96%) is injected until the entire gland is infiltrated and a change in echogenicity of the whole nodule is identified ultrasonographically (Long et al. 1999; Rasor et al. 2007). Total calcium and iCa are measured immediately and then every 12 hours for 3 days (Gear et al. 2005).

In the original report, seven of eight dogs (88%) were successfully treated with a single treatment (Long et al. 1999). More recently, 12 of 15 dogs (80%) were treated successfully with a single procedure, with hypercalcemia resolving in 1–4 days. One dog responded to a second treatment and two dogs failed to respond to a second treatment (Rasor et al. 2007). In a third study, two of five dogs showed a partial response with a reduction in blood calcium, although it remained above the reference range. The other three dogs failed to respond. This was attributed to attempts to ablate glands 5 mm or less in diameter, or to operator inexperience (Gear et al. 2005).

**Percutaneous ultrasound-guided heat ablation**

Patients are anesthetized and placed on a cauterization ground pad. Ultrasound locates the abnormal parathyroid gland and is then used to direct a 20G over-the-needle intravenous catheter into the gland. The catheter sleeve acts as an insulator for the surrounding normal soft tissues. Radiofrequency energy is applied at 10–20W until the entire gland becomes hyperechoic, redirecting the needle if necessary to ablate the entire gland (Pollard et al. 2001; Rasor et al. 2007) and causing cell death by thermal necrosis (Long et al. 1999).

In the original report, eight of nine dogs (89%) were successfully treated (Pollard et al. 2001). In another study, 43 of 48 dogs (90%) responded to a single treatment, with hypercalcemia resolving in 1–6 days, but mean time to resolution was significantly longer than following parathyroidectomy or ethanol ablation. One dog resolved after a second treatment and four dogs failed treatment and remained hypercalcemic (Rasor et al. 2007).

There is no significant difference between the success rate for parathyroidectomy and heat ablation, but there is a significant difference between the success rate for parathyroidectomy and ethanol ablation (Rasor et al. 2007). The disadvantage of both the ethanol and heat ablation techniques is the lack of tissue for histopathologic examination. Other than hypocalcemia, complications arise in a small number of dogs due to leakage of ethanol or extension of thermal necrosis from the parathyroid gland into the surrounding tissues, causing damage to structures such as the recurrent laryngeal nerve and vagosympathetic trunk (Long et al. 1999). Following percutaneous techniques, dysphonia/change in bark is reported in 8% of dogs, a cough in 4%, and Horner’s syndrome in 1% (Long et al. 1999; Pollard et al. 2001; Rasor et al. 2007).

**Recurrent/persistent hypercalcemia**

Persistent hypercalcemia can be seen due to multiglandular disease, ectopic parathyroid glands, incomplete excision of autonomously functioning parathyroid tissue, or malignant disease with residual functional metastasis (Feldman 2005). In one study, surgical failure was attributed to lack of parathyroid tissue being detected on histopathology (Rasor et al. 2007).

Recurrent hypercalcemia following parathyroidectomy can be seen in 4–17% of cases from a few months to years after surgery. In these reported cases it is caused by a second parathyroid adenoma or hyperplasia (Feldman 2005; Gear et al. 2005; Rasor et al. 2007; Ham et al. 2009).

Relapse of hypercalcemia has also been reported in 2% of dogs following ultrasound-guided heat ablation treatment (Rasor et al. 2007) and in 13% of dogs following ultrasound-guided ethanol ablation treatment (Long et al. 1999).

**Prognosis**

All patients should be examined 14 days postoperatively for suture removal and calcium measurement. It is prudent to recheck calcium at 3-month intervals thereafter, or more frequently if clinical signs suggestive of hypercalcemia arise.

Surgical excision alone is the most widely performed treatment for primary hyperparathyroidism and a cure rate of 94% is reported if all autonomously functioning parathyroid tissue is removed (Rasor et al. 2007). A greater than 50% decrease in serum PTH concentration by 30–45 min after parathyroidectomy can be used to confirm the removal of hyperfunctional tissue (Ham et al. 2009). What defines success of parathyroidectomy should be return to a normal calcium level, and not necessarily a normal PTH level. In people, up to 33% of patients will have a normal calcium but elevated PTH after parathyroidectomy, and this is attributed to the existence of a new PTH set point (Dolev et al. 2008).
Of note is the often witnessed phenomenon of asymptomatic dogs doing exceptionally well after surgery and improving in attitude and mobility, especially when the hypercalcemia was diagnosed incidentally. Many symptoms of hypercalcemia such as muscular weakness and lethargy are attributed to old age in many dogs, yet the atrophic changes to the muscle are reversible with successful treatment of the primary disease (Feldman 1989), and it is only then that owners become aware how affected their animals had been. Similar functional musculoskeletal improvements are witnessed in asymptomatic people following treatment of primary hyperparathyroidism, where a significant improvement in bone density is seen in the lumbar spine and femoral neck compared with untreated patients (Steward et al. 2008).

In one study 37% of dogs developed renal failure postoperatively, and these dogs had significantly higher preoperative total calcium concentrations (median 4.0 mmol/L) compared with those with normal renal function (median 3.3 mmol/L) (Gear et al. 2005).

Prognosis in cats is good if all autonomously secreting tissue is removed.

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