CHAPTER 4

Feline Hyperthyroidism

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CHAPTER CONTENTS

Hyperthyroidism, caused by autonomous growth and function of the thyroid follicular cells, was initially described in humans by Henry Plummer in 1913. Clinical observations led him to characterize two types of hyperthyroidism: exophthalmic goiter (Graves' disease) and toxic adenomatous goiter. In Graves' disease, the hyperthyroidism was associated with diffuse hyperplasia of the thyroid glands. Toxic adenomatous goiter was associated with either single or multiple nodules and variable histologic patterns. The latter disease involved the slow growth of autonomous functioning follicles. Toxic adenomatous goiter is very similar to the disorder seen in hyperthyroid cats, initially described as a clinical entity in 1979 by Peterson and colleagues and in 1980 by Holzworth and colleagues. For detailed information on the anatomy and physiology of the normal thyroid gland, see Chapter 3.

DEFINITION

Naturally occurring hyperthyroidism (thyrotoxicosis) is a clinical condition that results from excessive production and secretion of thyroxine (T_4) and triiodothyronine (T_3) by the thyroid gland. Hyperthyroidism in cats is almost always the result of a primary autonomous condition of the thyroid gland itself, most commonly due to adenomatous hyperplasia or a benign adenoma. Adenomatous hyperplasia is the most common pathologic change. Feline hyperthyroidism may also be caused by functional thyroid carcinoma. Thyroid-stimulating hormone (also known as thyrotropin; TSH) secreting pituitary adenoma is a rare cause of hyperthyroidism in people (Beck-Peccoz et al, 2009), but has yet to be described in cats. Other causes of hyperthyroidism, such as ingestion of excessive quantities of exogenous thyroid hormone (Köhler et al, 2012) or acute destruction of thyroid tissue causing excessive release of thyroid hormone, have also not been reported in cats.

HISTORY OF HYPERTHYROIDISM

Veterinary clinicians were not aware of the clinical syndrome of feline hyperthyroidism until the publication of three clinical reports by Peterson, et al., in 1979, Holzworth, et al., 1980, and Jones and Johnstone, 1981. After these publications, practitioners increasingly started to recognize cats with signs suggestive of hyperthyroidism (thyrotoxicosis). From 1980 to 1985, 125 hyperthyroid cats were identified at the University of California. During a similar period, hyperthyroid cats were being recognized at a rate of three per month at the Animal Medical Center in New York City (Peterson et al, 1983). By 1993, hyperthyroidism was a common disease in both the United States and the United Kingdom (Thoday and Mooney, 1992; Broussard et al, 1995). By 2004, a retrospective study suggested that the prevalence of feline hyperthyroidism in the United States was 3% of hospital visits (Edinboro et al, 2004). Feline hyperthyroidism is now recognized as a common clinical problem of cats in many countries in the world including Europe, Australia, New Zealand, Japan, and Hong Kong. Interestingly prevalence rates appear to vary substantially by geographic region. For example, the prevalence of hyperthyroidism in an urban area of Germany was estimated to be 11.4% (Sassnau, 2006), whereas the prevalence rate in Hong Kong was estimated to be 3.9% (De Wet et al, 2009). It has been proposed that the emergence of clinical hyperthyroidism is related to the gradual introduction of commercially-prepared cat foods by different cultures around the world. It is interesting that commercial cat foods were first test-marketed on both coasts of the United States in the mid-1960s. This means that the first generation of cats raised and maintained almost entirely on commercial foods was reaching middle and old age in the late 1970s and early 1980s, which coincides with the recognition of feline hyperthyroidism in Boston, New York, Philadelphia, Los Angeles, and San Francisco.

Factors that have contributed to the increased recognition of feline hyperthyroidism since the 1980s include increased awareness by owners and veterinarians, inclusion of total T_4 measurement on routine biochemical profiles for geriatric cats, improved feline health care, and increased feline life spans; however, there is little doubt that the true prevalence of the disease has also increased from the time the first reports in 1979 and 1980 were published until today. Unfortunately although there have been a number of epidemiological studies investigating the risk factors for feline hyperthyroidism, no single risk factor has been identified and it is thus believed that the cause is likely multifactorial.

PATHOLOGY

Background

A thorough review of feline thyroid pathology has not been published in the 20 to 25 years since clinical feline hyperthyroidism became common. However, reviews of surgically removed tissue and necropsy specimens have confirmed that multinodular adenomatous goiter is the most common pathologic abnormality. Benign tumors are much more common than malignant tumors.

Benign Thyroid Tumors

Multinodular Adenomatous Goiter

Follicular cell adenoma and multinodular adenomatous hyperplasia are the most common thyroidal histological abnormalities described in the thyroid glands from hyperthyroid cats. Both histopathologic abnormalities are benign changes, and both may occur together within the same thyroid gland. In both thyroid adenoma and adenomatous hyperplasia, the follicular cells are uniform and cuboidal to columnar in shape with occasional papillary infoldings that form follicles containing variable amounts of colloid (Maxie, 2007). Thyroid adenomas are grossly visible, have a thin fibrous capsule, and may compress the surrounding normal thyroid tissue. In thyroid adenomatous hyperplasia, one or more nodules of hyperplastic follicular cells are present within the thyroid gland. The nodules of hyperplastic tissue range in size from less than 1 mm to greater than 3 cm in diameter (Fig. 4-1). There is no clinically relevant difference between an adenoma

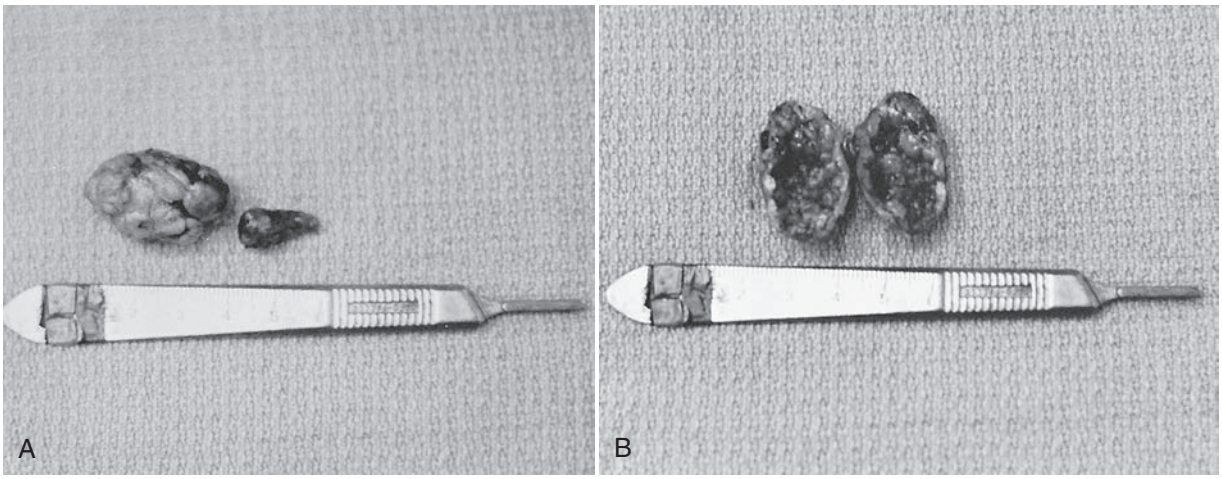

FIGURE 4-1 A, Multinodular adenomatous goiter, which has the gross appearance of a compressed cluster of grapes. This is an example of bilaterally asymmetric thyroid enlargement. **B,** After the larger mass is cut in half, cystic changes are revealed.

and adenomatous hyperplasia, and the two can coexist within the same thyroid gland. Adenomatous hyperplasia and adenomas are bilateral in approximately 70% of cats and unilateral in the remaining 30% of cats. Focal areas of necrosis, mineralization, and cystic degeneration are often present in larger adenomas and rarely may form large fluid filled cystadenomas. Normal follicular cells surrounding adenomas and hyperplastic nodules are low cuboidal or atrophied with little evidence of endocytotic activity (Maxie, 2007).

Malignant Thyroid Tumors

Thyroid Carcinoma

Malignant neoplasia is recognized to be the cause of hyperthyroidism in approximately 1% to 3% of hyperthyroid cats and may involve one or both thyroid lobes. There are a variety of clinical presentations ranging from tumors that are well encapsulated, freely moveable, and clinically indistinguishable from benign thyroid neoplasia, to thyroid masses that are very large, locally invasive, attached to overlying and underlying tissues, and metastatic to local lymph nodes. There may be multiple masses throughout the cervical region and may also be distant metastases. In cats, thyroid carcinomas are usually well differentiated adenocarcinomas that are composed of a uniform pattern of small follicles containing variable amounts of colloid (Maxie, 2007). Mixed compact and follicular morphologic patterns are most common although primary follicular and papillary patterns have also been reported (Turrel et al, 1988). There may be neoplastic invasion of blood vessels and the connective tissue capsule. The neoplastic cells may be subdivided into small lobules by strands of connective tissue with an abundant capillary network. Nonfunctional thyroid tumors in cats are rare (Turrel et al, 1988; Guptill et al, 1995). In one case series, the nonfunctional thyroid tumor was of the papillary type (Turrel et al, 1988).

Distinguishing between well-differentiated thyroid follicular carcinoma and benign proliferation of thyroid follicular epithelium on the basis of histologic features alone is not always possible (Guptill et al, 1995). Criteria used to diagnose follicular carcinoma include evidence of capsular and vascular invasion, cellular pleomorphism, extracapsular extension or distant metastasis. Clinical behavior of the tumor must be taken into consideration when interpreting the histopathology findings.

ETIOLOGY

Evidence for Primary Thyroid Dysfunction

Early studies of hyperthyroid cats in the 1980s suggested feline hyperthyroidism was due to a primary abnormality of the thyroid gland rather than the result of thyroid stimulation by a circulating hormone, such as TSH, thyrotropin-releasing hormone (TRH), or thyroid stimulating immunoglobulins. Thyroid tissue from hyperthyroid cats was transplanted subcutaneously into nude mice that had endogenous TSH secretion suppressed by administration of levothyroxine (also known as L-thyroxine; L-T_4). It was demonstrated that the thyroid cells retained their cuboidal shape, high growth potential, and functional autonomy in the nude mice (Peter et al, 1987). Furthermore administration of serum from hyperthyroid cats failed to stimulate iodine uptake in either normal or hyperplastic thyroid tissue. Similar findings have more recently been demonstrated in cells transfected with the feline TSH receptor (Nguyen et al, 2002).

Genetic Cause of Thyroid Autonomy

Stimulation of thyroid follicular cells by TSH results in thyroid follicular cell growth as well as synthesis and secretion of thyroid hormone via the receptor G protein–cyclic adenosine monophosphate (cAMP) signal transduction system. The normal feline thyroid gland contains subpopulations of follicular cells with high growth potential and TSH receptors that have detectable basal constitutive activity (Nguyen et al, 2002). In the thyroid gland of a cat that is destined to become hyperthyroid, subpopulations of follicular cells begin replicating autonomously. Once these subpopulations are present in sufficient numbers, growth and thyroid hormone synthesis becomes autonomous (Peter et al, 1991). It has been hypothesized that chronic stimulation of cells with a high growth potential ultimately causes them to become autonomous due to development of follicular cell mutations (Ward et al, 2005a). In humans, gain-of-function mutations of the TSH receptor or the alpha subunit of stimulatory G proteins have been described. Altered expression of the alpha subunits of the stimulatory and inhibitory G proteins has also been reported. Eleven TSH receptor mutations were detected in 134 hyperplastic nodules from 50 hyperthyroid cats (Watson et al, 2005). Five of

TABLE 4-1 **RISK FACTORS FOR FELINE HYPERTHYROIDISM IDENTIFIED IN CASE CONTROL STUDIES**

STUDY LOCATION	NUMBERS OF CASES (CONTROLS)	STUDY DATES	DIET STUDIED	REPORTED RISK FACTORS
New York State College of Veterinary Medicine, USA	56 (117)	1982-1985	Diet for past 5 years	• Non-Siamese breeds • More than 50% canned food • Partial or complete indoor housing • Exposure to lawn or flea control products
University of California, Davis, and Animal Medical Center, New York, USA	379 (351)	1986	Current and one previous diet	• Non-Siamese or Himalayan breeds • More than 50% canned food • Exposure to cat litter
Seattle, WA, USA	100 (163)	1996-1997	Diet for past 5 years	• Increasing age • Preference for certain canned food flavors
New Zealand	125 (250)	1996-1998	Current diet*	• Increasing age • Female sex • Domestic Short-Hair • Canned food of multiple flavors • Sleeping on the floor • Contact with flea and fly control products • Drinking puddle water and exposure to organic fertilizers
Purdue University, IN, USA	109 (173)	1998-2000	Lifetime diet until 1 year before presentation	• Increasing age • Female sex • More than 50% canned food • Food from pop-top cans • Baby food in regular kitten diet or as treat • Lack of iodine supplement in label ingredients • Increasing frequency of carpet cleaning • Increasing years of exposure to well water • Increasing years to exposure of gas fireplaces
Hong Kong	12 (293)	2006-2007	Not stated	• Increasing age • Non-domestic Short-Hair breed
United Kingdom	109 (196)	2006-2007	Diet for past 5 years	• Increasing age • Non-purebred • Litter box use • More than 50% wet (canned/pouched) food • Canned foods • Fish in diet • Lack of deworming medication

From Edinboro CH, et al.: Feline hyperthyroidism: potential relationship with iodine supplement requirements of commercial cat foods, *J Feline Med Surg* 12(9):672-679, 2010.
*This was not explicitly reported but apparent from the context.

the mutations that were identified have also been associated with human hyperthyroidism. Interestingly of the 41 cats for which more than one nodule was available, 14 had nodules with different mutations. In an in vitro study of thyroid adenomas obtained from hyperthyroid cats, a decreased amount of an inhibitory G protein was identified (Hammer et al, 2000). Decreased expression of this G protein in thyroid follicular cells could reduce the inhibitory effect on the cAMP cascade, leading to autonomous growth and hypersecretion of thyroxine (Ward et al, 2005b). A further study suggested that decreased expression of certain subsets of inhibitory G proteins, rather than a change in TSH-stimulated G protein activity, contributes to the molecular pathogenesis of feline hyperthyroidism (Ward et al, 2010). In another study, overexpression of the product of the oncogene c-Ras was detected in areas of nodular hyperplasia/adenoma in thyroid tissue from 18 hyperthyroid cats (Merryman et al, 1999). Taken together these studies suggest that multiple mutations in thyroid follicular cells may ultimately result in thyroid cell autonomy. What is still unclear is the underlying cause of these mutations and why clinical feline hyperthyroidism has become more common in the last 30 years.

Epidemiological Studies

Risk Factors

Numerous epidemiological studies have been performed in the last 25 years in an attempt to elucidate the cause of feline hyperthyroidism (Table 4-1). The first study published in 1988 suggested that feeding of canned cat foods, living strictly indoors, being a non-Siamese breed, and having reported exposure to flea sprays, fertilizers, insecticides, and herbicides increased the risk of developing hyperthyroidism (Scarlett et al, 1988). In

another study, two genetically related cat breeds (Siamese and Himalayan) were found to have a diminished risk of developing hyperthyroidism. In addition, there was a twofold to threefold increase in risk of developing hyperthyroidism among cats fed mostly canned cat food. There was also a threefold increase in risk among cats using cat litter (Kass et al, 1999). In a more recent study, there was no breed association with risk for developing hyperthyroidism. Exposure to fertilizers, herbicides, plant pesticides, or flea control products or the presence of a smoker in the home was not significantly associated with an increased risk for developing hyperthyroidism. Cats that preferred fish-flavored or liver and giblets–flavored canned cat food had an increased risk of hyperthyroidism (Martin et al, 2000). Finally in a study published in 2004, Edinboro et al. identified consumption of canned cat food (especially food consumed from pop top cans) as a risk factor for developing hyperthyroidism. In this study, female cats were at increased risk of developing hyperthyroidism. Other identified risk factors were consumption of baby food, lack of iodine supplement in label ingredients, and increasing frequency of carpet cleaning; increasing years of exposure to well water and increasing years of exposure to gas fireplaces were also identified as risk factors (Edinboro et al, 2010). Similar risk factors have been identified in widely diverse geographic locations, such as the United Kingdom, Germany, New Zealand, and Hong Kong (Wakeling et al, 2009b) (Table 4-1). These studies collectively suggest that the cause of feline hyperthyroidism is probably multifactorial; however the consistent identification of canned cat food as a risk factor suggests that diet likely plays a major role. Candidate dietary candidate risk factors fall into two categories; nutritional deficiencies or excesses and consumption of goitrogens (Peterson, 2012).

Nutritional Deficiencies or Excesses

Iodine

Iodine deficiency causes hypothyroidism and goiter in humans and other species. Low thyroid hormone concentrations cause increased TSH concentrations, which lead to thyroid hyperplasia and goiter. Mild or moderate iodine deficiency increases the risk of toxic nodular goiter in elderly humans (Laurberg et al, 1991; Pedersen et al, 2002). In some individuals, correction of iodine deficiency or administration of excess iodine can lead to thyrotoxicosis, which may be transient or persistent. Causes of iodine-induced thyrotoxicosis in humans include iodine supplementation for endemic iodine deficiency goiter, iodine administration to patients with euthyroid Graves' disease or underlying nodular or diffuse goiter, and administration of radiographic contrast material to patients with underlying thyroid disease. In areas of mild to moderate iodine deficiency, iodide administration can cause thyrotoxicosis in patients with no underlying thyroid disease (Roti and Vagenakis, 2013). It is therefore possible that iodine excess or deficiency could contribute to the pathogenesis of feline hyperthyroidism. Although acute changes in iodine intake result in inverse changes in thyroid hormone concentrations in cats, longer-term studies suggest that cats are able to auto regulate thyroid hormone synthesis and maintain thyroid hormone concentrations within reference range despite variable iodide intake (Mumma et al, 1986; Johnson et al, 1992; Edinboro et al, 2013). Longer-term effects of variation in iodide intake however are unknown. In a case control study of cats with hyperthyroidism, cats consuming diets that did not have iodine supplementation identified as a labeled ingredient were four times more likely to be hyperthyroid than those that did; however it should be recognized that iodine in the diet can result from overt supplementation, or be naturally present in the diet from both plant and animal sources—especially ocean fish. Thus the lack of explicit iodine supplementation in a diet does not necessarily equate with iodine deficiency. Studies have documented that the iodine content of commercial diets, especially canned diets, is extremely variable with some commercial diets being deficient in iodine while others contain iodine in excess (Johnson et al, 1992; Edinboro et al, 2013). There has been a recent trend toward less iodine supplementation of commercial cat foods, because recommended dietary requirements of iodine for cats have decreased over the last 30 years (Edinboro et al, 2010). In a study of urinary iodide concentrations in hyperthyroid cats, before and after treatment with radioactive iodine, it was demonstrated that iodine concentrations were lower in hyperthyroid cats compared to euthyroid cats (Wakeling et al, 2009a). Although it is possible that these findings indicate decreased iodine intake during development of hyperthyroidism, there are many complex influences on iodine metabolism in cats and further studies are necessary to establish a cause and effect relationship. Although it is unlikely that iodine deficiency is the sole cause of feline hyperthyroidism, it is possible that dramatic fluctuations in iodine intake or chronic iodine deficiency may contribute to the current increase in feline thyrotoxicosis.

Soy Isoflavones

Dietary soy is a potential dietary goitrogen that is commonly used as a source of high-quality vegetable protein in commercial cat food. In one study, soy isoflavones were identified in in 24 of 42 commercial cat foods with concentrations ranging from 1 to 163 μg/g of food; these amounts are predicted to have a biologic effect (Court and Freeman, 2002). Although soy is more commonly used as an ingredient in dry food, it is also present in some canned diets. The soy isoflavones genistein and daidzein are known to inhibit thyroid peroxidase, which is an enzyme essential to thyroid hormone synthesis (Doerge and Sheehan 2002), and also inhibit 5′-deiodinase activity, resulting in decreased conversion of T_4 to T_3. These compounds may also induce hepatic enzymes that are responsible for hepatic clearance of T_3 and T_4 (White et al, 2004). In a study of normal cats fed either soy or soy-free diets for 3 months, soy fed cats had a measurable increase in total T_4 and free T_4 (fT_4) concentrations with no change in total T_3 concentrations (White et al, 2004). These changes were hypothesized to be due to deiodinase inhibition and resulted in some cats having a fT_4 concentration above the reference range. These finding are consistent with the hypothesis that decreased total T_3 concentrations cause increased TSH, which stimulates the thyroid gland to increase thyroid hormone synthesis and normalize total T_3 concentrations. These compounds, therefore, could potentially cause chronic thyroid gland hyperplasia and play an etiologic role in feline thyrotoxicosis. Although compelling, this theory does not explain the increased risk of hyperthyroidism in cats fed canned food, because soy is less commonly found in canned diets. Interestingly the effects of soy on thyroid function are exacerbated in the presence of iodine deficiency (Doerge and Sheehan, 2002). It is conceivable that soy diets contribute to the pathogenesis of feline hyperthyroidism by interacting with other factors that impact the thyroid gland such as iodine deficiency. Further studies are necessary to confirm this hypothesis.

Selenium

The thyroid gland contains more selenium per gram than any other tissue, which suggests an important role for this trace element in thyroid homeostasis. Selenium modifies thyroid hormone

metabolism through the activity of selenoproteins, such as glutathione peroxidases and thioredoxin reductase, which protect thyrocytes from oxidative damage. In cats, the type I deiodinase is a selenium dependent enzyme, and selenium deficiency may impair thyroid function. In kittens fed a low selenium diet, total T_4 increased and total T_3 decreased (Yu et al, 2002). There was no difference in plasma selenium concentrations of either euthyroid or hyperthyroid cats from two geographic areas with an allegedly high incidence of hyperthyroidism (UK, Eastern Australia) and two regions with a lower incidence (Denmark, Western Australia); however, cats had higher concentrations of selenium in their plasma than do other species such as rats and humans (Foster et al, 2001). In another study, selenium concentrations were not different between hyperthyroid cats and control cats (Sabatino et al, 2013). The role, if any, of selenium in the pathogenesis of feline hyperthyroidism remains to be determined.

Goitrogens (Thyroid Disrupters)

A large number of environmental chemicals are known to disrupt thyroid function in various species, including humans (Boas et al, 2012). Known endocrine disrupting chemicals include polychlorinated biphenyls, dioxins, polybrominated diphenyl ether (PBDE) flame retardants, perfluorinated chemicals, phthalates, bisphenol A (BPA), and perchlorate. Many of these compounds have a high degree of structural similarity to T_4 (Fig. 4-2) and most are metabolized via glucuronidation, a process that is unusually slow in cats (Court and Greenblatt, 2000). The mechanisms by which goitrogens disrupt thyroid function are many and complex and include binding to the TSH receptor, stimulation or inhibition of the sodium iodide symporter, inhibition of thyroid peroxidase, binding to thyroid hormone plasma binding proteins, interference with other receptors on the thyrocyte, interference with membrane thyroid hormone transporters, changes in thyroid receptor (TR) expression or binding, and stimulation of hepatic enzymes responsible for thyroid hormone clearance. Although there are a large number of chemicals that have the potential to disrupt thyroid function in cats, recently most attention has focused on BPA and the PBDE flame retardants.

Bisphenol A

BPA is a chemical used to make epoxy resins and polycarbonate plastics. It has estrogenic activity and has been demonstrated to disrupt thyroid function both by inhibiting thyroid peroxidase and by binding to the thyroid hormone receptor, inhibiting TR mediated transcription. Epoxy resins are widely used for lining the interior of metal cans to prevent corrosion and maintain flavor and shelf life. BPA has been demonstrated to migrate from food can linings into human and pet food products during the cooking process (Kang and Kondo, 2002). It is hypothesized that BPA migration into canned cat food could explain the increased risk of hyperthyroidism in cats fed canned food (Edinboro et al, 2004). Further studies are needed to establish the relationship between BPA and hyperthyroidism in cats.

Polybrominated Diphenyl Ether Flame Retardants

PBDEs are a group of synthetic brominated compounds that are widely used as flame retardants in many consumer products. These chemicals interfere with thyroid function at multiple levels including binding with the TR, interacting with thyroid hormone binding proteins, inhibition of deiodinases, and increasing hepatic clearance of thyroid hormone. Studies have demonstrated that house cats have high plasma concentrations of a variety of PBDEs, although concentrations do not differ between euthyroid and hyperthyroid cats. In a recent study, although the serum concentrations of PBDEs did not differ between euthyroid and hyperthyroid cats, there were higher concentrations of PBDEs in dust collected from the households of hyperthyroid cats than from the households of euthyroid cats (Mensching et al, 2012). Clearly domestic cats have a significant burden of PBDEs presumably due to ingestion of household dust during grooming; however a causal association between PBDEs and feline hyperthyroidism has yet to be proven.

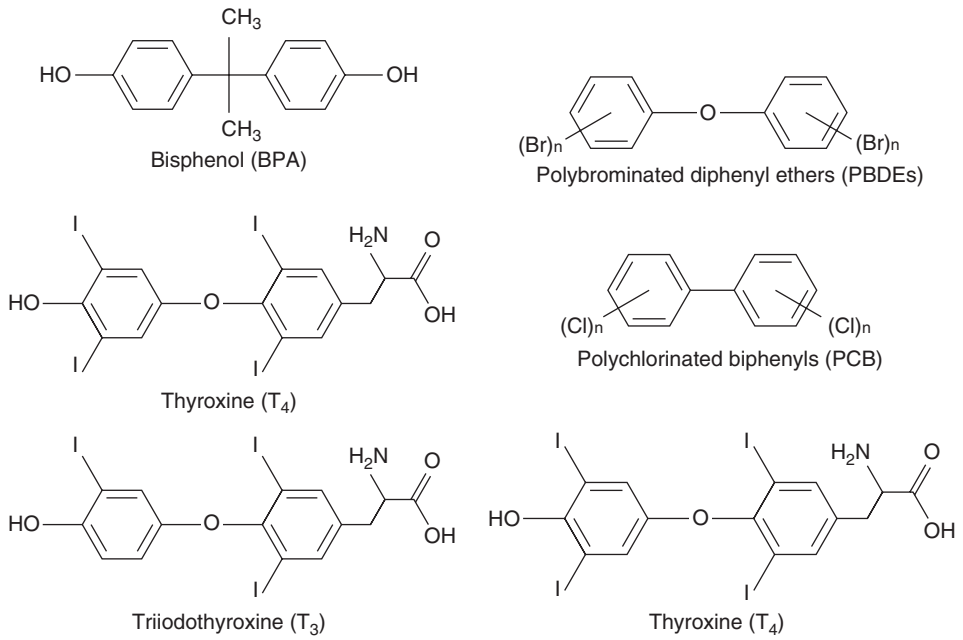

FIGURE 4-2 Chemical structure of bisphenol A (BPA), polybrominated diphenyl ethers (PBDEs), polychlorinated biphenyls (PCB), thyroxine (T_4), and triiodothyronine (T_3). (From Peterson ME: Hyperthyroidism in cats: what's causing this epidemic of thyroid disease and can we prevent it? *J Feline Med Surg* 14[11]:804-818, 2012.)

CLINICAL FEATURES OF FELINE HYPERTHYROIDISM

Signalment

Hyperthyroidism is the most common endocrinopathy affecting cats (Edinboro et al, 2004). The reported age range is 4 to 22 years with a mean of 13 years. Interestingly the mean age of onset has not changed over the time period of 1983 to 2004 (Peterson et al, 1983; Broussard et al, 1995; Edinboro et al, 2004). A small number of cats younger than 4 years has been diagnosed with hyperthyroidism, although the disorder remains rare in this age group (Gordon et al, 2003). Fewer than 5% of cats diagnosed with hyperthyroidism are younger than 8 years of age. Pure bred cats, particularly Siamese and Himalayan cats, have a decreased risk of developing hyperthyroidism (Scarlett et al, 1988; Kass et al, 1999; Olczak et al, 2005).

Clinical Signs and Pathophysiology

Overview

Most hyperthyroid cats have a range of clinical signs that reflect the effects of thyroid hormone on almost every organ in the body. Feline hyperthyroidism is a chronically progressive and insidious disease, and the clinical effects can vary from mild to severe. Early in the disease process, the clinical signs are subtle enough to be missed by both the owner and the veterinarian and the diagnosis may only be made when routine thyroid hormone testing is performed. Even if the diagnosis is made by routine testing, clinical signs (e.g., weight loss) can often be identified retrospectively. In some cases, weight loss is ignored because it occurs after intentional calorie restriction to manage obesity, but the weight loss continues even after calorie restriction is discontinued. In other cases, subtle clinical changes (e.g., tachycardia and increased activity) are blamed on stress during the office visit. Clinical signs may be present for months to 1 to 2 years prior to the diagnosis being made (Thoday and Mooney, 1992). Because hyperthyroid cats usually have a good to ravenous appetite and are active or even overactive, the owners often perceive that an elderly cat has a new lease on life and do not initially worry about the clinical signs. Only when the signs worsen or other more serious clinical signs appear do owners seek veterinary help. The most common reasons for owners to seek veterinary care are weight loss, polyphagia, polydipsia/polyuria, vomiting, and/or diarrhea. The spectrum of clinical signs reported in the first large case series reported in the veterinary literature is shown in Table 4-2.

Because owner and veterinary awareness of the clinical syndrome of feline hyperthyroidism is now very high and measurement of serum thyroxine concentration is a routine component of geriatric feline serum biochemistry profiles, cats with hyperthyroidism are being diagnosed earlier in the course of the disease. This means that the clinical signs observed by owners and veterinarians are less severe than those which were described when the disease was first recognized in the 1980s; thus diagnosis of feline hyperthyroidism has become more challenging particularly in cats with other concurrent illness (Broussard et al, 1995; Bucknell, 2000). There was a dramatic decrease in the frequency and severity of clinical findings in cats diagnosed with hyperthyroidism from 1983 to 1993 (Broussard et al, 1995; Fig. 4-3). Unfortunately studies evaluating the frequency of clinical signs in hyperthyroid cats have not been published in the peer reviewed literature since 2000, but subjectively the trend for decreasing severity of clinical signs at the time of diagnosis has continued. A significant percentage of cats presented for radioactive iodine treatment at our institution did not have clinical signs recognized by the owner prior to diagnosis of hyperthyroidism.

Weight Loss

Weight loss is the most common clinical sign observed in cats with hyperthyroidism. Approximately 90% of hyperthyroid cats have evidence of mild to severe weight loss documented at the time of diagnosis. Some hyperthyroid cats become severely cachectic (Fig. 4-4), but this is less common now than previously because of the increased awareness of the disease and resultant earlier diagnosis. The weight loss typically occurs gradually over a period of months to years. Owners may comment that the weight loss was not recognized until someone who had not seen the cat for several months noticed the change.

Polyphagia

Polyphagia and weight loss are quite common in feline hyperthyroidism. This is an extremely important historical finding, because the combination of polyphagia and weight loss has fewer differential diagnoses than anorexia and weight loss (Box 4-1). Cats previously thought to be finicky eaters may develop excellent appetites, which is a change that may not initially be perceived as a problem by the owner. In severe cases of polyphagia, cats can become aggressive in obtaining food.

Polyphagia and weight loss occur due to the increased metabolic rate and increased energy expenditure of the hyperthyroid state, which results in reduced efficiency of physiologic functions.

TABLE 4-2 **HISTORICAL AND PHYSICAL EXAMINATION FINDINGS FROM THE FIRST LARGE CASE SERIES OF 131 CATS WITH HYPERTHYROIDISM**

SIGN	PERCENT OF CATS
Weight loss	98
Polyphagia	81
Increased activity/restless	76
Tachycardia	66
Polydipsia/polyuria	60
Vomiting	55
Cardiac murmur	53
Diarrhea	33
Increased fecal volume	31
Anorexia	26
Polypnea	25
Muscle weakness	25
Muscle tremor	18
Congestive heart failure	12
Increased nail growth	12
Dyspnea	11
Alopecia	7
Ventroflexion of neck	3

Modified from Peterson ME, et al.: Feline hyperthyroidism: pretreatment clinical and laboratory evaluation of 131 cases, *J Am Vet Med Assoc* 183(1):103-110, 1983.

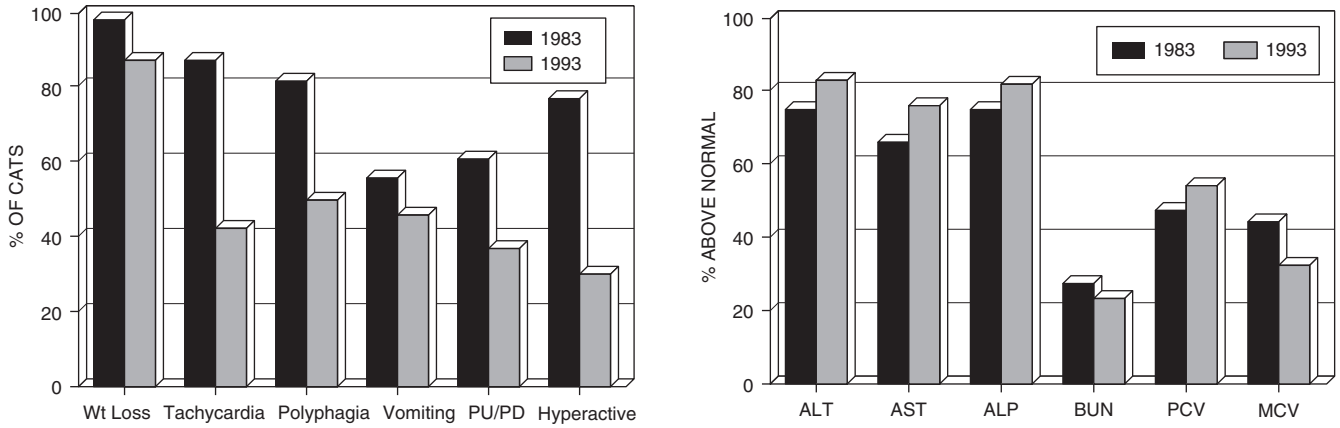

FIGURE 4-3 Percentage of cats with common clinical findings in 1983 (n = 131) compared to 1993 (n = 202). (From Broussard JD, et al.: Changes in clinical and laboratory findings in cats with hyperthyroidism from 1983 to 1993, *J Am Vet Med Assoc* 206[3]:302-305, 1995.) *ALP,* alkaline phosphatase; *ALT,* alanine aminotransferase; *AST,* aspartate aminotransferase; *BUN,* blood urea nitrogen; *MCV,* mean corpuscular volume; *PCV,* packed cell volume; *PD,* polydipsia; *PU,* polyuria.

FIGURE 4-4 **A,** Hyperthyroid 13-year-old cat showing severe emaciation due to severe hyperthyroidism **B,** Same cat as in **A** 2 months after return to a euthyroid condition. **C,** Hyperthyroid cat choosing the cool cage floor rather than a warm fleece pad. **D,** Hyperthyroid cat with marked ventroflexion of the head, a finding suggestive of concomitant thiamine or potassium deficiency. (**D,** Courtesy of Dr. Jane Turrel, Pacifica, CA.)

BOX 4-1 Differential Diagnosis for Cats with Polyphagia and Weight Loss

Hyperthyroidism
Diabetes mellitus
Poor quality or insufficient diet
Gastrointestinal disease
  Malabsorption (inflammatory bowel disease, gastrointestinal lymphoma, gastrointestinal parasitism)
  Maldigestion (exocrine pancreatic insufficiency)
Hyperadrenocorticism

Increased food intake and utilization of stored energy can initially compensate for the increased energy expenditure; however, ultimately chronic caloric and nutritional deficiency occurs. Although both synthesis and degradation of proteins are increased, the net effect is protein catabolism. In addition to weight loss, negative nitrogen balance is evidenced by muscle wasting and weakness. The exact mechanism for the increase in appetite associated with hyperthyroidism is poorly understood but studies suggest that suppression of leptin, increased hypothalamic neuropeptide Y, and enhanced phosphorylation of adenosine monophosphate (AMP)-activated protein kinase may play a role (Pétervári et al, 2005; Ishii et al, 2008). Although polyphagia is one of the most common clinical signs of hyperthyroidism, a small percentage of hyperthyroid cats exhibit periods of decreased appetite (see Decreased Appetite).

Nervousness, Hyperactivity, Aggressive Behavior

Approximately 50% of humans with thyrotoxicosis exhibit trembling, nervousness, emotional lability, and depression and anxiety, which are presumably due to a direct effect of thyroid hormone concentrations on the nervous system (Burch, 2013). In cats, these signs are characterized by restlessness, irritability, and/or aggressive behavior (see Table 4-2; Table 4-3). Many hyperthyroid cats appear to have an intense desire to move about constantly. Owners may note that their cats wander, pace, sleep for only brief periods, and waken easily. Many hyperthyroid cats appear "anxious" and cannot be held for the short time required to complete a physical examination. Some become aggressive if an attempt is made to further restrain them. The cause of these clinical signs is multifactorial; however some of the signs are due to increased adrenergic activity, because a degree of improvement occurs during treatment with adrenergic antagonists.

Polydipsia and Polyuria

Polyuria and polydipsia are commonly reported in feline hyperthyroidism. Although the two clinical signs invariably occur together, it is common for owners to report polydipsia in the absence of polyuria, or vice versa. Polyuria and polydipsia occur in 30% to 40% of hyperthyroid cats, and changes in the amount of water consumed and urine excreted are highly variable. There are a number of mechanisms involved in the pathogenesis of polydipsia and polyuria in hyperthyroidism. Primary (psychogenic) polydipsia increases water and solute intake, and down regulation of Aquaporin 1 and Aquaporin 2 channels may contribute to the polyuria (Wang et al, 2007). Occult renal disease may also play a role. Polyuria and polydipsia may be present in hyperthyroid cats without evidence of renal disease, but because hyperthyroidism increases glomerular filtration rate (GFR) and decreases urine specific gravity (USG), it is difficult to assess true renal function in hyperthyroid cats. After resolution of hyperthyroidism (regardless of the treatment method), renal perfusion typically decreases, which in some cats may unmask occult renal failure (see Treatment of Hyperthyroidism and Renal Function).

TABLE 4-3 PHYSICAL EXAMINATION FINDINGS ASSOCIATED WITH HYPERTHYROIDISM IN CATS

FINDING	PERCENT OF CATS
Palpable thyroid	91
Thin	71
Tachycardia (more than 240 beats/min)	48
Hyperactive/difficult to examine	48
Heart murmur	41
Skin changes (patchy alopecia, matting, dry coat, greasy seborrhea, thin skin)	36
Small kidneys	26
Increased rectal temperature	14
Gallop cardiac rhythm	12
Easily stressed	12
Dehydrated/cachectic appearance	11
Aggressive behavior	8
Premature cardiac beats	8
Increase nail growth	2
Depressed/weak	2
Ventroflexion of the neck	< 1

Gastrointestinal Dysfunction

The most common clinical signs of hyperthyroidism referable to the gastrointestinal tract are polyphagia and weight loss (see earlier). Other signs of gastrointestinal dysfunction include anorexia, vomiting, diarrhea, increased fecal volume, increased frequency of defecation, and foul smelling feces. Vomiting is relatively common, occurring in approximately 50% of hyperthyroid cats. Anorexia and watery diarrhea are less common but when present are usually seen in cats with severe hyperthyroidism or in those with coexistent primary intestinal problems. Reasons for diarrhea and increased frequency of defecation in hyperthyroidism include hypermotility of the gastrointestinal tract, leading to rapid gastric emptying, and shortened intestinal transit times (Papasouliotis et al, 1993; Schlesinger et al, 1993). Rapid eating or overeating leading to gastric distension and direct action of thyroid hormone on the chemoreceptor trigger zone are potential causes of vomiting. Steatorrhea is also reported in cats with severe hyperthyroidism; however, fat malabsorption may be due to other concurrent illness, such as exocrine pancreatic insufficiency.

Hair Loss/Unkempt Coat

Nonspecific hair coat changes (e.g., unkempt hair, matted hair, and a lusterless coat) occur commonly in hyperthyroid cats. Less commonly, patchy alopecia may occur due to excessive grooming activity. Some cats may pull hair out in clumps. Heat intolerance is a classic sign of thyrotoxicosis in humans, and hair pulling may also be a result of heat intolerance in cats.

Panting and Respiratory Distress

Open-mouth breathing (panting) is rare in cats and is usually associated with heart or respiratory disease. Some hyperthyroid cats exhibit panting, dyspnea, or hyperventilation at rest; these signs are most common in hyperthyroid cats that are stressed by physical restraint or transportation. Dyspnea on exertion is common in thyrotoxic people and is due to respiratory muscle weakness, enhanced ventilatory drive, decreased pulmonary compliance, and concurrent cardiovascular complications (Burch, 2013). Thyrotoxicosis is associated with shallow rapid breathing, enhanced oxygen utilization and carbon dioxide output, and a low anaerobic threshold (Burch, 2013).

Decreased Appetite

Although most hyperthyroid cats are polyphagic, some hyperthyroid cats exhibit inappetence, anorexia, or a waxing and waning appetite. Potential causes of a poor appetite include congestive heart failure, severe debilitation and muscle weakness, thiamine or cobalamine deficiency, hypokalemia, or other concurrent nonthyroidal illness (e.g., inflammatory bowel disease, pancreatitis, renal disease, and neoplasia) (Cook et al, 2011).

Weakness and Lethargy

Decreased activity, weakness, fatigability, and lethargy occur in some cats with severe hyperthyroidism. Some cats progress from over-activity and restlessness to listlessness and weakness. Weakness and fatigability are also frequent complaints in humans with thyrotoxicosis. In one study, 67% of hyperthyroid people had complaints of muscle weakness, mainly in the proximal muscles of the legs, and 19% had symmetrical distal sensory abnormalities and depressed distal tendon reflexes (Duyff et al, 2000). The biochemical basis of the muscular weakness is uncertain; it may simply be caused by weight loss and the catabolic state. Hypokalemia, cobalamine deficiency, and thiamine deficiency may also contribute to muscle weakness and weight loss (Ruaux et al, 2005).

Heat and Stress Intolerance

Heat intolerance is a subtle sign that may be observed by cat owners. Most normal cats seek warm, sunny places to sleep. Hyperthyroid cats may reverse this heat-seeking behavior and sleep in cool places, such as the bath tub or a cool tile floor (see Fig. 4-4, *C*). In addition to heat intolerance, some hyperthyroid cats have an obvious impaired tolerance for stress. Brief car rides, bathing, and visits to boarding kennels or veterinary hospitals may cause marked clinical deterioration, respiratory distress, weakness, or even cardiac arrest. The clinician should always take into consideration this inability to cope with stress when diagnostic or therapeutic procedures are being planned.

Heat intolerance and an inability to cope with stress are classic clinical signs of human thyrotoxicosis. Many of these effects are similar to those induced by epinephrine, including heat intolerance, excessive sweating (in humans), tremor, and tachycardia. Because these signs are partly alleviated by adrenergic antagonists, it has been hypothesized that a state of increased adrenergic activity exists in thyrotoxicosis; however investigators have been unable to demonstrate increased catecholamine production, increased concentrations of serum catecholamine concentrations, or excretion of urinary catecholamine metabolites. Furthermore, although increased numbers of adrenergic receptors have been demonstrated in thyrotoxicosis, evidence of increased sensitivity to catecholamines in thyrotoxicosis is lacking (Liggert et al, 1989).

Concurrent Nonthyroidal Illness

Because feline hyperthyroidism is a geriatric disease, concurrent nonthyroidal illness is common and often complicates the clinical picture. Because the clinical signs of hyperthyroidism are so variable and overlap with those of many other concurrent illnesses, the presence or absence of any one clinical sign cannot be used to diagnose or exclude hyperthyroidism. In some cases, the only way to determine whether all the clinical signs exhibited by a particular patient can be explained by hyperthyroidism is to treat the hyperthyroidism and determine if the clinical signs resolve.

Subclinical Hyperthyroidism

Subclinical hyperthyroidism is defined in humans as the presence of hormone test results indicating hyperthyroidism (usually decreased TSH) in a person without clinical signs of hyperthyroidism (Biondi et al, 2005). It is likely that a similar condition exists in cats; however, documentation of this condition is hampered by the lack of a sensitive assay for TSH in cats. In one study of 104 geriatric cats with normal thyroid hormone concentrations, 7.5% of cats became hyperthyroid during 12 months of follow up (Wakeling et al, 2011). Cats with undetectable TSH at baseline were more likely to become hyperthyroid, but not all cats with a suppressed TSH became hyperthyroid. Furthermore, geriatric cats with a low TSH are more likely to have histologic evidence of nodular thyroid disease (Wakeling et al, 2007).

PHYSICAL EXAMINATION

General

Although many cats with mild hyperthyroidism appear asymptomatic to the owner, in the vast majority of cases abnormalities consistent with a diagnosis of hyperthyroidism can be detected by a careful physical examination. Weight loss and tachycardia are usually present and support a diagnosis of hyperthyroidism. Most importantly, a palpable cervical mass is detected in over 90% of hyperthyroid cats at the time of diagnosis.

Palpable Cervical Mass (Goiter)

In healthy cats, the thyroid lobes are positioned just below the cricoid cartilage and extend ventrally over the first few tracheal rings; they lie dorsolateral to and on either side of the trachea. The thyroid lobes are not palpable in normal cats. Hyperthyroidism is invariably associated with enlargement of one or both thyroid lobes (goiter)—an enlargement that is palpable in more than 90% of hyperthyroid cats. Careful palpation is required to identify small goiters, which can be challenging in a stressed cat.

Palpation of a cervical mass is not pathognomonic for hyperthyroidism; some cats with palpable thyroid glands are clinically normal, and some cervical masses arise from structures other than the thyroid gland. In one study of euthyroid geriatric cats (more than 9 years of age) a palpable goiter was present in 27 of 104 (26%) of cats. Sixteen percent of these cats ultimately became hyperthyroid over 4½ years of follow up (Wakeling et al, 2011). Causes of thyroid gland enlargement, other than adenomatous hyperplasia or adenoma, include thyroiditis, and thyroid cystadenoma (Norsworthy et al, 2002). Other causes of palpable cervical masses

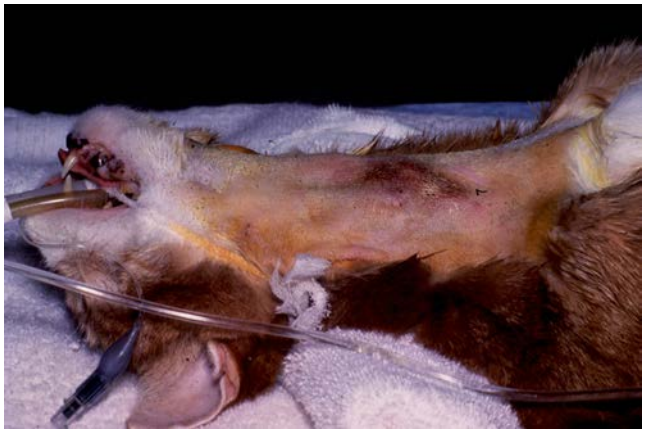

FIGURE 4-5 The clipped ventrocervical area of a cat with an obvious goiter.

include salivary mucoceles, parathyroid gland masses or cysts, thyroglossal cysts, dermoid cysts, and pharyngeal (branchial) cysts (Norsworthy et al, 2002; Phillips et al, 2003; Lynn et al, 2009; Tolbert et al, 2009; Nelson et al, 2012).

Because the thyroid lobes are only loosely attached to the trachea, the increased weight associated with thyroid enlargement causes migration of the lobes ventrally in the neck. Sometimes the abnormal lobe (or lobes) descends through the thoracic inlet and into the anterior mediastinum. This may be one explanation for being unable to palpate a goiter in a hyperthyroid cat. In cats with thyroid carcinoma, thyroid gland palpation may be similar to that of a hyperthyroid cat with benign disease; however, in other cases the masses associated with thyroid carcinoma are large, fixed rather than freely moveable and attached to underlying or overlying tissues.

Palpation Technique

Evaluation of the thyroid area should be part of the physical examination of every cat seen by a veterinarian. This allows the clinician to develop expertise and confidence when palpating a cat suspected of having hyperthyroidism, and it occasionally allows identification of a mass that would otherwise go undetected.

For the evaluation, the cat's head should be gently extended. The thumb and index finger of one hand are gently placed on either side of the trachea in the jugular furrows at the level of the larynx. The area is gently compressed, and the fingers are smoothly slid down to the thoracic inlet and back up again to the larynx. The fingertips should remain within the jugular furrows. Thyroid enlargement is usually felt as a somewhat movable, subcutaneous (SC) nodule that may vary between the size of a lentil and the size of a lima bean. Success in this maneuver depends on not squeezing too hard; the pressure exerted must be gentle enough to allow the abnormal nodule to slide under the fingertips but firm enough to detect the mass. Sometimes it is possible for owners to visualize a goiter by moistening the neck with alcohol; the enlarged thyroid glands can often be visualized as the fingers palpating the neck slide toward the thoracic inlet. Occasionally a large cervical mass can be directly direct visualized if the ventrocervical area is clipped free of hair (Fig. 4-5). If thyroid enlargement is not palpated after two or three attempts in a cat with compatible clinical signs, the cats head and neck should be extended further and the palpation repeated. This maneuver will sometimes result in an intrathoracic nodule moving back out into the neck where it can be palpated. Alternatively gradual pressure applied just below the thoracic inlet may move a thyroid mass located just inside the thoracic inlet back into the neck.

Alternative Palpation Technique

An alternative semi-quantitative palpation technique has been described in which the clinician stands behind the cat and elevates the head at a 45-degree angle while turning the head to the right and left (Norsworthy et al, 2002). The size of the thyroid gland is scored from 0 to 6 with 0 being a non-palpable thyroid gland, 1 being a barely palpable thyroid gland and 6 being a lobe measuring 2.5 cm or greater in length. Using this technique, an enlarged thyroid gland was detected in 96% of hyperthyroid cats and 59% of euthyroid cats (Norsworthy et al, 2002); however, the technique was not compared to the standard palpation technique. None of the enlarged thyroid glands detected in euthyroid cats had a score of 3 or more, whereas 18 of the 23 hyperthyroid cats had a score of 4 or greater.

Cardiac Disturbances

Tachycardia, Murmurs, Premature Beats, and Gallop Rhythm

The heart is very sensitive to the effects of thyroid hormone, and many hyperthyroid cats have clinical evidence of heart disease. Common cardiovascular abnormalities include tachyarrhythmias, heart murmurs, and gallop rhythms. Less commonly, clinical signs of congestive heart failure (e.g., dyspnea, muffled heart sounds, and ascites) may be present. In a study of approximately 200 hyperthyroid cats evaluated from 1992 to 1993, 8% of cats had evidence of congestive heart failure compared to 20% of cats evaluated between 1979 and 1982 (Fox et al, 1999). Congestive heart failure due to feline hyperthyroidism is even less common now that it was in the 1990s (Connolly et al, 2005).

Tachycardia is the most common cardiovascular abnormality present in hyperthyroid cats, but it is sometimes difficult to distinguish tachycardia due to thyrotoxicosis from other causes of tachycardia, such as stress, hypovolemia, and primary cardiac disease. Sinus tachycardia is the most common cause of tachycardia and is reported in about 30% of hyperthyroid cats. Other less common arrhythmias include atrial extrasystoles, atrial tachycardia, ventricular extrasystoles, first degree atrioventricular block, left anterior fascicular block, right bundle branch block, and left bundle branch block.

The tachycardia present in the majority of hyperthyroid cats is due to both an increase in sympathetic tone and a decrease in parasympathetic tone (Fig. 4-6; Klein and Ojamaa, 2001). Cardiac output is increased due to tachycardia, increased ejection fraction, increased blood volume, and decreased vascular resistance (Klein and Ojamaa, 2001). The direct vasodilatory effect of T_3 on smooth muscle results in decreased peripheral resistance that leads to activation of the renin-angiotensin-aldosterone system (RAAS) and increased blood volume. Thyroid hormones also directly activate genes that encode structural and regulatory cardiac proteins (Box 4-2), which ultimately results in an increase in contractile function (Connolly et al, 2005; Klein and Ojamaa, 2001). The increased metabolic rate of the hyperthyroid state increases peripheral oxygen demand and also contributes to the high-output state. The normal heart compensates for these changes by cardiac dilation and hypertrophy. Although the increased heart rate and increased cardiac output of the hyperthyroid state resemble a state of increased adrenergic activity and various components of the adrenergic receptor complex in the plasma membrane are altered by changes in thyroid hormone concentrations, there is no net effect on the sensitivity of the heart to adrenergic stimulation (Klein and Ojamaa, 2001).

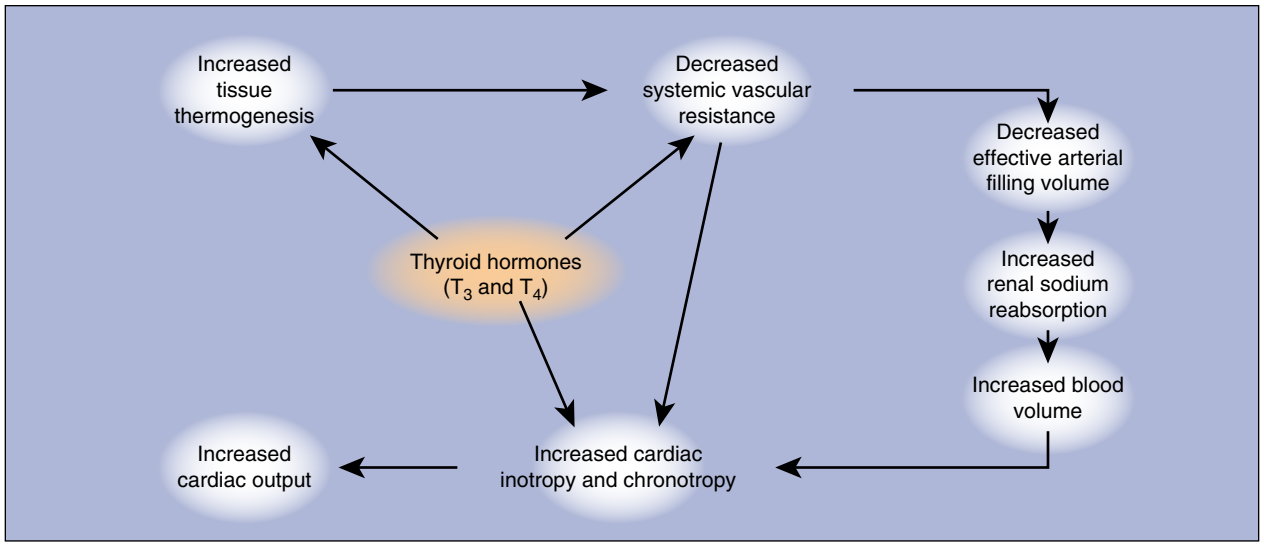

FIGURE 4-6 Effects of thyroid hormone on cardiovascular dynamics. The diagram shows the way that thyroid hormones increase cardiac output by affecting tissue oxygen consumption, vascular resistance, blood volume, cardiac contractility, and heart rate. *T_3,* Triiodothyronine; *T_4,* thyroxine. (Adapted from Klein I, Ojamaa K: Thyroid hormone and the cardiovascular system, *N Engl J Med* 344[7]:501-509, 2001.)

BOX 4-2 Regulation of Genes Coding for Cardiac Proteins by Thyroid Hormone

Positive Regulation
α-Myosin heavy chain
Sarcoplasmic reticulum Ca^{2+}-ATPase
β_1-Adrenergic receptors
Guanine-nucleotide-regulatory proteins
Na^+/K^+-ATPase
Voltage-gated potassium channels (Kv1.5, Kv4.2, Kv4.3)

Negative Regulation
β-Myosin heavy chain
Phospholamban
Adenylyl cyclase types V and VI
Triiodothyronine (T_3) nuclear receptor α1
Na^+/Ca^{2+} exchanger

From Klein I, Ojamaa K: Thyroid hormone and the cardiovascular system, *N Eng J Med* 344(7):504, 2001.
ATPase, Adenosine triphosphatase.

Some cats with hyperthyroidism develop secondary hypertrophic cardiomyopathy, which may result in heart failure. In a study of 103 hyperthyroid cats, the most common echocardiographic findings were ventricular or interventricular hypertrophy; only four cats had subnormal cardiac performance and ventricular dilatation, and all of these cats had clinical and radiographic evidence of congestive heart failure (Bond et al, 1988). Severe heart failure appears to be more common among hyperthyroid cats with the dilated form of cardiomyopathy (Jacobs et al, 1986; Jacobs and Panciera, 1992). Dilated cardiomyopathy in hyperthyroid cats may be due to concurrent primary heart disease rather than secondary to hyperthyroidism. Approximately 50% of hyperthyroid cats have detectable concentrations of serum troponin I, which is a sensitive and specific marker of myocardial cellular damage (Connolly et al, 2005); this would be expected in a systemic disease that increases myocardial oxygen demand and predisposes the myocardium to cellular hypoxia. The serum troponin concentrations normalize in most cats after effective treatment of hyperthyroidism.

Ventroflexion of the Head

Early reports of hyperthyroid cats included occasional cats exhibiting pronounced ventroflexion of the head (see Fig. 4-4, *D*). The head of an affected cat could be lifted without difficulty, but the cat immediately resumed the abnormal posture when released. Clinical signs usually seen in association with cervical ventroflexion were anorexia, mild ataxia, and mydriasis. There have been no published reports of this syndrome since 1994 (Nemzek et al, 1994). It has been hypothesized that either thiamine deficiency or hypokalemia could be the cause of cervical ventroflexion; but because it is now so rare, there have been no further investigations of the pathogenesis. Potassium depletion may occur in hyperthyroidism secondary to vomiting, diarrhea, anorexia, or excess urine loss. Vitamin deficiencies (e.g., thiamine and cobalamine deficiency) occur in hyperthyroidism secondary to polyuria, malabsorption, diarrhea, vomiting, and anorexia.

Ocular Lesions

Systolic hypertension is documented in approximately 10% to 15% of hyperthyroid cats at the time of diagnosis (Williams et al, 2010). Despite this, retinopathy secondary to hypertension is uncommonly detected in feline hyperthyroidism. In a study of 100 hyperthyroid cats and 30 control cats, there were no ophthalmologic abnormalities that were more commonly identified in hyperthyroid cats than in euthyroid cats (van der Woerdt and Peterson, 2000). Two hyperthyroid cats had retinal changes consistent with hypertensive retinopathy, including retinal hemorrhage and focal retinal detachment with subretinal effusion. The authors concluded that ocular abnormalities are uncommon in hyperthyroid cats (see also Blood Pressure and Hypertension).

Thyroid Storm

Thyroid storm is the term used in humans to describe an acute exacerbation of clinical signs of thyrotoxicosis in conjunction with varying degrees of organ decompensation. The cause is believed to be an increased cellular response to thyroid hormone in conjunction with increased or abrupt availability of free thyroid hormones. Thyroid storm is usually precipitated by a superimposed insult, such as infection, thyroid surgery, other nonthyroidal illness, or withdrawal of anti-thyroid drugs (Chiha et al, 2013). The diagnosis is based on documentation of four major clinical signs: fever, central nervous system (CNS) manifestations, gastrointestinal or hepatic dysfunction, and cardiovascular effects, such as tachycardia, atrial fibrillation, and congestive heart failure. Although cats with hyperthyroidism may have an acute exacerbation of clinical signs either due to complications of thyrotoxicosis (e.g., congestive heart failure, hypertension) or presence of concurrent nonthyroidal illness, thyroid storm as defined in humans has yet to be described (Ward, 2007; Tolbert, 2010).

IN-HOSPITAL DIAGNOSTIC EVALUATION

Background

Cats with hyperthyroidism are usually geriatric, and therefore abnormalities identified on the diagnostic evaluation may be due either to thyrotoxicosis or other underlying concurrent disease. It can sometimes be difficult to distinguish which abnormalities are due to hyperthyroidism and which are due to other concurrent illness. In addition, hyperthyroidism increases the metabolic rate and GFR and can mask underlying chronic kidney disease (CKD). The goals of the diagnostic evaluation in a cat with suspected hyperthyroidism are to confirm the diagnosis, identify complications of hyperthyroidism (e.g., hypertension and heart failure that require either further evaluation or specific treatment), and evaluate for the presence of other disorders that require treatment or whose presence may influence the choice of treatment for hyperthyroidism. Minimum diagnostic testing should include a complete blood count (CBC), serum biochemistry profile, urinalysis, serum T_4 concentration, thoracic radiography, and measurement of indirect blood pressure. Electrocardiography and echocardiography are indicated if clinically significant heart disease is suspected. Further diagnostic testing may be necessary in cats in which the diagnosis of hyperthyroidism cannot be confirmed by measurement of serum T_4 concentration alone, and in those cats in which the initial evaluation reveals abnormalities that cannot be explained by hyperthyroidism alone.

Complete Blood Count

Erythron

Approximately 40% to 50% of hyperthyroid cats have a mild elevation in the packed cell volume (PCV) (Broussard et al, 1995). The increase in the red blood cell count may be directly related to thyrotoxicosis, because thyroid hormone stimulates secretion of erythropoietin (Klein and Ojamaa, 2001). Additionally, 20% of hyperthyroid cats have macrocytosis (Broussard et al, 1995). Heinz bodies are a more common finding on evaluation of the blood film in hyperthyroid cats than in control cats. Although cats with Heinz bodies tend to have a lower hematocrit than those without Heinz bodies, anemia is a rare finding in hyperthyroid cats (Christopher, 1989). Depletion of antioxidants and excessive fat and protein catabolism has been proposed as the reason for Heinz body formation in hyperthyroid cats (Christopher, 1989; Branter et al, 2012).

Leukon

Hyperthyroid cats usually have a normal leukogram or may have nonspecific changes, such as a stress response characterized by leukocytosis, neutrophilia, lymphopenia, and eosinopenia.

Platelets

Hyperthyroid cats have been demonstrated to have larger platelets than normal control cats, but platelet counts were similar (Sullivan et al, 1993).

Serum Chemistry Profile

Liver Enzyme Activities

Increased liver enzymes are among the most frequently observed screening test alterations seen in hyperthyroid cats (Table 4-4). More than 75% of hyperthyroid cats have abnormalities in both serum alanine aminotransferase (ALT) and serum alkaline phosphatase (ALP) activities, and more than 90% show increases of at least one of these enzymes. The increases are usually only mild to moderate (less than 500 IU/L), although higher values are noted occasionally. The influence of underlying concurrent hepatic disease should be considered in hyperthyroid cats with more markedly increased liver enzyme activities (more than 500 IU/L), although not all hyperthyroid cats with higher increases in ALT have concurrent hepatic dysfunction. Hepatic hypoxia is thought to be the major cause of abnormalities in

TABLE 4-4 **LABORATORY ABNORMALITIES ON ROUTINE TESTING OF HYPERTHYROID CATS**

TEST	PERCENTAGE OF CATS
Complete Blood Count	
Erythrocytosis	39
Increase in MCV	27
Lymphopenia	22
Leukocytosis	19
Eosinopenia	13
Serum Chemistry Profile	
Increased ALT	85
Increased serum ALP	62
Azotemia (increased BUN)	26
Increased creatinine	23
Hyperphosphatemia	18
Electrolyte abnormalities	11
Hyperglycemia	5
Hyperbilirubinemia	3
Urinalysis	
Specific gravity > 1.035	63
Specific gravity < 1.015	4
Glucosuria	4
Inflammation/infection	2

ALP, Alkaline phosphatase; *ALT*, alanine aminotransferase; *BUN*, blood urea nitrogen; *MCV*, mean cell volume.

ALT but increased hepatic enzyme activity may also be due in part to malnutrition, congestive heart failure, infection, and direct toxic effects of thyroid hormones on the liver. Separation of the different isoenzymes of serum ALP has demonstrated that 50% to 80% of the increased serum ALP in hyperthyroid cats is the bone isoenzyme of serum ALP, presumably because of increased bone turnover (Archer and Taylor, 1996; Foster and Thoday, 2000). Increased AST and creatine kinase (CK) have also been reported in some hyperthyroid cats (Archer and Taylor, 1996). Increases in gamma glutamyl transferase (GGT) have not been reported in hyperthyroid cats (Archer and Taylor, 1996; Berent et al, 2007).

Liver Dysfunction

In addition to increased hepatic enzymes, cats with hyperthyroidism have significantly higher fasting serum ammonia concentrations than euthyroid cats; these values return to normal with effective treatment of the hyperthyroidism (Berent et al, 2007). The reason for increased ammonia concentrations is unknown, but it may be secondary to accelerated protein catabolism and deamination due to the increased metabolic rate. Pre and post prandial bile acid concentrations and results of hepatic ultrasonography were normal in all hyperthyroid cats with increased ammonia concentrations. Four of the 19 hyperthyroid cats evaluated had ALT concentrations greater than 500 I/L; however, the ALT returned to normal in all cats after treatment. This implies that there were no functional or clinically relevant hepatic changes in these hyperthyroid cats and that a high ALT with no other indication of hepatic dysfunction should not necessarily prompt further hepatic evaluation in a cat whose clinical signs are consistent with hyperthyroidism. Other indicators of hepatic dysfunction may include hypoglycemia, hypocholesterolemia, hypoalbuminemia, and decreased blood urea nitrogen (BUN). In the cats studied by Berent et al., (2007), none of the hyperthyroid cats were hypoglycemic or hypocholesterolemic, although the hyperthyroid cats had lower concentrations of glucose and cholesterol than age matched control cats. These changes also normalized after treatment of the hyperthyroidism. Serum albumin and BUN concentrations did not differ between hyperthyroid cats and age matched control cats and did not change after treatment. The differences likely relate to the increased metabolic rate of hyperthyroid cats, but the changes do not appear to be clinically relevant or supportive of hepatic dysfunction. There have been no published studies evaluating hepatic histopathology in cats with hyperthyroidism. One author reported that liver biopsies typically reveal increased pigment within hepatocytes, aggregates of mixed inflammatory cells in the portal regions, and focal areas of fatty degeneration; and some cats have mild hepatic necrosis (Feldman and Nelson, 2004). In severe cases of thyrotoxicosis, it was reported that centrilobular fatty infiltration may occur together with patchy portal fibrosis, lymphocytic infiltration, and proliferation of bile ducts (Feldman and Nelson, 2004). Liver enzyme activities, regardless of their origin, usually return to normal with successful management of the hyperthyroidism (Berent et al, 2007).

Altered Bone Metabolism

People with hyperthyroidism have decreased bone mineral density and increased concentrations of bone resorption markers and bone formation markers such as ALP and osteocalcin (Williams, 2013). There is believed to be an increased risk of fracture in people with either overt or subclinical hyperthyroidism, but studies are confounded by multiple other factors that influence fracture risk, such as age, sex, use of hormone therapy, and other factors. Increased bone metabolism is attributed to the direct effects of thyroid hormones on osteoclasts and osteoblasts.

Hyperthyroid cats also have evidence of increased bone turnover as evidenced by increased activity of the bone isoenzyme of serum ALP and osteocalcin concentrations (Archer and Taylor, 1996; Foster and Thoday, 2000). In a study of 36 hyperthyroid cats, 44% of cats had increased osteocalcin concentrations. There were no correlations between magnitude of serum ALP bone isoenzyme, osteocalcin, and serum thyroxine concentrations (Archer and Taylor, 1996). Derangements in calcium homeostasis also occur in hyperthyroid cats. Hyperthyroid cats have been reported to have increased serum phosphate concentrations and decreased ionized calcium concentrations (Archer and Taylor, 1996; Williams et al, 2012; Barber and Elliott, 1996). The mechanism for ionized hypocalcemia in hyperthyroid cats is unknown but does not appear to be due to concurrent CKD or reduced plasma calcitriol concentrations (Williams et al, 2013). In a study of 30 cats with untreated hyperthyroidism, hyperthyroid cats had lower blood ionized calcium concentrations and higher phosphate concentrations than a group of age matched controls; 43% of the cats were hyperphosphatemic, and 27% of the cats had an ionized calcium concentration below the reference range (Barber and Elliott, 1996). Hyperparathyroidism was documented in 77% of the cats with parathyroid hormone (PTH) concentrations reaching up to 19 times the upper limit of the reference range. Other studies also suggest that 60% to 80% of hyperthyroid cats have increased serum concentrations of PTH (Williams et al, 2012; Barber and Elliott, 1996). This finding is very different from thyrotoxic human patients that typically have hypoparathyroidism. The changes usually normalize after treatment of hyperthyroidism (Williams et al, 2012), although some cats with underlying CKD have persistent increases in PTH presumably due to secondary renal hyperparathyroidism. Although indications of increased bone turnover have been documented in hyperthyroid cats, clinical consequences (e.g., increased fracture risk) are very rare.

Blood Glucose

Cats have a remarkable ability to increase their blood glucose concentrations in response to acute stress. Acutely stressed cats can have blood glucose concentrations as high as 300 mg/dL (17 mmol/l) (Rand et al, 2002). This hyperglycemia is believed to result from an acute release of epinephrine. Blood glucose concentrations may become even higher (400 to 500 mg/dL, 22-28 mmol/L) due to the stress of chronic illness, although it is difficult to assess the contribution of concurrent beta cell dysfunction in clinically ill cats. Surprisingly the majority of hyperthyroid cats have normal blood glucose concentrations, and as a group, hyperthyroid cats have lower blood glucose concentrations than age matched controls.

In humans, the increased energy expenditure of thyrotoxicosis is compounded by the inefficient maintenance of basic physiologic functions. To compensate for increased energy expenditure, increases in food consumption, utilization of stored energy, and enhanced oxygen expenditure alter the metabolism of carbohydrate, lipid, and protein. Intestinal absorption of glucose and the rate of glucose production from glycogen, lactate, glycerol, and amino acids are increased. Hepatic glycogen stores are decreased, owing to increased glucose utilization by muscle and adipose tissue. It is likely that multiple factors influence the blood glucose concentration in hyperthyroid cats with factors such as depletion of hepatic glycogen stores tending to decrease the blood sugar, whereas stress and peripheral insulin resistance tend to increase the blood glucose. Diabetes mellitus and hyperthyroidism are both common diseases of the geriatric cat and occasionally can occur together. This scenario should be considered in

hyperthyroid cats with persistent mild hyperglycemia (more than 200 mg/dL; 11 mmol/l) (Hoenig and Ferguson, 1989).

Cholesterol

Serum cholesterol concentration is usually within the reference range in hyperthyroid cats. The synthesis and especially clearance of cholesterol and triglycerides are increased in hyperthyroidism, resulting in modest reductions in both the serum cholesterol and triglyceride concentrations, although the cholesterol concentrations do not typically decrease below the reference range. Lipolysis is also accelerated, resulting in increased plasma free fatty acid concentrations.

Blood Urea Nitrogen and Creatinine

CKD is estimated to be present in 15% of cats older than 15 years of age and is therefore a common concurrent disorder in hyperthyroid cats. Recent studies suggest that approximately 10% of hyperthyroid cats are azotemic at the time of diagnosis of hyperthyroidism based on measurement of a serum creatinine above the laboratory reference range (Williams et al, 2010). Increased serum BUN is found in a slightly larger number (10% to 20%) of hyperthyroid cats. It is important to recognize, however, that merely including the proportion of cats with azotemia underestimates the prevalence of CKD in hyperthyroid cats because of physiologic changes in hyperthyroidism that lead to an increased GFR. Untreated hyperthyroid cats have a higher GFR, as measured by iohexol clearance or scintigraphy, than the same cats after reestablishment of the euthyroid state (Adams et al, 1997; Graves et al, 1994; DiBartola et al, 1996; van Hoek et al, 2008a). Hyperthyroidism increases renal blood flow due to increased cardiac output and intra-renal vasodilation. Changes in afferent and efferent arteriolar resistance increases the glomerular transcapillary hydraulic pressure, which increases GFR. Activation of the RAAS possibly via changes in β-adrenergic activity has been implicated as a mechanism for this alteration in renal hemodynamics. Despite the increase in renal perfusion pressure in hyperthyroidism, resorption of sodium and chloride from the proximal tubule and loop of Henle is increased rather than decreased due to impairment of the pressure-diuresis-natriuresis response (Syme, 2007), which may explain how plasma volume can increase and sodium excretion can decrease. In addition to the renal hemodynamic changes in hyperthyroidism, weight loss and muscle atrophy further decrease serum creatinine concentrations in hyperthyroid cats. For these reasons, it may be difficult or impossible to diagnose CKD in cats with concurrent hyperthyroidism.

The increased GFR normalizes after treatment of hyperthyroidism, so from 15% to 49% of cats that are non-azotemic at the time of diagnosis of hyperthyroidism become azotemic after treatment. The variability in the percentage of cats becoming azotemic likely reflects variability in adequacy of control of hyperthyroidism (Williams et al, 2010b). Numerous studies have failed to identify pretreatment parameters other than measurement of GFR that allow prediction of which cats will have clinically significant worsening of azotemia after treatment. The fact that cats with hyperthyroidism and CKD may have similar clinical signs (e.g., polyuria, polydipsia, and weight loss) and that the two diseases commonly occur together compounds the problem of establishing the severity of CKD in hyperthyroid cats. Whether the long-term effects of hyperthyroidism actually contribute to progression of renal disease in cats is still unclear. Glomerular hypertension, proteinuria, and hyperparathyroidism have all been proposed as mechanisms for intrinsic progression of CKD in the cat. Further epidemiological studies are required to determine whether CKD is more common in hyperthyroid cats than in the population at large.

Urinalysis

Urine abnormalities that may be present in hyperthyroid cats include a decreased USG, proteinuria, evidence of urinary tract infection, and ketonuria. As discussed earlier, concurrent CKD is common in hyperthyroid cats and may result in a decreased USG. Polyuria and polydipsia may also occur in hyperthyroid cats without CKD by mechanisms that are poorly understood. Mechanisms that have been proposed include disturbances in the vasopressin axis and primary polydipsia possibly due to heat intolerance (Feldman and Nelson, 2004). In one study of 21 hyperthyroid cats treated with radioactive iodine, USG did not change after treatment in most cats (van Hoek et al, 2009a) suggesting that CKD was the most common reason for a low USG. Proteinuria is detected in 75% to 80% of hyperthyroid cats and usually resolves following treatment (Berent et al, 2007; van Hoek et al, 2009a; Williams et al, 2010b). Studies suggest that the proteinuria associated with hyperthyroidism is primarily due to increased excretion of proteins other than albumin (Williams et al, 2010b). Reasons for proteinuria in hyperthyroid cats could include glomerular hypertension and hyperfiltration, changes in tubular protein handling, and changes in the structure of the glomerular barrier (van Hoek et al, 2009a). Although proteinuria usually resolves after treatment of hyperthyroidism, its presence prior to treatment is correlated with reduced survival but not development of azotemia (Williams et al, 2010b). Urinary tract infection is relatively common in cats with hyperthyroidism. In one study urine culture was positive in 11 of 90 (12%) of hyperthyroid cats, and 17 of 77 (22%) cats with CKD. Only two of the hyperthyroid cats had clinical signs of lower urinary tract disease (Mayer-Roenne et al, 2007). Interestingly in one study, trace ketonuria was detected in 9 of 19 hyperthyroid cats (Berent et al, 2007). This had not been previously reported in hyperthyroid cats but has been described in humans with hyperthyroidism. Potential reasons for ketonuria in hyperthyroidism include β-adrenergic induced lipolysis, which results in increased fatty acid delivery to the liver, or increased hepatic ketogenesis due to carnitine deficiency (Wood and Kinlaw, 2004). A number of recent studies have investigated urinary markers of renal tubular injury such as urinary retinol binding protein and N-acetyl-β–D-glucosaminidase that might be useful in prediction of azotemia after treatment of hyperthyroid cats. Although these markers are present in the urine of hyperthyroid cats, they have not proved useful in predicting which cats are likely to become azotemic after treatment (Lapointe et al, 2008; van Hoek et al, 2009b).

Plasma Cortisol/Urine Cortisol:Creatinine Ratio

Adrenocortical hyperplasia is an uncommon finding in cats, but it was found in one-third of hyperthyroid cats in one study (Liu et al, 1984). Increased cortisol secretion due to increased pituitary secretion of adrenocorticotropic hormone (ACTH) also occurs in hyperthyroid humans, although it does not result in hypercortisolemia, because hyperthyroidism in humans is also associated with increased metabolic clearance of cortisol. In a study of 17 hyperthyroid cats, 18 healthy geriatric cats, and 18 cats with concurrent nonthyroidal illness, basal and ACTH stimulated cortisol concentrations were higher in hyperthyroid cats than in control cats, but the urinary cortisol creatinine ratio (UCCR) and adrenal size as measured by ultrasound were not different between the groups (Ramspott et al, 2012).

Other studies have documented mild adrenomegaly in hyperthyroid cats compared with healthy euthyroid cats, and higher UCCR in hyperthyroid cats compared to healthy cats (de Lange et al, 2004; Combes et al, 2012). Taken together, these studies suggest that there is some degree of hypercortisolemia and adrenal gland hyperplasia in hyperthyroid cats. These findings are important because although hyperadrenocorticism is rare in cats, there are some similarities between the clinical signs of the two diseases.

Serum Fructosamine

Fructosamine is produced by an irreversible reaction between glucose and plasma proteins. Serum fructosamine concentrations in cats are thought to reflect the mean blood glucose concentration during the preceding 1 to 2 weeks (Link and Rand, 2008). However, fructosamine concentrations are also affected by the concentration and metabolism of serum proteins, and hyperthyroidism increases protein metabolism. Serum fructosamine concentrations in hyperthyroid cats have been documented to be significantly lower than in healthy control cats (Reusch and Tomsa, 1999). Fifty percent of hyperthyroid cats had serum fructosamine concentrations less than the reference range. Serum fructosamine concentrations in hyperthyroid, normoproteinemic cats did not differ from values in hypoproteinemic cats. During treatment for hyperthyroidism, an increase in serum fructosamine concentration was documented. It was concluded that the concentration of serum fructosamine in hyperthyroid cats may be low because of accelerated protein turnover—independent of blood glucose concentration. For these reasons, the serum fructosamine concentration should not be considered a reliable monitoring tool in hyperthyroid cats with concurrent diabetes mellitus. Additionally, serum fructosamine concentrations should not be considered reliable for differentiating between diabetes mellitus and stress-related hyperglycemia in hyperthyroid cats (Reusch and Tomsa, 1999).

Blood Pressure and Hypertension

Although in earlier studies systolic hypertension was reported to be common in hyperthyroid cats (Kobayashi et al, 1990), more recent studies suggest that only 10% to 20% of hyperthyroid cats have hypertension diagnosed at the time of diagnosis of hyperthyroidism; end-organ damage due to hypertension (e.g., retinal detachment) appears to be extremely uncommon (van der Woerdt and Peterson, 2000; Syme, 2007; Williams et al, 2010). Reasons for the lower prevalence of hypertension in more recent studies include earlier diagnosis of feline hyperthyroidism, more conservative cut-offs for diagnosis of hypertension (blood pressure of more than170 mm Hg on a least two occasions, or more than170 mmHg and evidence of hypertensive retinopathy), and increased recognition of the white coat effect (Belew et al, 1999; see also Ocular Lesions). The low prevalence of hypertension is similar to findings in humans and is likely because the decrease in systemic vascular resistance results in a decrease in diastolic resistance, and the increase in cardiac output results in only modest increases in systolic blood pressure (Syme, 2007). Interestingly a recent report found that approximately 20% to 25% of cats that were normotensive prior to treatment of hyperthyroidism became hypertensive several months (median 5 months) after treatment of hyperthyroidism (Syme and Elliott, 2003). Whether this is due to a decline in renal function after treatment or other undetermined mechanism is unclear. Posttreatment hypertension was not limited to cats that became azotemic after therapy, and no differences were detected between cats that developed hypertension and those that did not in regard to RAAS activation (Syme, 2007).

Radiography

Thoracic radiographs should ideally be performed as part of the diagnostic evaluation of all hyperthyroid cats to assess for evidence of heart disease or concurrent illness. Even if there are no clinical signs of heart disease, thoracic radiographs allow detection of occult concurrent illness, such as pulmonary or cranial thoracic neoplasia. Abnormalities on physical examination that increase the importance of obtaining thoracic radiographs include respiratory distress, tachypnea or panting, muffled heart sounds, tachycardia, arrhythmias, or a heart murmur. The most common findings on thoracic radiographs include mild cardiomegaly. Signs of congestive heart failure such as pulmonary edema, enlarged pulmonary vessels, and pleural effusion are uncommon in hyperthyroid cats (Jacobs et al, 1986). In a study reporting radiographic abnormalities in hyperthyroid cats diagnosed from 1992 to 1993, 8% of cats had radiographic evidence of congestive heart failure compared to 20% in cats evaluated from 1979 to 1982 (Fox et al, 1999). The prevalence of congestive heart failure in hyperthyroid cats is now likely even lower than it was in the 1990s.

Electrocardiography

Electrocardiographic changes are common in hyperthyroid cats but rarely require specific treatment. The electrocardiographic changes seen in cats with thyrotoxicosis are listed in Table 4-5 and are illustrated in Figs. 4-7 to 4-9. Tachycardia (heart rate above 240/min) and an increased R-wave amplitude in lead II (greater than 1.0 mv) are the abnormalities most frequently seen, although each is now detected less commonly than in the 1980s (Broussard et al, 1995). Other less common arrhythmias include atrial extrasystoles, atrial tachycardia, ventricular extrasystoles, first degree atrioventricular block, left anterior fascicular block, right bundle branch block, and left bundle branch block. In a study of hyperthyroid cats evaluated in 1993, evidence of right or left atrial enlargement was present on the electrocardiogram (ECG) in 42% of cats (Fox et al, 1999). Most electrocardiographic abnormalities resolve with successful management of the thyrotoxicosis.

TABLE 4-5 **PRETREATMENT ELECTROCARDIOGRAM FINDINGS IN 131 CATS WITH HYPERTHYROIDISM PRESENTING IN 1992-1993**

FINDING	PERCENTAGE OF CATS
Sinus tachycardia	66
Increased R-wave amplitude (lead II)	29
Left anterior fascicular block	8
Atrial asystoles	7
Ventricular asystoles	2
First degree atrioventricular block	2
Right bundle branch block	2
Atrial tachycardia	1

Data modified from Fox PR, et al.: Electrocardiographic and radiographic changes in cats with hyperthyroidism: comparison of populations evaluated during 1992-1993 vs. 1979-1982, *J Am Anim Hosp Assoc* 35(1):27-31, 1999.

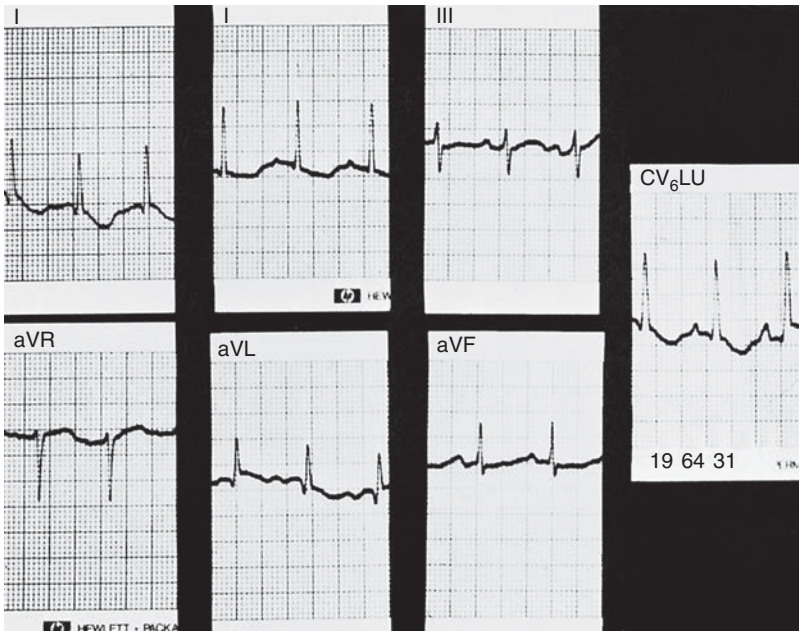

FIGURE 4-7 Electrocardiogram (ECG) from a thyrotoxic cat showing R waves of increased amplitude in all leads and deviation of the mean electrical axis to 30 degrees, suggestive of left heart enlargement.

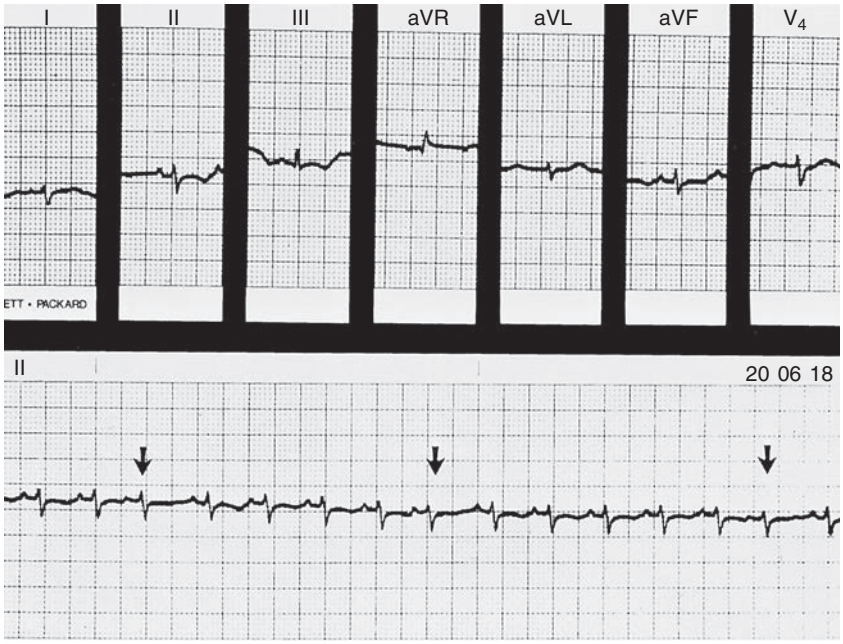

FIGURE 4-8 Electrocardiogram (ECG) from a thyrotoxic cat showing normal P-QRS-T complex amplitudes. However, three atrial premature contractions can be seen in the rhythm strip *(arrows),* and an abnormal heart rate of 300 beats per minute is present.

Echocardiography

Echocardiographic abnormalities frequently identified in hyperthyroid cats include left ventricular caudal wall hypertrophy and hypertrophy of the interventricular septum; these changes are largely reversible after treatment of the hyperthyroidism state (Bond et al, 1988). Hyperthyroid cats also may have increased left atrial diameter, aortic end-diastolic diameter, and left atrial to aortic root ratio. Myocardial hypercontractility is also common as evidenced by increased percentage of shortening of the minor axis and velocity of circumferential shortening (Bond et al, 1988). Less commonly, a dilated form of cardiomyopathy is observed. Echocardiographic abnormalities in these cats include subnormal myocardial contractility and marked ventricular dilation. These cats usually have radiographic evidence of congestive heart failure (Jacobs et al, 1986; Bond et al, 1988).

The radiographic, electrocardiographic, and echocardiographic changes observed in feline hyperthyroidism occur due to the marked cardiovascular effects of thyroid hormone on the heart. Increased cardiac output, decreased systemic vascular resistance, direct positive chronotropic and inotropic stimulation, β-adrenergic stimulation, and underlying cardiomyopathy all may contribute to the abnormalities detected. In a study of 91 cats that were studied before and 2 to 3 months after treatment with radioiodine, 37% of cats had one or more echocardiographic variables outside the reference range prior to treatment. The most common findings were primarily increases in interventricular septal and left ventricular wall thickness; the findings were considered clinically relevant in less than 10% of cats (Table 4-6) (Weichselbaum et al, 2005). Interestingly 32% of the cats studied had one or more echocardiographic abnormalities present following treatment; almost half of these cats had been normal before

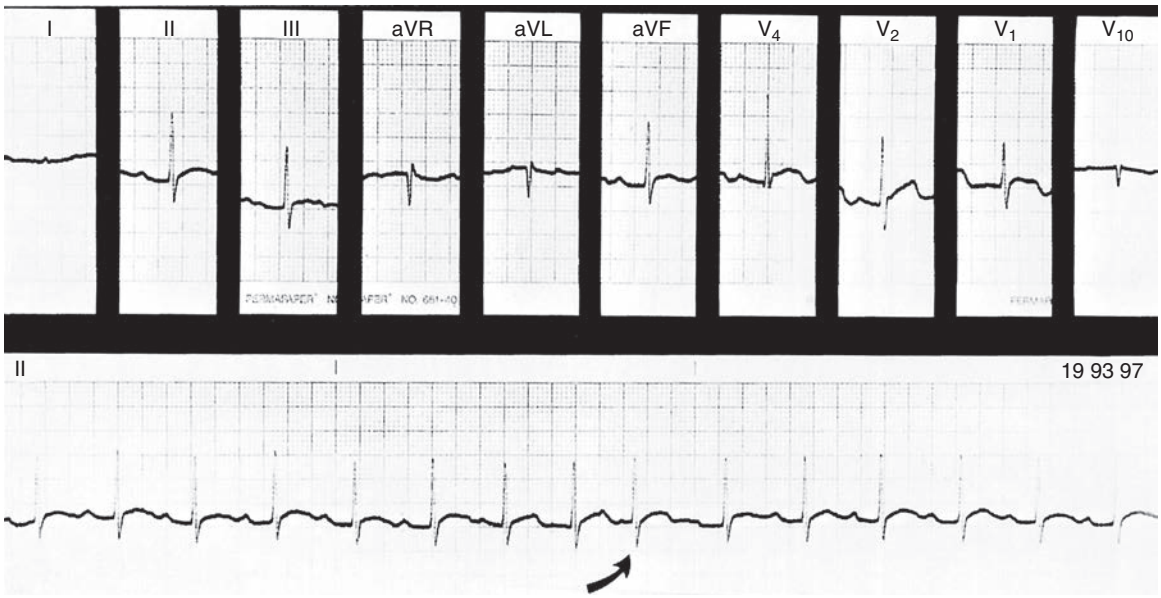

FIGURE 4-9 Electrocardiogram (ECG) from a thyrotoxic cat showing both increased amplitude in the R waves and an atrial premature contraction *(arrow).*

TABLE 4-6 **NORMAL FELINE REFERENCE, PRE-RADIOIODINE, AND POST-RADIOIODINE M-MODE ECHOCARDIOGRAPHIC VALUES FOR 91 HYPERTHYROID CATS**

	Feline Normal Reference Values (2.7 to 8.2 kg*)			Feline Pre- and Post-Radioiodine Treatment Values (2.2 to 8.9 kg*)					
	Observed Range			Observed Range			Observed Range		
ECHOCARDIOGRAPH VARIABLE (UNIT)	MEAN ± SD	MINIMUM	MAXIMUM	PRERADIOIODINE MEAN ± SD	MINIMUM	MAXIMUM	POSTRADIOIODINE MEAN ± SD	MINIMUM	MAXIMUM
Number of cats	76-79			91			91		
IVSED (cm)	0.42 ± 0.07	0.30	0.60	0.44 ± 0.07	0.27	0.72	0.43 ± 0.13	0.27	0.55
IVSES (cm)	0.67 ± 0.12	0.40	0.90	0.78 ± 0.12	0.41	1.14	0.72 ± 0.11	0.34	1.08
LVEDD (cm)	1.50 ± 0.20	1.08	2.14	1.63 ± 0.22	0.64	2.09	1.64 ± 0.22	1.17	2.22
LVESD (cm)	0.72 ± 0.15	0.40	1.12	0.80 ± 0.15	0.42	1.13	0.87 ± 0.19	0.55	1.73
LVWED (cm)	0.41 ± 0.07	0.25	0.60	0.47 ± 0.10	0.28	0.89	0.42 ± 0.56	0.29	0.59
LVWES (cm)	0.68 ± 0.11	0.43	0.98	0.78 ± 0.10	0.49	1.02	0.69 ± 0.80	0.53	0.90
A_0 (cm)	0.95 ± 0.14	0.60	1.21	0.99 ± 0.11	0.72	1.21	1.02 ± 0.13	0.72	1.36
LA (cm)	1.17 ± 0.17	0.70	1.70						
LA Max (cm)				1.34 ± 0.15	0.99	1.82	1.32 ± 0.18	0.99	2.14
FS (%)	52.1 ± 7.11	40.00	66.70	50.60 ± 7.29	34.00	66.00	46.60 ± 7.24	21.00	62.90

From Weichselbaum RC, et al.: Relationship between selected echocardiographic variables before and after radioiodine treatment in 91 hyperthyroid cats, *Vet Radiol Ultrasound* 46(6):506-513, 2005.

A_0, Aortic root maximum dimension (from M-mode); *FS,* LV fractional shortening, i.e.,¼((LVEDDLVESD)/LVEDD) 100); *IVSED,* interventricular septum at end-diastole (from M-mode); *IVSES,* interventricular septum at end-systole (from M-mode); *LA,* left atrium dimension (from M-mode); *LA Max,* left atrium maximum dimension (from two-dimensional long-axis); *LVEDD,* left ventricular end-diastolic dimension (from M-mode); *LVESD,* left ventricular end-systolic dimension (from M-mode); *LVWED,* left ventricular posterior wall thickness at end-diastole (from M-mode); *LVWES,* left ventricular posterior wall thickness at end-systole (from M-mode).

*Body weight range.

treatment. The conclusions of the authors were that changes in echocardiographic variables in hyperthyroid cats are less common than previously reported, presumably due to earlier diagnosis. The emergence of new abnormalities after treatment of hyperthyroidism may reflect underlying cardiac disease unrelated to hyperthyroidism, permanent hyperthyroidism related damage, or incomplete recovery from the effects of hyperthyroidism or possibly the effects of iatrogenic hypothyroidism. These findings underscore the complexity of the interactions between hyperthyroidism and the heart. There was no correlation between the total T_4 concentration and the presence of clinically relevant echocardiographic changes. The heart rate of hyperthyroid cats rather

than presence of echocardiographic changes may be a more useful parameter for determining which cats require medical management with cardiac drugs during and after treatment of hyperthyroidism (Weichselbaum et al, 2005).

DIFFERENTIAL DIAGNOSIS

Because hyperthyroidism is a disease of geriatric cats and because the clinical signs of hyperthyroidism often mimic those of other disorders, the differential diagnosis for hyperthyroidism is extensive (Table 4-7). The most common disorders that should be considered in the differential diagnosis include CKD, gastrointestinal disorders, heart disease, and diabetes mellitus.

SERUM THYROID HORMONE CONCENTRATIONS

For an overview of thyroid hormone physiology and the assays used for diagnosis of thyroid disorders in dogs and cats, see Chapter 3. Thyroid hormone measurements commonly used to confirm the diagnosis of feline hyperthyroidism include the serum total T_4 and fT_4 concentrations. Measurement of serum T_3 concentration is rarely useful for diagnosis of feline hyperthyroidism, and serum TSH concentrations have limited utility because of poor sensitivity of the current commercial assays for measurement of feline TSH.

Basal Total Serum Thyroxine Concentration

The initial screening test of choice for diagnosis of feline hyperthyroidism is the basal serum T_4 concentration. Reference range for total T_4 is typically 1 to 4.5 μg/dL for healthy cats, although the reference ranges of individual laboratories vary. The total T_4 concentration has both high sensitivity and specificity for diagnosis of feline hyperthyroidism. In a study of 917 untreated hyperthyroid cats, 221 cats with nonthyroidal illness, and 172 normal cats, 91% of the hyperthyroid cats had high serum total T_4 concentrations, whereas none of the cats with nonthyroidal illness had high total T_4 concentrations, giving an assay sensitivity of 91% and assay specificity of 100% (Peterson et al, 2001; Fig. 4-10). Similar findings have been reported in other smaller studies. Commercial veterinary laboratories now include serum total T_4 concentrations as a component of most geriatric feline chemistry profiles, which has resulted in the diagnosis of feline hyperthyroidism being made much earlier in the disease process. This approach to screening is appropriate for diagnosis of feline hyperthyroidism because of the high specificity of total T_4 for diagnosis of hyperthyroidism; however the cautions that apply to evaluation of a low total T_4 concentration in the dog also apply to the cat because of the influence of nonthyroidal illness on the measured total T_4 concentration. Despite the high specificity of total T_4 concentration for diagnosis of feline hyperthyroidism, if the total T_4 is increased in a cat with no reported clinical signs of hyperthyroidism, it is important to rule out laboratory and other sample handling errors before confirming the clinical diagnosis; in most cats with

TABLE 4-7 DIFFERENTIAL DIAGNOSIS FOR HYPERTHYROIDISM IN CATS

DIFFERENTIAL DIAGNOSIS	MAJOR CLINICAL AREAS OF OVERLAP WITH HYPERTHYROIDISM
Nonthyroid endocrine disease	
Diabetes mellitus	PD, PU, polyphagia, weight loss
Hyperadrenocorticism (rare)	PD, PU, polyphagia, weight loss
Diabetes insipidus (rare)	PD, PU, mild weight loss
Acromegaly (uncommon)	PD, PU, polyphagia
Renal disease	PD, PU, anorexia, weight loss, elevated BUN
Heart disease and failure	
Hypertrophic cardiomyopathy Congestive cardiomyopathy Idiopathic arrhythmia	Respiratory distress, weight loss, tachycardia, murmur, arrhythmia: radiography, ECG, echocardiogram abnormalities are not specific for hyperthyroidism
Gastrointestinal disease	
Pancreatic exocrine insufficiency	Bulky, foul-smelling stool, weight loss, polyphagia
Diffuse gastrointestinal disorders	
Inflammatory	Diarrhea, vomiting, anorexia, chronic weight loss
Cancer (including lymphosarcoma)	
Hepatopathy	Elevated liver enzymes
Inflammatory	
Cancer	
Pulmonary disease	Respiratory distress, panting

BUN, Blood urea nitrogen; *ECG,* electrocardiogram; *PD,* polydipsia; *PU,* polyuria.

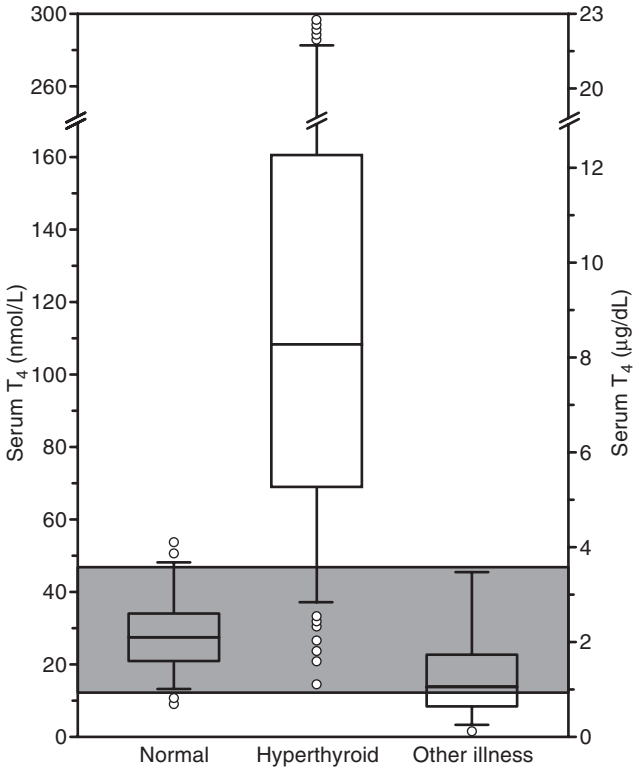

FIGURE 4-10 Box plots of serum total thyroxine (T_4) concentrations in 172 clinically normal cats, 917 cats with untreated hyperthyroidism, and 221 cats with nonthyroidal disease. The box represents the interquartile range (i.e., 25th to 75th percentile range, or the middle half of the data). The horizontal bar in the box represents the median value. For each box plot, the *T bars* represent the main body of data, which in most instances is equal to the range. Outlying data points are represented by *open circles.* The *shaded area* indicates the reference range for the serum T_4 concentration. (From Peterson ME, et al.: Measurement of serum concentrations of free thyroxine, total thyroxine, and total triiodothyronine in cats with hyperthyroidism and cats with nonthyroidal disease, *J Am Vet Med Assoc* 218[4]:529-536, 2001).

apparent asymptomatic hyperthyroidism, there are usually some subtle clinical signs detected once a more detailed history is collected and a physical examination is performed.

Although the total T_4 concentration is a relatively sensitive assay, in some cats with early hyperthyroidism and those with concurrent nonthyroidal illness, the initial measured total T_4 concentration may be within the reference range (usually within the upper 50% of the reference range).

Fluctuations in Serum Thyroxine Concentrations

In a study in which blood samples were collected from hyperthyroid cats hourly during the day and daily over a 15 day period, there were hourly and daily fluctuations in the measured serum total T_4 concentration that sometimes exceeded the expected coefficient of variation of the assay (Peterson et al, 1987), although another study showed less variability (Broome et al, 1988a). Despite fluctuations in total T_4, the measured total T_4 concentration in most hyperthyroid cats is usually persistently above the reference range (Fig. 4-11); however, in cats with only mild increases in the total T_4 concentration, the serum T_4 concentration may fluctuate in and out of the reference range. For this reason, in a cat that has appropriate clinical signs and physical examination findings, a diagnosis of hyperthyroidism should not be excluded on the basis of one "normal" total T_4 measurement (especially if there is a palpable thyroid gland).

Effect of Nonthyroidal Illness on Serum Total Thyroxine Concentrations

As in dogs, the presence of concurrent illness can influence the measured total T_4 concentration. In a study of 98 euthyroid cats with concurrent illness, 76 cats had values within the reference range, 21 cats had values below the reference range, and one cat had a very mild increase in serum total T_4 concentration (less than 3 SD from the reference mean) (Mooney et al, 1996a). In another study that included 221 euthyroid ill cats, none had an abnormally increased serum total T_4 concentration, whereas 38% of the cats had a low concentration (Peterson et al, 2001; see Fig. 4-10). These studies demonstrate that illness can lower serum T_4 concentrations in euthyroid cats with the severity of the decrease correlated with the severity of the disease (Fig. 4-12). In fact the total T_4 concentration is a good prognostic indicator in cats with nonthyroidal illness syndrome (NTIS); mortality increases as the measured total T_4 decreases (Mooney et al, 1996a; Peterson et al, 2001). Diseases that are commonly associated with a decreased total T_4 concentration include diabetes mellitus, hepatopathy, CKD, gastrointestinal disease, and systemic neoplasia; however, severity of disease has more significant effect than does disease category (Peterson et al, 1990b; 2001). The presence of concurrent

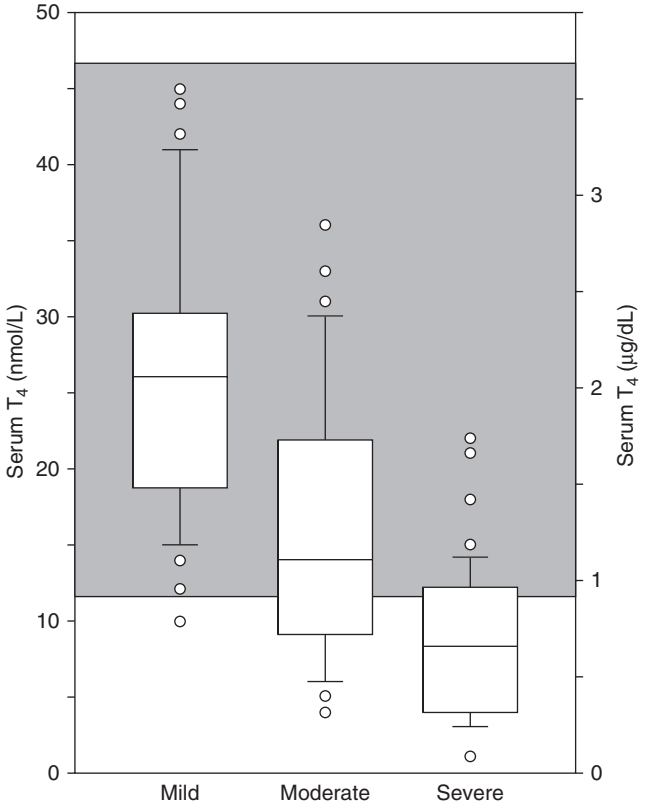

FIGURE 4-12 Box plots of serum total T_4 concentration in 221 cats with nonthyroidal illness grouped according to severity of illness. Of the 221 cats, 65 had mild disease, 83 had moderate disease, and 73 had severe disease (see Fig. 4-10 for key). (Peterson ME, et al.: Measurement of serum concentrations of free thyroxine, total thyroxine, and total triiodothyronine in cats with hyperthyroidism and cats with nonthyroidal disease, *J Am Vet Med Assoc* 218[4]:529-536, 2001.)

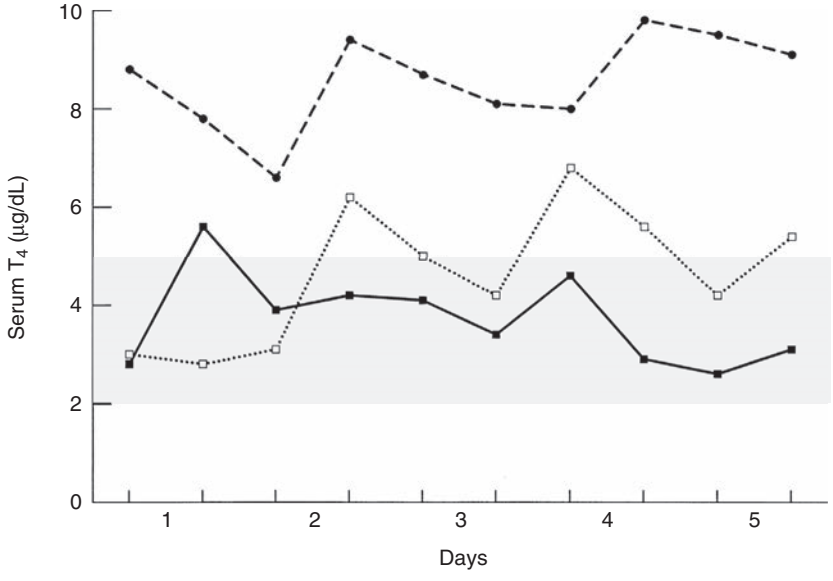

FIGURE 4-11 Serum thyroxine (T_4) concentrations fluctuate in normal and hyperthyroid cats. This figure demonstrates the amount of fluctuation typical of cats with hyperthyroidism. Cats with significantly increased serum T_4 concentrations usually have persistently abnormal results *(dashed line),* whereas cats with "borderline" values have serum T_4 concentrations that can be "non-diagnostic" and occasionally abnormally increased *(dotted line)* or *(solid line). Light gray area* is the reference range. T_4 laboratory reference range: 2.4 to 4.6 µg/dL.

illness also decreases the measured total T_4 in cats with hyperthyroidism. In one study of 110 cats with hyperthyroidism, systemic disease was diagnosed in 36% of the cats, and the serum total T_4 was significantly lower in the cats with nonthyroidal illness than in those without (McLoughlin et al, 1993). Fourteen of the hyperthyroid cats in this study had serum T_4 concentrations within or below the reference range with total T_4 concentrations ranging from 1.3 to 4.0 μg/dL. Ten of these 14 cats had evidence of nonthyroidal illness. For this reason, the history and physical examination findings are critical in determining whether the diagnosis of hyperthyroidism should be pursued further in a cat with a normal or subnormal total T_4 concentration. Although in most hyperthyroid cats with NTIS, the total T_4 is in the upper half of the reference range, as in the study discussed above with severe concurrent illness the T_4 can occasionally be below the reference range in a cat with confirmed hyperthyroidism (Tomsa et al, 2001). The effect of nonthyroidal illness on the total serum T_4 concentration in hyperthyroid cats was further evaluated in a study of cats with hyperthyroidism and concurrent CKD. In 16 cats with a normal serum total T_4 that were later confirmed to be hyperthyroid, the total T_4 ranged from 1.8 to 3.6 μg/dL whereas the total T_4 in cats with CKD alone ranged from 0.4 to 2.3 μg/dL. Most of the hyperthyroid cats with CKD had a total T_4 greater than 2.3 μg/dL, whereas all the cats with CKD alone had a total T_4 less than 2.3 μg/dL (Wakeling et al, 2008).

Other Factors Affecting Serum Total Thyroxine Concentrations

Factors other than NTIS that are believed to influence serum total T_4 concentrations in cats include age and concurrent medication administration. There is little published information on how thyroid hormone concentrations change with age in cats. In a group of more than 13,000 cats of varying ages that had total T_4 concentrations either within or below the reference range, there was no decline in total T_4 with age (Table 4-8). There is also limited information on the effect of drugs on the thyroid axis in cats. It is presumed that most of the medications that influence thyroid hormone concentrations in dogs have similar effects in cats, but the data is lacking to confirm this. Drugs that are known to influence thyroid hormone concentrations in cats include thioureylene drugs, iodinated contrast agents, and glucocorticoids.

TABLE 4-8 **MEAN AND MEDIAN SERUM TOTAL THYROXINE CONCENTRATION OF SAMPLES SUBMITTED TO A REFERENCE LABORATORY FOR CATS OF DIFFERENT AGES**

76.61 PT	MEAN THYROXINE, μG/DL	MEDIAN THYROXINE, μG/DL	NUMBER OF PATIENTS
0-2	1.93	2.0	414
3-5	2.01	2.1	733
6-8	2.02	2.1	2183
9-11	2.08	2.1	2480
12-14	2.12	2.1	3644
> 14	2.13	2.1	4477
All ages	2.08	2.1	13,931
Total T_4 reference range	0.8-4.7		

Data provided by IDEXX Laboratories, Inc.; From Scott-Moncrieff JC: Thyroid disorders in the geriatric veterinary patient, *Vet Clin North Am Small Anim Pract* 42(4):707-725, 2012. Patients with an age listed as 0 were excluded. Samples from cats in which the thyroxine (T_4) concentration was greater than 4.7 μg/dL were excluded from the analysis.

APPROACH TO CATS WITH SUSPECTED HYPERTHYROIDISM THAT HAVE A THYROXINE CONCENTRATION WITHIN THE REFERENCE RANGE

If hyperthyroidism is suspected in a cat based on the history and physical examination, but the total T_4 concentration is within the upper half of the reference range, it is possible that the cat either has mild disease in which the total T_4 is fluctuating in and out of the reference range, or that the cat has hyperthyroidism and concurrent nonthyroidal illness (Fig. 4-13). The clinical approach to diagnosis depends upon the severity of clinical signs. If the signs are mild and early hyperthyroidism is considered likely, the most appropriate approach is to repeat the total T_4 at later date. Because thyroid hormone concentrations vary more over a period of days than over a period of several hours, repeat measurement of the serum T_4 concentration should be performed days to weeks after the initial result was obtained (Peterson et al, 1987). This also allows for disease progression such that there is less likely to be fluctuation into the reference range. If the cat has more severe clinical signs and it is therefore important that a diagnosis be made in a more timely fashion, further diagnostic testing such as measurement of serum fT_4 concentration, a T_3 suppression test, or thyroid scintigraphy should be considered. TRH stimulation tests have also been recommended in this situation; however, they are rarely performed because they are expensive and do not perform well in the presence of concurrent nonthyroidal illness (Tomsa et al, 2001). Administration of TRH also causes adverse clinical signs in cats. If concurrent NTIS is diagnosed and the disease is amenable to treatment, the most appropriate course of action is to reassess thyroid function after resolution of any nonthyroidal illness if immediate treatment of hyperthyroidism is not required.

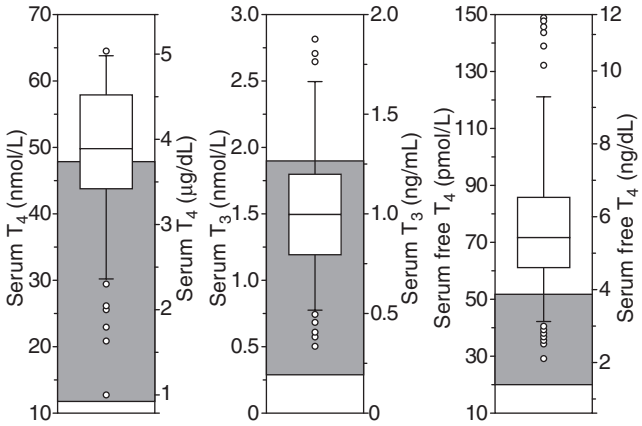

FIGURE 4-13 Box plots of serum total thyroxine (T_4), triiodothyronine (T_3), and free T_4 (fT_4) concentrations in 205 cats with mild hyperthyroidism (defined as total T_4 concentration less than 66 nmol/L; see Fig. 4-10 for key.) (From Peterson ME, et al.: Measurement of serum concentrations of free thyroxine, total thyroxine, and total triiodothyronine in cats with hyperthyroidism and cats with nonthyroidal disease, *J Am Vet Med Assoc* 218[4]:529-536, 2001.)

Basal Total Serum Triiodothyronine Concentrations

T_3 is the most biologically active thyroid hormone; however, the primary hormone secreted from the canine and feline thyroid gland is T_4, which is metabolized to T_3. Studies suggest that as many as 25% to 33% of cats with confirmed hyperthyroidism have serum T_3 concentrations within the reference range (Broussard et al, 1995; Peterson et al, 2001; Fig. 4-14). For this reason routine measurement of T_3 concentration for diagnosis of feline hyperthyroidism is not recommended and is rarely performed. A small percentage (< 5%) of human patients with hyperthyroidism have a normal total and fT_4 but an increased T_3 concentration (so-called *T_3 thyrotoxicosis*; Ladenson 2013). This syndrome has not been reported in cats, although as noted earlier T_4 thyrotoxicosis (high total T_4 and normal T_3) is relatively common in cats (Peterson et al, 2001).

Basal Free Thyroxine Concentration

The total T_4 concentration includes both the protein-bound fraction (more than 99% of the total) and the free, unbound fraction of thyroid hormone (< 1% of the total). Only the free fraction of thyroid hormone is available for entry into cells and is biologically active. Measured serum thyroid hormone concentrations can be altered by many illnesses that do not directly affect the thyroid gland (NTIS; see Effect of Nonthyroidal Illness on Serum Total Thyroxine Concentrations and also Chapter 3). Total T_4 concentrations can also be affected by alterations in metabolism, hormone binding to plasma carrier proteins, transport into cells, and intracellular binding. For these reasons, measurement of serum free thyroid hormone concentrations (fT_4) should provide a more consistent assessment of thyroid gland function than measurement of the total thyroid hormone concentration.

Although the gold standard technique for measurement of fT_4 is equilibrium dialysis, this technique is expensive and time consuming and is usually only performed in research laboratories. In commercial laboratories feline serum fT_4 is measured by one of three methods: modified equilibrium dialysis (MED), analog radioimmunoassay (RIA), or analog chemiluminescent assay. In MED assays, a short dialysis step is used to separate free from protein-bound T_4 followed by radioimmunoassay for fT_4. MED techniques have been regarded as the gold standard technique for determining serum fT_4 concentrations in cats. In one study, the sensitivity and specificity of fT_4 concentration for diagnosis of hyperthyroidism in cats measured using the MED technique was 98.5% and 93%, respectively (Peterson et al, 2001; Fig. 4-15). It is important to note that in this study, although the sensitivity of fT_4 measurement was higher than measurement of total T_4, specificity was lower, because some euthyroid cats with nonthyroidal illness had a fT_4 that was above the reference range. Other studies have confirmed that approximately 6% to 12% of euthyroid cats with nonthyroidal illness may have fT_4 concentrations above the reference range using the MED assay. Other commercial assays have now been validated for measurement of fT_4 in cats (Table 4-9). Although the specificity and sensitivity of the assays vary, overall diagnostic accuracy is remarkably similar and all of the assays listed in the table appear to have acceptable performance for the

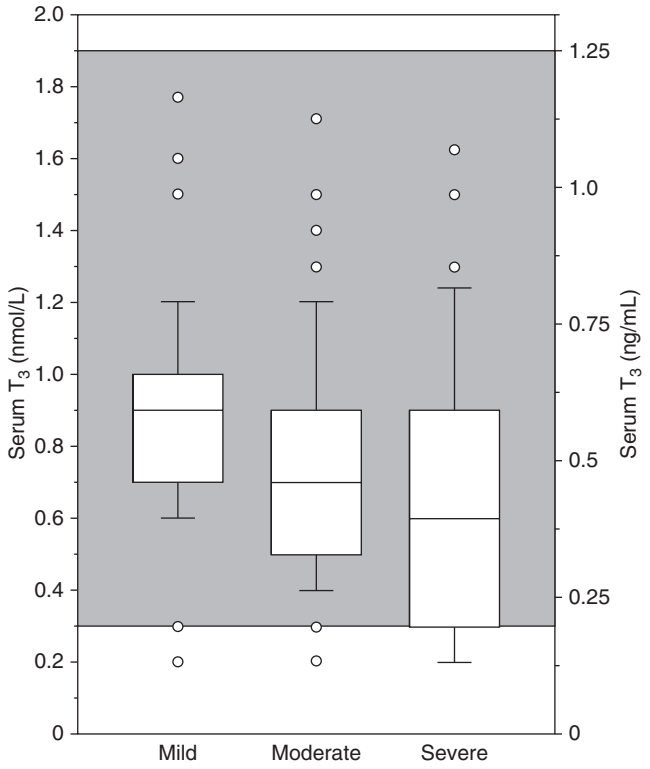

FIGURE 4-14 Box plots of serum T_3 concentrations in 221 cats with nonthyroidal illness grouped according to severity of illness. Of the 221 cats, 65 cats had mild disease, 83 had moderate disease, and 73 had severe disease. (From Peterson ME, et al.: Measurement of serum concentrations of free thyroxine, total thyroxine, and total triiodothyronine in cats with hyperthyroidism and cats with nonthyroidal disease, *J Am Vet Med Assoc* 218[4]:529-536, 2001.)

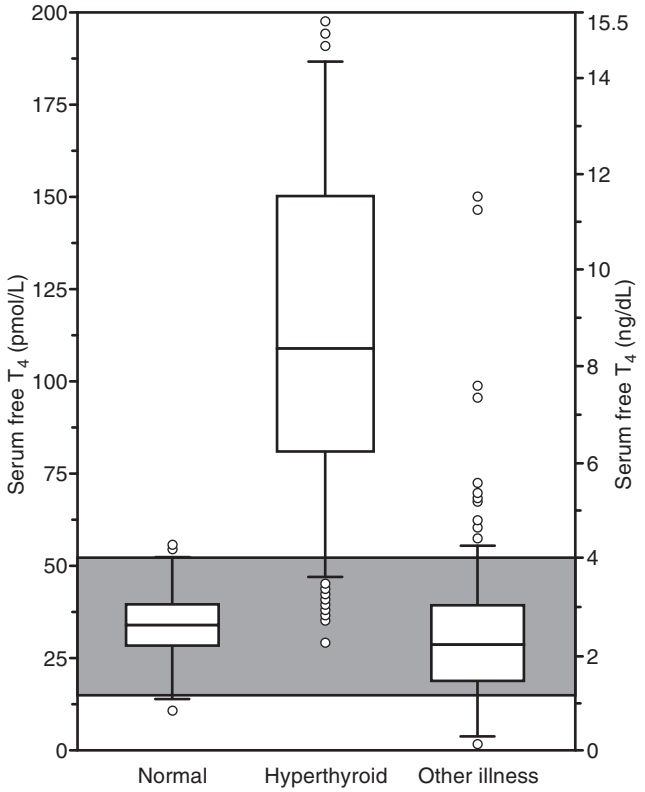

FIGURE 4-15 Box plots of serum free T_4 (fT_4) concentrations in 172 clinically normal cats, 917 cats with untreated hyperthyroidism, and 221 cats with nonthyroidal disease (see Fig. 4-10 for key). (From Peterson ME, et al.: Measurement of serum concentrations of free thyroxine, total thyroxine, and total triiodothyronine in cats with hyperthyroidism and cats with nonthyroidal disease, *J Am Vet Med Assoc* 218[4]:529-536, 2001.)

TABLE 4-9 **PERFORMANCE OF FREE THYROXINE ASSAY IN DIAGNOSIS OF FELINE HYPERTHYROIDISM**

ASSAY	SENSITIVITY (%)	SPECIFICITY (%)	ACCURACY (%)
Analog free T_4 (fT_4)	87	100	89
MED IVD	87	100	89
MED AN	92	67	89
Two step Diasorin	89	100	91

From Peterson ME, et al.: Accuracy of serum free thyroxine concentrations determined by a new veterinary chemiluminescent immunoassay in euthyroid and hyperthyroid cats [abstract]. Proceedings of the 21st ECVIM-CA Congress. Seville (Spain), September 8-10, 2011.

Sensitivity, sensitivity, and accuracy of four assays for fT_4 in cats. The cat population included 53 clinically healthy cats and 45 cats with clinical signs of hyperthyroidism (6 euthyroid, 39 hyperthyroid). Assays included the Immulite 2000 Veterinary fT_4 (analog fT_4), Direct fT_4 by dialysis (IVD technologies; MED IVD), fT_4 by equilibrium dialysis (Antech Diagnostics; MED AN), and the Gammacoat fT_4 (two step) Radioimmunoassay (Diasorin).

diagnosis of hyperthyroidism in cats (Peterson et al, 2011). It should be noted however that none of the assays evaluated in this study, including the MED assays, had as good sensitivity as was originally reported in the first study evaluating performance of the MED assay by Peterson and colleagues in 2001. Because of the problem of specificity of the fT_4 measurement, an increased fT_4 concentration must never be used alone for diagnosis of feline hyperthyroidism; rather it should be interpreted in conjunction with the history, physical examination, and total T_4 concentration. Measurement of fT_4 concentration is most useful for evaluation of cats with suspected hyperthyroidism that have a total T_4 concentration in the upper half of the normal reference range. In cats with a high fT_4 and a low normal or low total T_4 concentration, other diagnostic testing (e.g., scintigraphy) should be utilized for confirmation of the diagnosis if hyperthyroidism is suspected clinically.

Baseline Serum Thyrotropin Concentration

TSH is a highly glycosylated glycoprotein hormone that has an alpha and beta subunit. The alpha subunit is identical to that of the alpha subunit of the related glycoprotein hormones luteinizing hormone (LH), follicle-stimulating hormone (FSH), and chorionic gonadotrophin, whereas the beta chain is unique and confers the unique biologic properties of TSH. Human TSH assays cannot be used to measure TSH in other species. The first assay for canine TSH was validated in 1996, and since that time there have been a number of commercial assays developed. A canine TSH assay (Immulite canine TSH assay, DPC) has been validated for use in cats (Wakeling et al, 2008; 2011). Although the sensitivity of the assay is suboptimal, a high TSH concentration in a cat with a low total T_4 concentration is highly specific for a diagnosis of hypothyroidism. Because of the extremely poor sensitivity of this TSH assay in cats, measurement of TSH has a limited role in diagnosis of feline hyperthyroidism; however in one study of 104 geriatric cats evaluated for a routine health evaluation, cats with an undetectable TSH at baseline were significantly more likely to be diagnosed with hyperthyroidism in the follow-up time period of up to 54 months (Wakeling et al, 2011). It should be noted however that not all cats with an undetectable TSH became hyperthyroid during the study period.

Triiodothyronine Suppression Test

Traditionally, humans suspected of having hormonal deficiencies are tested with provocative (stimulation) tests, and those suspected of having hormonal excesses are tested with suppression tests. Administration of thyroid hormone to an individual with a normal pituitary-thyroid axis should suppress pituitary TSH secretion and in turn suppress endogenous thyroid hormone secretion. Administration of T_3 to normal cats should suppress pituitary TSH secretion, causing a subsequent decrease in the serum T_4 concentration. Measurement of serum T_4 is a valid marker of thyroid gland function, because exogenous T_3 cannot be converted to T_4.

Cats with hyperthyroidism have autonomous secretion of thyroid hormone (i.e., hormone secretion is independent of pituitary control). Thus administration of T_3 to hyperthyroid cats has no effect on the serum T_4 concentration, because pituitary TSH secretion has already been chronically suppressed and T_3 administration has no further suppressive effect. The T_3 suppression test should therefore allow discrimination between cats with a normal pituitary-thyroid axis from those with autonomous thyroid secretion resulting in hyperthyroidism. The protocol for T_3 suppression testing in cats involves measurement of serum T_3 and T_4 concentration and takes advantage of the relatively short (6 to 8 hours) serum half-life of T_3 in cats (Broome et al, 1987; Hays et al, 1988; Peterson et al, 1990a; Refsal et al, 1991).

Protocol

Initially, serum is obtained for determination of both serum T_3 and T_4 concentrations. Owners are then instructed to administer T_3 (liothyronine [Cytomel]; King Pharmaceuticals) beginning the next morning at a dosage of 25 µg given orally three times daily for 2 days. On the morning of day 3, a seventh 25 µg dose should be administered and the cat returned to the hospital so that a second blood sample can be obtained. This blood sample, for measurement of both serum T_3 and T_4 concentrations, should be obtained 2 to 4 hours after administration of the seventh dose of liothyronine (Peterson et al, 1990a; Table 4-10). The pretreatment and posttreatment serum samples should be submitted to the laboratory together to eliminate any concern about a possible effect of interassay variation on the results.

Change in Serum Thyroxine

Normal cats demonstrate a marked reduction in the serum T_4 concentration after seven doses of synthetic T_3. Cats with hyperthyroidism, however, demonstrate minimal or no decrease in serum T_4 concentrations (Fig. 4-16). This is true even for cats with mild hyperthyroidism and high-normal or marginally increased resting T_4 concentrations. Normal cats consistently have post-pill serum T_4 concentrations of less than 1.5 µg/dL (20 nmol/l). Hyperthyroid cats have post-pill T_4 concentrations greater than 1.5 µg/dL. Values close to the cut-off of 1.5 µg/dL should be considered nondiagnostic. The percentage of decrease in the serum T_4 concentration is not as reliable a criterion as the absolute value, although suppression of greater than 50% below the baseline value was observed only in euthyroid

TABLE 4-10 **COMMONLY USED PROTOCOLS FOR DYNAMIC THYROID FUNCTION TESTS IN CATS***

	TRIIODOTHYRONINE SUPPRESSION	THYROID-STIMULATING HORMONE STIMULATION	THYROTROPIN-RELEASING HORMONE STIMULATION
Drug	Liothyronine (Cytomel)	Human recombinant TSH	TRH
Dose	25 µg every 8 hours × 7 doses	0.025 to 0.2 mg	0.1 mg/kg
Route	Oral	IV	IV
Sampling times	Before and 2 to 4 hours after last dose	0 and 6 to 8 hours	0 and 4 hours
Assays	Total T_3 and T_4	Total T_4	Total T_4
Interpretation			
a) Euthyroid	< 1.5 µg/dL (20 nmol/L) with > 50% suppression	> 100%	> 60%
b) Hyperthyroid	> 1.5 µg/dL (20 nmol/L) ± < 50% suppression	Minimal or no increase from baseline	< 50%
Reference	Peterson et al, 1990a	Mooney et al, 1996b	Peterson et al, 1994

IV, Intravenous; *T_3,* triiodothyronine; *T_4,* thyroxine; *TRH,* thyrotropin-releasing hormone; *TSH,* thyroid-stimulating hormone.
*Values quoted are guidelines only. Each laboratory should furnish its own reference ranges.

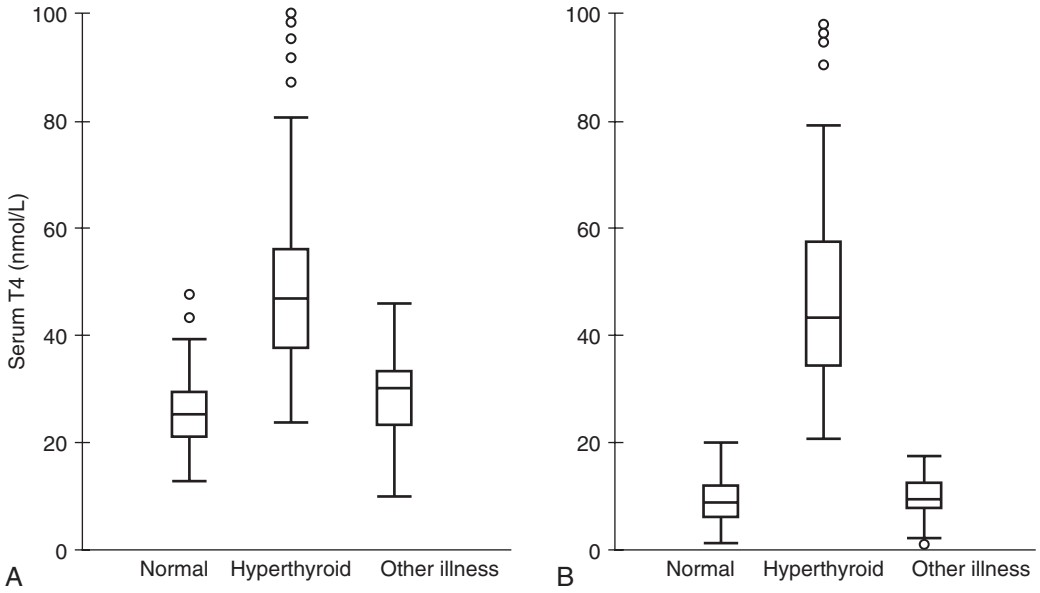

FIGURE 4-16 Box plots of the serum thyroxine (T_4) concentrations before **(A)** and after **(B)** administration of liothyronine to 44 clinically normal cats, 77 cats with hyperthyroidism, and 22 cats with nonthyroidal disease. Data plotted as described in Fig. 4-10. (From Peterson ME, et al.: Triiodothyronine [T_3] suppression test: an aid in the diagnosis of mild hyperthyroidism in cats, *J Vet Intern Med* 4[5]:233-238, 1990.)

cats (Peterson et al, 1990a; Refsal et al, 1991). As for any endocrine test, it is important for laboratory to establish laboratory specific reference ranges.

Change in Serum Triiodothyronine

Assay results for the serum T_3 concentration are not used to evaluate the status of the pituitary-thyroid axis. Rather, serum T_3 results are used to determine whether the owner successfully administered the T_3. The serum T_3 concentration should increase in all cats that are successfully medicated, regardless of the status of thyroid gland function (Fig. 4-17). If the serum T_4 concentration fails to decline in a cat that does not demonstrate an increase in the serum T_3 concentration, problems with owner compliance could explain these results, and the test results should not be trusted.

The T_3 suppression test is particularly useful in distinguishing euthyroid from mildly hyperthyroid cats with borderline resting serum T_4 concentrations. The disadvantages of the test are the 3 days required to complete the regimen and the need to rely on owners to administer the drug seven times (Peterson et al, 1990a; Refsal et al, 1991).

Thyroid-Stimulating Hormone Response Test

The TSH response test is the gold standard for diagnosis of canine hypothyroidism and may have value for evaluating cats suspected of having hypothyroidism (see Chapter 3). The TSH stimulation test has also been evaluated for diagnosis of hyperthyroidism in cats (see Table 4-10). The test involves obtaining serum for determination of the T_4 level before and after TSH administration. The most recently reported protocol evaluated in healthy cats used intravenous (IV) administration of 0.025 to 0.2 mg recombinant human thyrotropin (rhTSH) with total T_4 concentration measured prior to injection and 6 to 8 hours later (Stegeman et al, 2003).

Interpretation

Euthyroid cats have greater responsiveness to TSH than hyperthyroid cats; however, hyperthyroid cats with a normal or

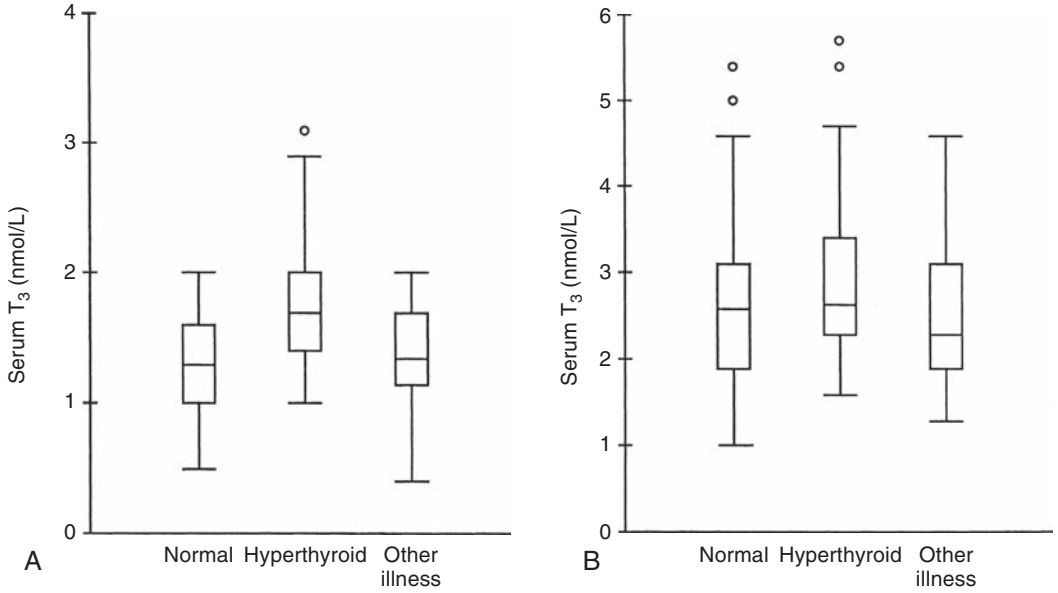

FIGURE 4-17 Box plots of the serum triiodothyronine (T_3) concentrations before **(A)** and after **(B)** administration of liothyronine to 44 clinically normal cats, 77 cats with hyperthyroidism, and 22 cats with nonthyroidal disease. Data plotted as described in Fig. 4-10. (From Peterson ME, et al.: Triiodothyronine [T_3] suppression test: an aid in the diagnosis of mild hyperthyroidism in cats, *J Vet Intern Med* 4[5]:233-238, 1990.)

borderline T_4 concentration are indistinguishable from euthyroid cats. Therefore the TSH stimulation test is not recommended for diagnosing feline hyperthyroidism (Mooney et al, 1996b).

Thyrotropin-Releasing Hormone Stimulation Test

Protocol

In cats, the TRH stimulation test (see Table 4-10) is performed by evaluating changes in the serum T_4 concentration in response to TRH (Peterson et al, 1994). Blood is collected for serum T_4 determination before and 4 hours after IV administration of TRH at a dosage of 0.1 mg/kg body weight. Adverse reactions (e.g., salivation, vomiting, tachypnea, defecation) are common with IV administration of TRH. Side effects usually begin immediately after TRH administration and may continue as long as 4 hours. Side effects are reported to be the result of activating central cholinergic and catecholaminergic mechanisms and direct neurotransmitter effects of TRH on specific binding sites (Holtman et al, 1986; Beleslin et al, 1987a; 1987b).

Interpretation

Healthy cats and those with nonthyroidal illness usually have a twofold increase in the serum T_4 concentration 4 hours after IV administration of TRH. Cats with mild hyperthyroidism have little or no increase in the serum T_4 concentration (see Fig. 4-18; Fig. 4-19). Serum T_3 assessments have been less consistent and are not recommended. A percentage increase in the post-TRH serum T_4 concentration of less than 50% above basal values was also consistent with the diagnosis of hyperthyroidism. Post-TRH T_4 values greater than 60% above basal concentrations were observed only in normal cats and in those with nonthyroidal illness. Increases of 50% to 60% should be considered nondiagnostic (Peterson et al, 1994; Tomsa et al, 2001).

The TRH stimulation test has been reported to be as reliable as the T_3 suppression test for diagnosis of hyperthyroidism in cats and has the advantage of being less time-consuming and less dependent on owner compliance (Sparkes et al, 1991; Peterson and Becker, 1995). However, in the most recent study investigating this test, the TRH stimulation test did not reliably distinguish between sick euthyroid and sick hyperthyroid cats (Tomsa et al, 2001). Because this is the population of cats that is most likely to need additional testing beyond measurement of the total T_4 and the fT_4, the TSH stimulation test currently has little place in diagnostic evaluation for hyperthyroidism.

Summary of Diagnostic Testing for Hyperthyroidism

The clinician should gain a suspicion of hyperthyroidism based on careful review of the history and physical examination findings. Careful palpation of the cat's neck, especially in the area of the thoracic inlet, is very important. Most cats with hyperthyroidism have a palpable thyroid mass. If a thyroid mass is not palpable, the clinician should consider that the abnormal thyroid tissue might be in the mediastinum, but other possible causes of the clinical signs observed by the owners should be considered (see Table 4-7).

The diagnosis of hyperthyroidism can usually be confirmed by evaluating a single, random, serum total T_4 concentration (Fig. 4-20). If a cat that appears to be hyperthyroid does not have a diagnostic baseline serum total T_4 concentration and no other cause for the clinical signs is identified, the test should be repeated days to weeks later, together with a serum fT_4 concentration. If the serum T_4 concentrations (total and free) fail to confirm hyperthyroidism at the time of the second evaluation, the T_3 suppression test or a radionuclide imaging (scintigraphy) should be considered. Trial therapy with methimazole as a means to confirm the diagnosis is not recommended.

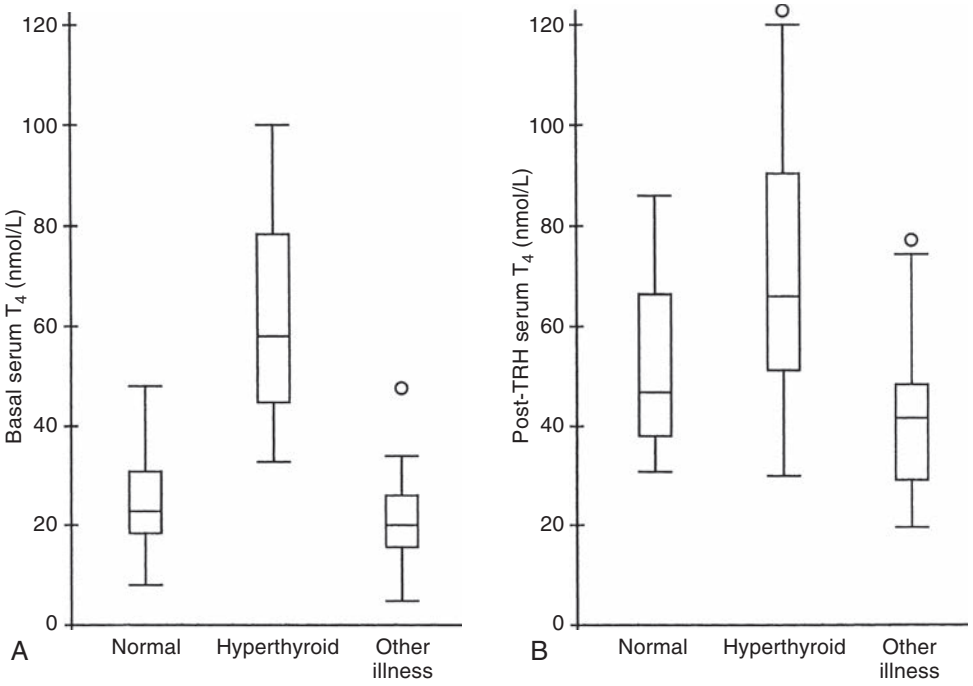

FIGURE 4-18 Box plots of the serum thyroxine (T_4) concentrations before **(A)** and after **(B)** thyrotropin-releasing hormone (TRH) stimulation in 31 clinically normal cats, 35 cats with hyperthyroidism, and 15 cats with nonthyroidal illness. Data plotted as described in Fig. 4-10. (From Peterson ME, et al.: Use of the thyrotropin releasing hormone stimulation test to diagnose mild hyperthyroidism in cats, *J Vet Intern Med* 8[4]:279-286, 1994.)

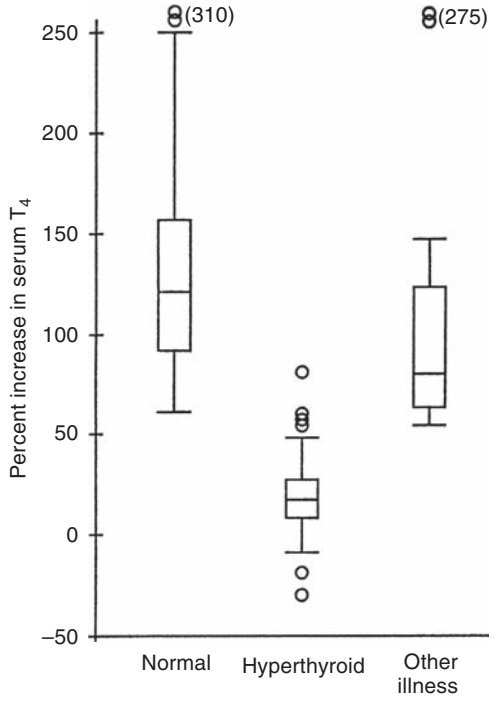

FIGURE 4-19 Box plots of the relative change in serum thyroxine (T_4) concentrations after thyrotropin-releasing hormone (TRH) administration (percent increase) in 31 clinically normal cats, 35 cats with hyperthyroidism, and 15 cats with nonthyroidal disease. Data plotted as described in Fig. 4-10. (From Peterson ME, et al.: Use of the thyrotropin releasing hormone stimulation test to diagnose mild hyperthyroidism in cats, *J Vet Intern Med* 8[4]:279-286, 1994.)

RADIONUCLIDE IMAGING: THYROID SCINTIGRAPHY

Thyroid scintigraphy provides both anatomic and functional information about the thyroid gland. Scintigraphy is useful for determining the functional status of the thyroid gland, establishing whether thyroid disease is unilateral or bilateral, identifying ectopic tissue or metastatic thyroid tissue and may give insight into differentiation of malignant from benign thyroid disease. Thyroid scintigraphy can also be used to determine the dose of radioactive iodine for treatment of a hyperthyroid cat (see Dose Determination). Several radionuclides are available for thyroid scintigraphy in cats. The iodine isotopes (iodine-131 [^{131}I] and iodine-123 [^{123}I]) are both trapped and concentrated within thyroid follicular cells in a similar manner to stable iodine and are incorporated into the tyrosine groups of thyroglobulin and then into T_3 and T_4. Radioactive technetium-99m pertechnetate ($^{99m}TcO_4$) is referred to as a *pseudohalogen* because it mimics the biologic behavior of iodine and chloride. It is therefore trapped and concentrated within thyroid follicular cells, although it is not incorporated into thyroid hormone and therefore is not retained in the thyroid gland. Some other epithelial structures (salivary glands, gastric mucosa) also concentrate iodine and pertechnetate without organic binding or storage within the tissue (Nap et al, 1994). Both iodine and pertechnetate are primarily excreted in the urine, so the bladder is also visible on whole body scintigraphy.

Choice of Radionuclide

All three radionuclides (^{131}I, ^{123}I, and pertechnetate) provide excellent thyroid images, but pertechnetate, for several reasons, is the most commonly used radionuclide for thyroid scintigraphy (Table 4-11). ^{131}I is inexpensive and readily available, but it has a long physical half-life (8 days) and emits a high-energy γ-photon (364 keV) that is inefficiently collimated by the camera. ^{131}I also emits beta-particles that are not detected by the camera but that increase total body and thyroid radiation exposure. The increased risk to technicians administering ^{131}I makes this material less suitable for routine use (Beck et al, 1985). In contrast to ^{131}I, ^{123}I has a short physical half-life (13.3 hours), emits low-energy γ-rays (159 keV) that are well

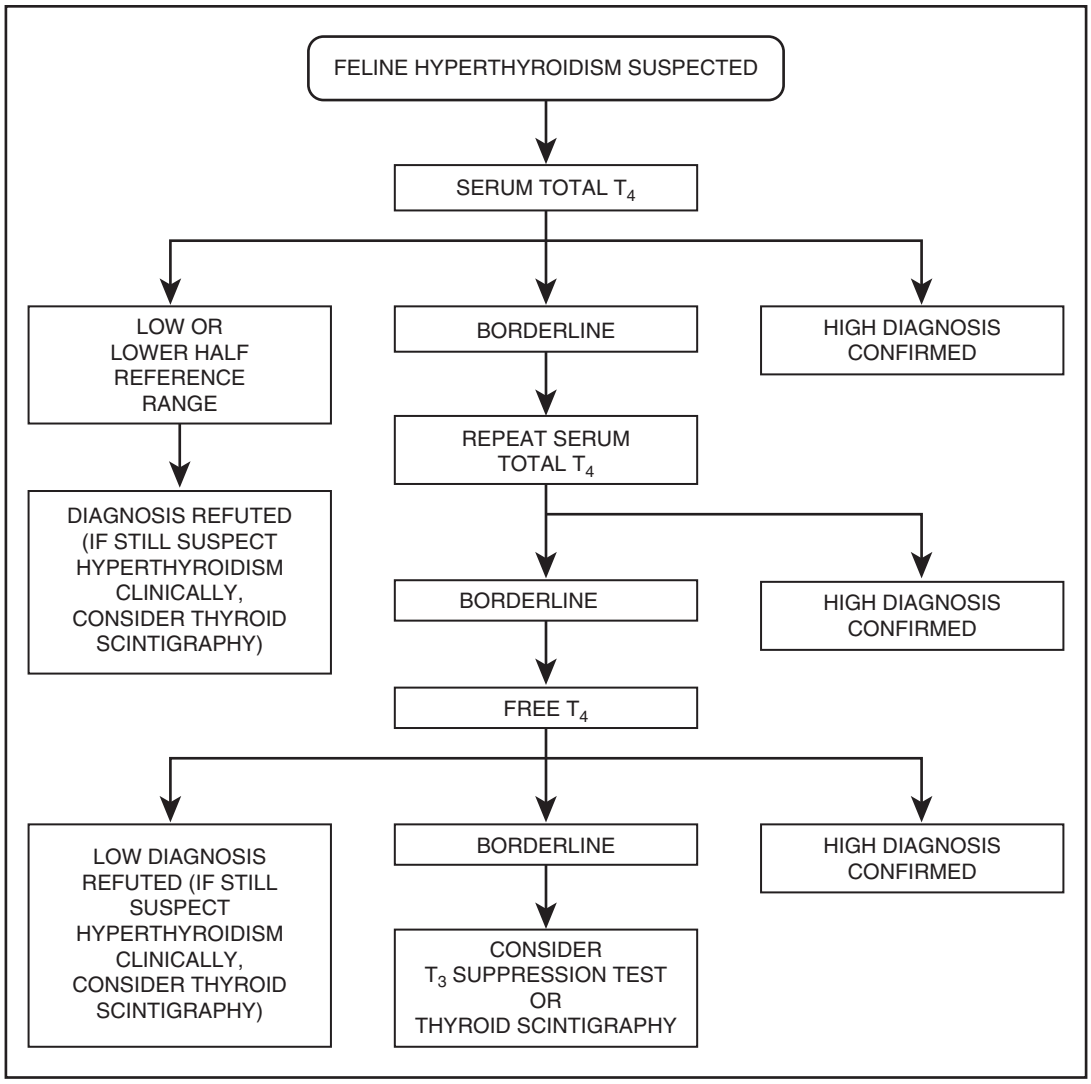

FIGURE 4-20 Algorithm for the diagnosis of hyperthyroidism in cats.

suited for scanning, and has no β-emission. The imaging procedure can begin as soon as 4 hours after administration. For these reasons, ^{123}I is a good agent for thyroid scanning; until recently the high cost of ^{123}I limited its use, but it has recently become more affordable.

Pertechnetate, a widely available and relatively inexpensive radionuclide, is considered by most investigators to be the best choice for routine imaging of thyroid glands in humans and cats (Broome et al, 2006). Pertechnetate has a short physical half-life (6 hours), and imaging procedures can begin as soon as 20 minutes after administration because of its rapid uptake by the thyroid. Pertechnetate emits low-energy γ-particles (140 keV), has no β-emission, and gives the lowest radiation dose to the thyroid of all available scanning agents.

Protocol for Technetium-99m Pertechnetate

Thyroid scanning using pertechnetate is accomplished after IV administration of radiolabeled pertechnetate (37 to 185 MBq [1 to 5 mCi]). One report described successful thyroid scintigraphy in cats after SC administration of the isotope; however, a direct comparison between IV and SC administration was not made (Page et al, 2006). The image is typically acquired 60 minutes after isotope administration; however, good quality scans can be acquired any time from 20 minutes to 2 hours after isotope administration (Broome et al, 2006). At the time of scanning, the cat is placed over a gamma scintillation camera, using a low energy all purpose (LEAP) collimator that interfaces with a dedicated nuclear imaging computer. Ventral, dorsal, and right and left lateral images are acquired of the cervical region and ventral and right and left lateral views of the thorax (after shielding the activity arising from the stomach and thyroid area to increase the count density within the thoracic region). Some protocols also use a pin-hole collimator that acquires a magnified image to acquire a more detailed image of the thyroid gland(s). Although many facilities perform scintigraphy without sedation or anesthesia, sedation is required when using a pinhole collimator, because the effect of patient motion is exacerbated when using a pin-hole collimator. In one of our hospitals all scintigraphy in small animal patients is done under general anesthesia to minimize exposure of personnel to radiation; in other hospitals anesthesia is not used.

Protocol for Iodine-123

Thyroid scanning using ^{123}I is accomplished after oral or IV administration of 200 to 400 μCi ^{123}I. The image is typically acquired 8 and 24 hours after isotope administration (Nieckarz and Daniel, 2001; van Hoek et al, 2008b).

TABLE 4-11 **RADIONUCLIDES USED IN THYROID IMAGING STUDIES**

ISOTOPE	EXPENSE/AVAILABILITY	PRINCIPAL GAMMA ENERGY (KEV)	TIME FROM INJECTION TO SCANNING PROCEDURE	PHYSICAL HALF-LIFE	RISK TO TECHNICIANS
Iodine-131	Inexpensive/available	364	24 hours	8.1 days	Yes
Iodine-123	More expensive/less available	159	8, 24 hours	13.3 hours	Low
$^{99m}TcO_4$ (pertechnetate)	Inexpensive/available	140	20 minutes	6.0 hours	Low

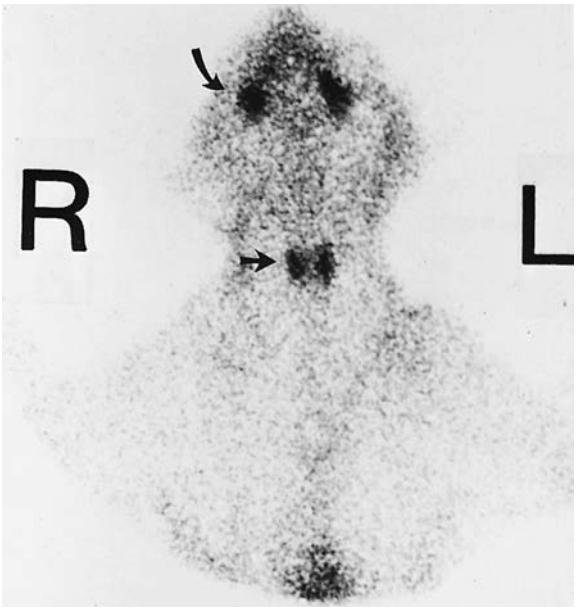

FIGURE 4-21 Thyroid scan (radioactive technetium-99m [^{99m}Tc]) of a normal cat. Note the similar size and density of the thyroid lobes *(straight arrow)* and the salivary glands *(curved arrow).*

Tissue Identified

Scintigraphy identifies all functional thyroid tissue in the body and allows determination of whether the abnormal thyroid tissue is unilateral, bilateral, or ectopic. In a study of 120 hyperthyroid cats, 12% had ectopic thyroid tissue identified on scintigraphy (Harvey et al, 2009). Pertechnetate also concentrates in the gastric mucosa, the salivary glands, and the bladder; the relative uptake of technetium by the thyroid glands and the salivary glands is used to subjectively assess thyroid gland function. A euthyroid cat should have close to a 1:1 ratio of salivary gland to thyroid lobe uptake (Fig. 4-21). In most hyperthyroid cats, the thyroid lobe(s) have much more intense uptake than the salivary glands, and this is usually easily determined by subjective visual inspection of the images (Figs. 4-22 to 4-25) (Broome et al, 2006; Harvey et al, 2009). The relative uptake of the thyroid lobe(s) and the salivary tissue can be also be quantified by drawing regions of interest around the thyroid lobe(s) and the ipsilateral zygomatic/molar salivary gland. The percentage uptake of radioisotope by the thyroid gland, the thyroid-to-salivary (T:S) ratio, and rate of isotope uptake by the thyroid gland are all significantly correlated with the T_4 concentration, indicating that scintigraphy is a good indicator of the metabolic activity of the thyroid gland (Daniel et al, 2002). The best correlation is obtained by using the 20 minute T:S ratio using only the most intense of the thyroid lobes (Daniel et al, 2002). It is important to remember that in certain circumstances other tissues can concentrate pertechnetate. In one study, in addition to concentrating in the tissues previously described, the imaging radionuclides accumulated in bronchogenic carcinomas in two cats (Cook et al, 1993).

Clinical Indications for Scintigraphy

Clinical indications for performing thyroid scintigraphy in cats are shown in Box 4-3.

Determine Whether Thyroid Autonomy Is Unilateral or Bilateral

Approximately 30% of hyperthyroid cats have unilateral hyperthyroidism, whereas in 70% of cats there is autonomous tissue present within both thyroid lobes. In either case, the normal thyroid tissue is atrophic due to lack of stimulation by TSH. In cats with unilateral disease, surgical thyroidectomy is a straightforward and simple procedure, whereas in cats with bilateral disease it may be complicated by postoperative hypothyroidism and/or hypoparathyroidism—so other modes of therapy may be more appropriate. Unfortunately it is not always possible to determine the functional activity of the thyroid glands by palpation or by visual inspection at surgery. In some cases, both glands are grossly enlarged and both are clearly abnormal, but in other cases, a small lobe may contain small numbers of adenomatous cells but be grossly indistinguishable from an atrophic normal thyroid gland. Scintigraphy allows determination of the functional status of both thyroid glands prior to thyroidectomy so that treatment planning can be optimized (see General Concepts in Treatment for more information on treatment choice for hyperthyroid cats). In cats with unilateral disease, only one thyroid lobe is detected on the scan, because there is no uptake of isotope into the contralateral atrophic thyroid gland (see Fig. 4-22). If any isotope uptake is visualized in the contralateral thyroid gland, bilateral disease should be assumed to be present (see Figs. 4-23 to 4-25). It is important to review all the cervical views of the scintigram in order to determine whether the disease is unilateral or bilateral, because particularly on the lateral views, one thyroid gland may overlie the other, leading to the appearance of unilateral disease when actually both thyroid glands are abnormal.

Determine Presence of Mediastinal or Ectopic Thyroid Tissue

In some hyperthyroid cats, an enlarged thyroid lobe may descend into the thoracic cavity where it is not palpable. In addition, additional ectopic thyroid tissue may be present anywhere from the base of the tongue to within the thoracic cavity (Knowles et al, 2010; Reed et al, 2011). A study of 120 hyperthyroid cats undergoing scintigraphy documented that 12% of hyperthyroid cats had more than two areas of increased radionuclide uptake (IRU) with the number of areas of IRU ranging from 1 to 5 (Harvey et al, 2009). Areas of IRU were located in the neck in 61% of cats, the thoracic inlet in in 53% of cats, and the thorax in in 22% of cats. Most of the cats with more than two areas of IRU had IRU

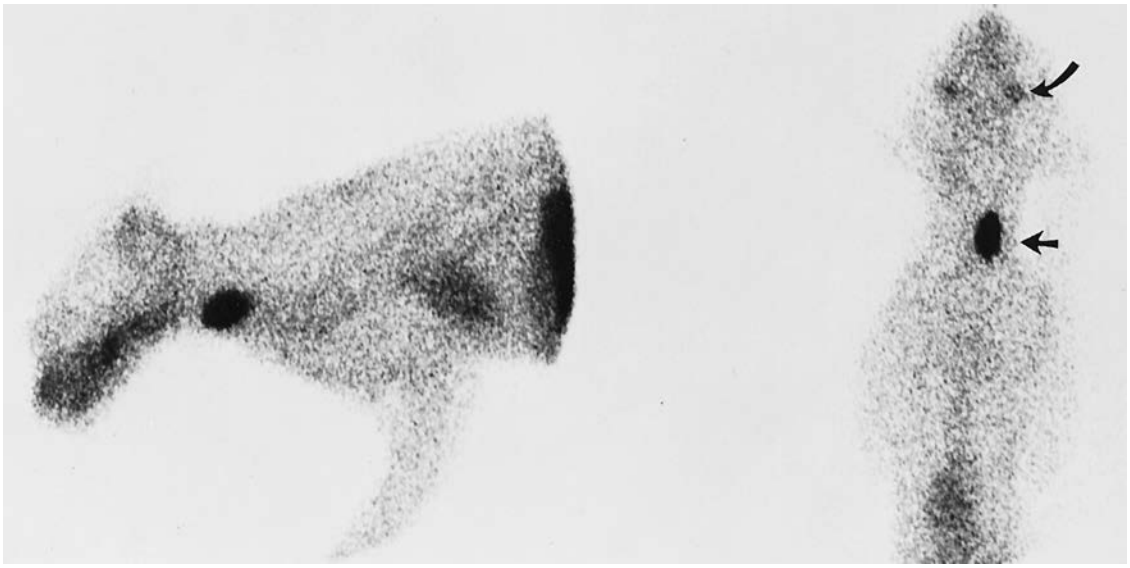

FIGURE 4-22 Thyroid technetium-99m (^{99mm}Tc) scan from a thyrotoxic cat with a unilateral thyroid tumor. Note the density of the thyroid *(straight arrow)* compared with that of the salivary glands *(curved arrow).*

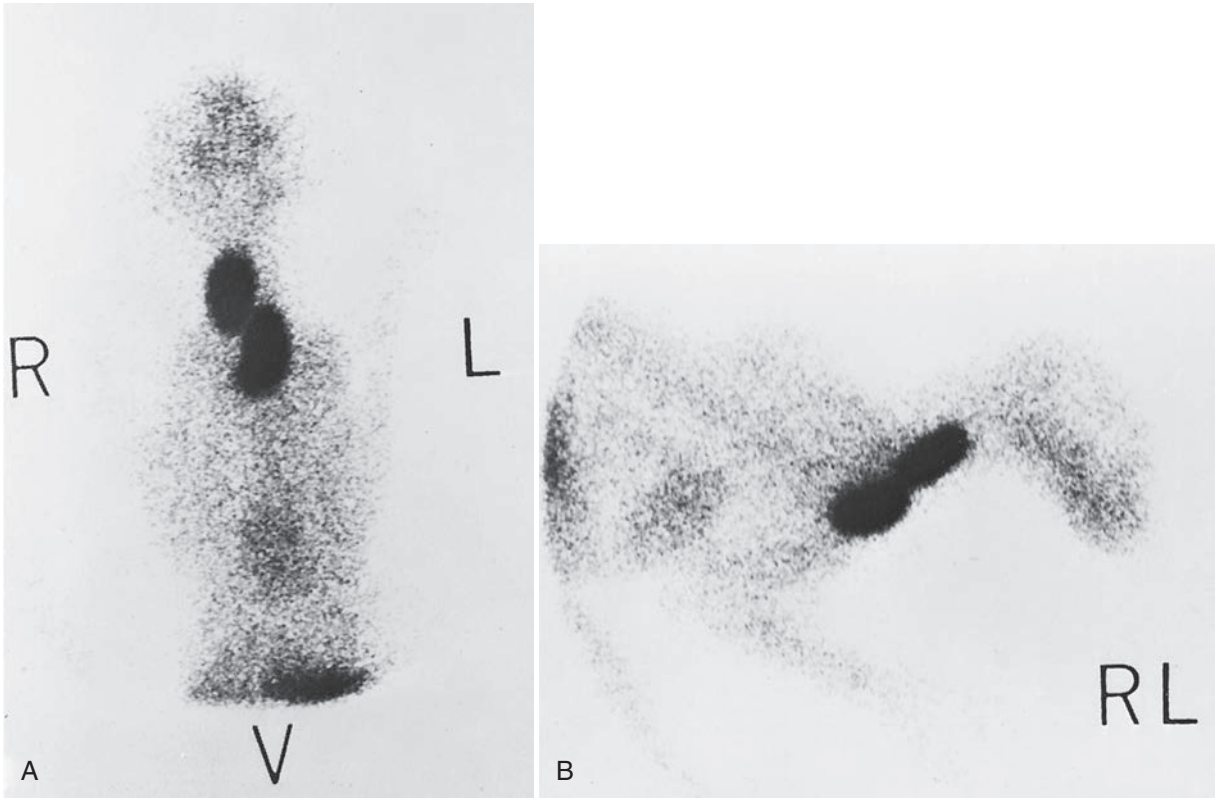

FIGURE 4-23 A and **B,** Thyroid technetium-99m (^{99m}Tc) scan from a thyrotoxic cat with bilaterally symmetric adenomatous hyperfunctional thyroids.

in the thorax. Although thyroid scintigraphy is an excellent diagnostic tool for locating ectopic or intra-thoracic thyroid tissue, it can be difficult to distinguish benign ectopic thyroid tissue from metastasis of thyroid carcinoma by scintigraphy (Figs. 4-26 to 4-29). There are no scintigraphic features that by themselves can distinguish benign from malignant disease (see discussion later), and in some cats with thyroid carcinoma, scintigraphic studies are identical to those of cats with benign disease.

Determine Presence of Functional Thyroid Carcinoma

The incidence of thyroid malignancy in hyperthyroid cats is believed to be approximately 3%, although it may be more common in hyperthyroid cats treated with medical therapy for long periods of time. Thyroid carcinoma should be suspected in hyperthyroid cats with large cervical masses, particularly when the masses are fixed or are attached to underlying or overlying tissues. Thyroid carcinoma should also be considered in cats with

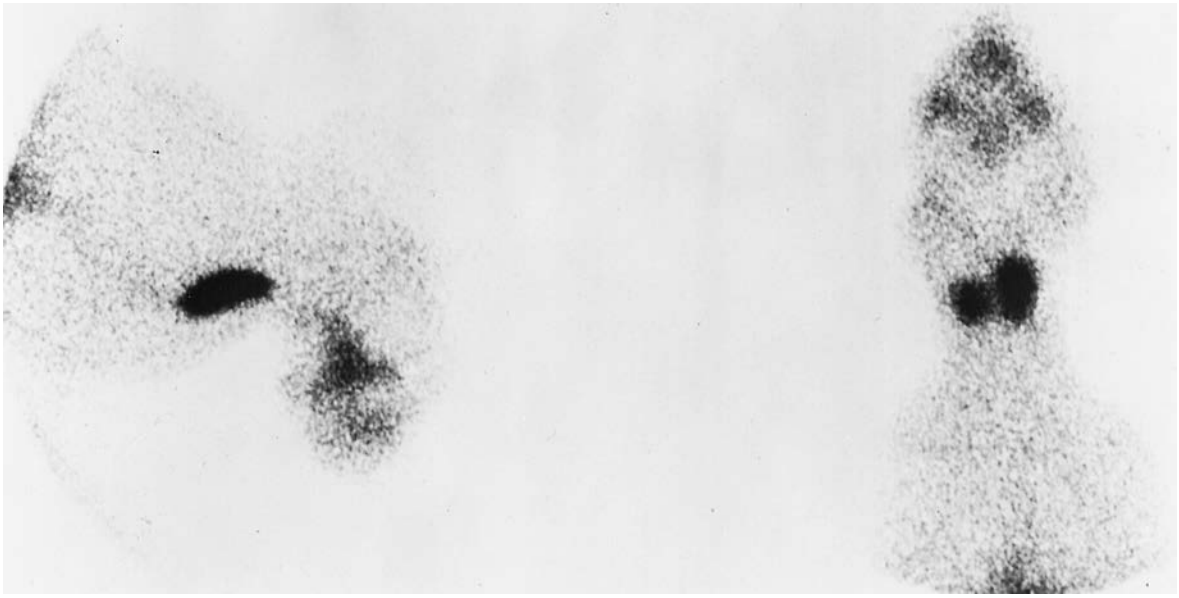

FIGURE 4-24 Thyroid technetium-99m (^{99m}Tc) scan from a thyrotoxic cat with bilaterally asymmetric adenomatous hyperfunctional thyroids. Note that on the lateral view one thyroid lobe overlies the other.

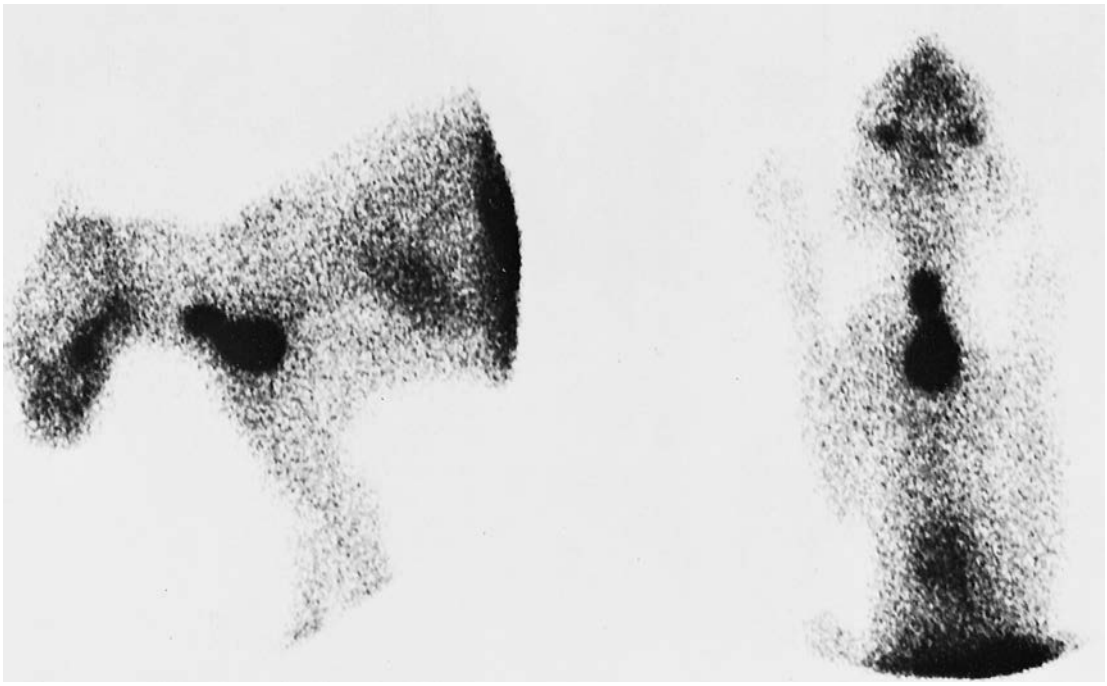

FIGURE 4-25 Thyroid technetium-99m (^{99m}Tc) scan from a thyrotoxic cat with bilaterally asymmetric adenomatous hyperfunctional thyroids. Note that this scan shows the larger thyroid below the smaller rather than the side-by-side location seen in Fig. 4-24.

ectopic tissue or a mediastinal mass on scintigraphy (see Figs. 4-27 to 4-29). Scintigraphic features such as distortion of the thyroid lobe, multiple foci of radionuclide uptake, heterogenous or irregular uptake with spiculated margins, extension caudally into the thoracic inlet, and the presence of linear multifocal patterns suggesting tumor extension along fascial planes, are considered suspicious for carcinoma, but definitive diagnosis requires histopathology (see Feline Thyroid Carcinoma). Some cats with thyroid carcinoma do not display these features, and some cats with benign thyroid disease have multifocal or irregular uptake of isotope (Harvey et al, 2009). Scintigraphy is also very helpful to identify the presence of metastatic disease in cats with known thyroid carcinoma both before and after surgical resection.

Scintigraphy as a Diagnostic Aid in Cats with Nonthyroidal Illness

The thyroid scan may be used as a diagnostic test for cats with clinical signs of hyperthyroidism but normal or borderline serum total T_4 and fT_4 concentrations. Scintigraphy is particularly useful in suspected hyperthyroid cats with concurrent illness in which other tests do not perform well. The thyroid gland to salivary gland ratio in euthyroid cats should normally be 1:1 (see Fig. 4-21), but in hyperthyroid cats the ratio is higher (Broome et al, 2006). In

this setting the thyroid scan has the potential for both diagnosing hyperthyroidism and locating the abnormal tissue.

Scintigraphy as an Aid to Planning Treatment

Scintigraphy can be useful in planning treatment, especially in cases in which thyroidectomy would be an option if the thyroid dysfunction was unilateral (see Treatment with Surgery). Some investigators have used scintigraphy to estimate thyroid mass volume and then utilized this information to determine the dose of radioactive iodine to be administered for treatment (Forrest et al, 1996). Unfortunately this approach has not proved to be reliable in predicting radioactive iodine uptake (RAIU) after treatment, because the biologic half-life of ^{131}I determined by tracer studies does not correlate well with the biologic half-life after administration of therapeutic doses of radioactive iodine. This is probably because of cellular necrosis and resultant changes in thyroid physiology after administration of large doses of ^{131}I.

Drugs That Cause Interference with Scintigraphy

Compounds that interfere with iodine uptake or thyroid hormone synthesis can influence the results of scintigraphy. Methimazole has been documented to increase iodine trapping as measured by technetium and ^{123}I uptake in euthyroid cats (Nieckarz and Daniel, 2001). This effect was documented after 3 weeks of methimazole treatment, and iodine uptake was maximal 4 days after methimazole withdrawal. Uptake of radioisotope returned to baseline by 15 days after methimazole withdrawal. No effect of methimazole on pertechnetate uptake was documented in hyperthyroid cats after 30 days of methimazole treatment (Fischetti et al, 2005), presumably because TSH suppression was not relieved by methimazole treatment; in most of the cats, TSH concentration remained suppressed during methimazole treatment. Two cats with mild hyperthyroidism that had unilateral uptake before methimazole treatment developed bilateral uptake after methimazole treatment. For these reasons, when nuclear scintigraphy is used as a diagnostic tool to confirm hyperthyroidism, it is very important that methimazole treatment should be withdrawn at least 2 weeks prior to scintigraphy. Methimazole should also be discontinued prior to scintigraphy when it is used to identify the location of ectopic tissue, because it may cause errors in distinguishing unilateral from bilateral disease (Fischetti et al, 2005). Iodine and iodinated contrast agents (e.g., iohexol) may decrease uptake of radioiodine into the thyroid gland. Iohexol is often used to determine GFR in hyperthyroid cats prior to treatment with radioactive iodine. Studies suggest that treatment with iohexol within 24 hours of radioactive iodine administration decreases iodine uptake in the thyroid gland, although the effect was relatively small and the clinical outcome did not appear to be affected (Peremans et al, 2008). In a similar study, thyroid scintigraphy was performed in euthyroid cats before and after administration of iohexol (Lee et al, 2010). There was a significant decrease in technetium uptake on days 1, 3, and 14 after iohexol administration; however, uptake did not fall below the published reference ranges for euthyroid cats (Lee et al, 2010). Ideally concurrent administration of iohexol or other iodine containing compounds should be avoided prior to scintigraphy or treatment with ^{131}I. The protocol used

BOX 4-3 Indications for Thyroid Scintigraphy

1. Evaluation of the functional status of the thyroid glands
2. Determination of unilateral or bilateral thyroid lobe involvement
3. Detection and localization of ectopic thyroid tissue
4. Differentiation between benign and malignant thyroid diseases
5. Determination of the origin of a cervical mass
6. Detection of functional metastasis
7. Evaluation of the efficacy of therapy
8. Evaluation for residual tissue after thyroidectomy

From Daniel GB, Neelis DA: Thyroid scintigraphy in veterinary medicine, *Semin Nucl Med* 44(1):24-34, 2014.

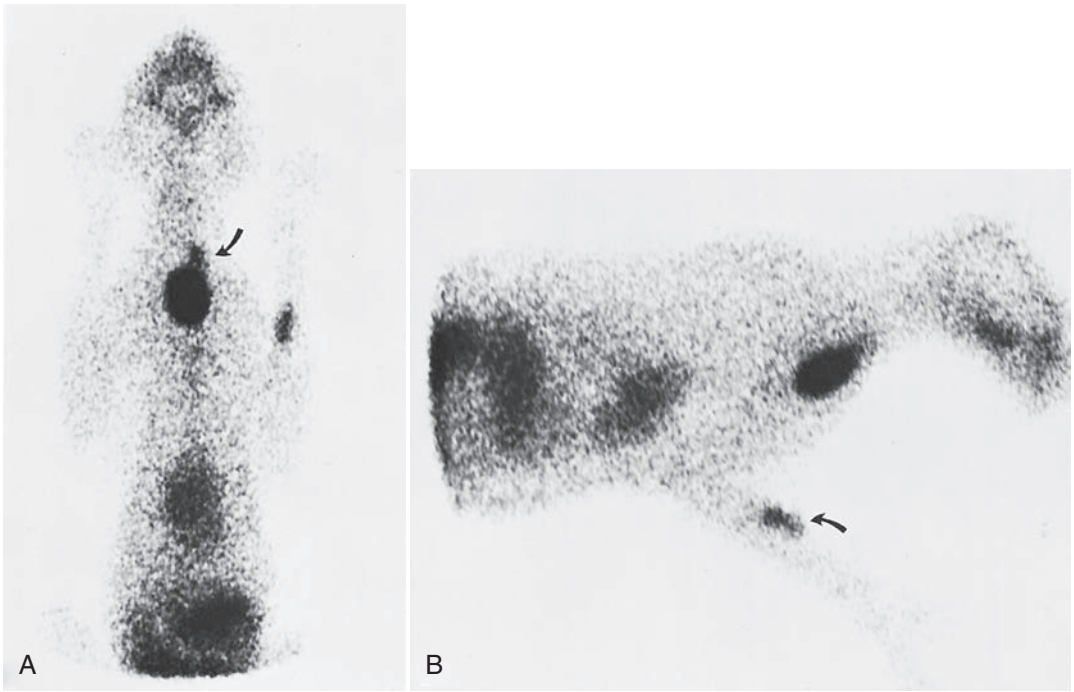

FIGURE 4-26 Dorsoventral **(A)** and lateral **(B)** views of a large intrathoracic anterior mediastinal thyroid mass with a small active gland just cranial to it (*arrow* in **A**). Also note that a small amount of pertechnetate leaked into the subcutaneous (SC) space during administration (*arrow* in **B**).

for sedation or anesthesia can also influence the results of scintigraphy, because drugs used commonly for sedation may increase or decrease salivation and thus influence the T:S ratio (Schaafsma et al, 2006). For example in a study of euthyroid cats, the T:S ratio for technetium was significantly higher at 40 minutes when ketamine-midazolam was used than when propofol or ketamine-midazolam-atropine protocols were used. Unfortunately this study did not include a control group without sedation. Although statistically significant changes were identified between the different sedation protocols, in most cats the T:S ratio was still within or close to the typical range of the normal T:S ratio of 0.8 to 1.2. It is recommended that a consistent protocol for sedation or anesthesia is used when scintigraphy is performed and that each facility develop appropriate reference ranges for T:S ratios for the protocols used.

CERVICAL (THYROID) ULTRASONOGRAPHY/ COMPUTED TOMOGRAPHY

Although scintigraphy is the imaging procedure of choice for evaluation of the feline thyroid gland, cervical ultrasonography can also be used to evaluate feline thyroid glands and estimate thyroid gland volume. Cervical ultrasound usually requires no anesthesia or sedation, although more consistent positioning can be achieved

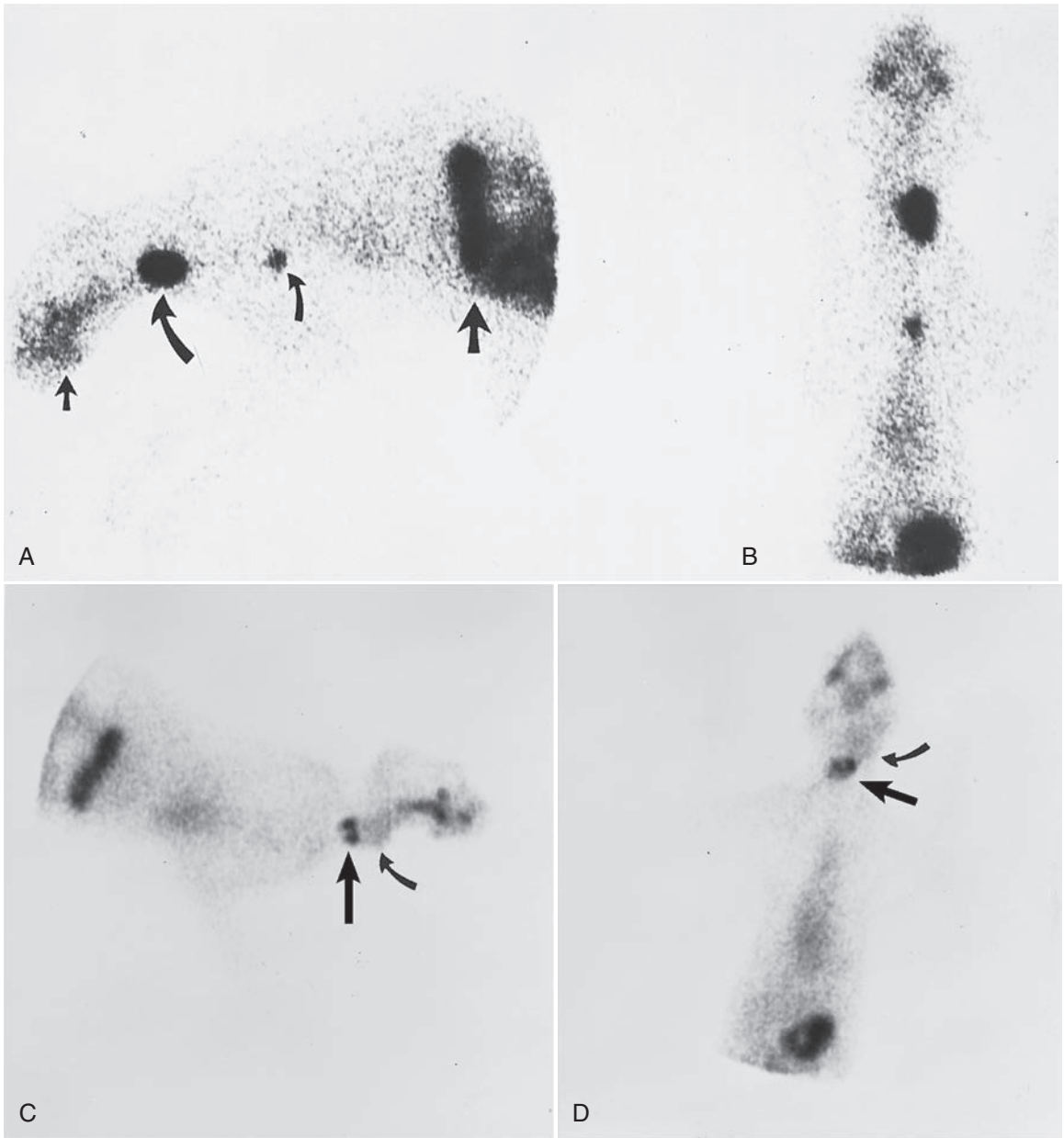

FIGURE 4-27 Lateral **(A)** and dorsoventral **(B)** views of a pertechnetate scan performed on a hyperthyroid cat. Note the large thyroid in the neck (*large curved arrow* on lateral view); the small, adenomatous thyroid tissue in the anterior mediastinum *(small curved arrow);* the salivary glands and the saliva, which concentrates pertechnetate *(small straight arrow);* and the gastric mucosa, which concentrates pertechnetate *(large straight arrow).* In the lateral **(C)** and dorsoventral **(D)** views of the pertechnetate scans from another cat, note the large intracervical mass *(curved arrows)* that does not concentrate pertechnetate displacing the normal thyroid glands *(straight arrows).* This mass was a salivary carcinoma, demonstrating that not all cervical masses are thyroid.

if cats are sedated for the procedure. As with any ultrasound evaluation, the value of cervical studies depends heavily on the skill of the operator.

In a study of six healthy cats and 14 cats with confirmed hyperthyroidism, a significant difference in the mean estimated thyroid volume of hyperthyroid cats compared with healthy cats was identified (Wisner et al, 1994). Although in most cases, there was good correlation between thyroid scintigraphy and ultrasound in regard to identifying unilateral versus bilateral thyroid dysfunction; thyroid lobes that could not be identified ultrasonographically were hyperfunctional on scintigraphy in two cats. Ultrasound cannot replace scintigraphy for locating ectopic or metastatic tissue, but it is considerably more available and less expensive.

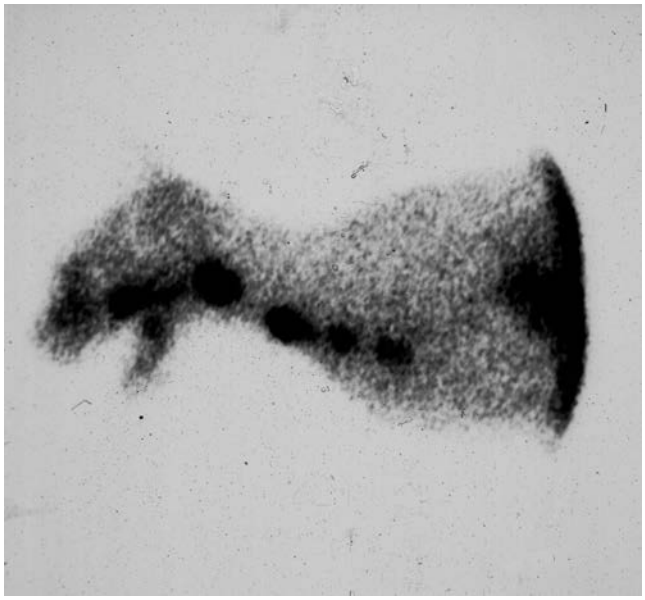

FIGURE 4-28 Lateral view of a thyroid technetium-99m (^{99m}Tc) scan from a thyrotoxic cat with multiple functioning hyperactive thyroid masses within the cervical region. This could be either ectopic adenomatous neoplasia or metastasis of thyroid carcinoma.

Normal thyroid lobes are thin, fusiform-shaped structures that are moderately and uniformly echogenic (Fig. 4-30). The lobes are located adjacent and medial to the common carotid arteries and are surrounded by a thin, hyperechoic fascia. The cranial and caudal ends of each thyroid lobe usually taper within this sheath, which sometimes makes the exact margins difficult to discern. Linear measurements of each lobe are easiest to make in the long axis plane. Normal thyroid lobes are usually 15 to 25 mm long with calculated volumes of 40 to 140 mm^3 (Wisner et al, 1994; Table 4-12). Thyroid lobe parenchyma ranges from low to moderate echogenicity compared with surrounding tissue. Thyroid lobes from hyperthyroid cats are usually uniformly enlarged and are less echogenic than normal thyroid lobes. Some lobes have mildly or moderately lobulated outer margins and/or poor delineation from surrounding tissue. Although most abnormal glands are uniformly echogenic, a mottled echogenicity occasionally is seen. Cystic structures within the thyroid gland can be identified on ultrasound in a significant number of hyperthyroid cats. Cysts vary in shape and structure, some being unicameral and others containing one or several internal septae. It is not unusual for abnormal thyroid lobes to be "normal" in length but obviously rounder and thicker; this accounts for the abnormal volume, which usually ranges from 140 to 1000 mm^3 despite a length similar to that of the thyroid lobes of a healthy cat (see Fig. 4-30 and Table 4-12) (Wisner et al, 1994; Goldstein et al, 2001; Wells et al, 2001; Barberet et al, 2010).

Computed tomography (CT) has also been used to evaluate feline thyroid glands. Although the thyroid glands can be identified on CT and an estimate of thyroid lobe size obtained, CT is not able to reliably distinguish unilateral versus bilateral thyroid gland dysfunction and ectopic tissue cannot be identified (Lautenschlaeger et al, 2013).

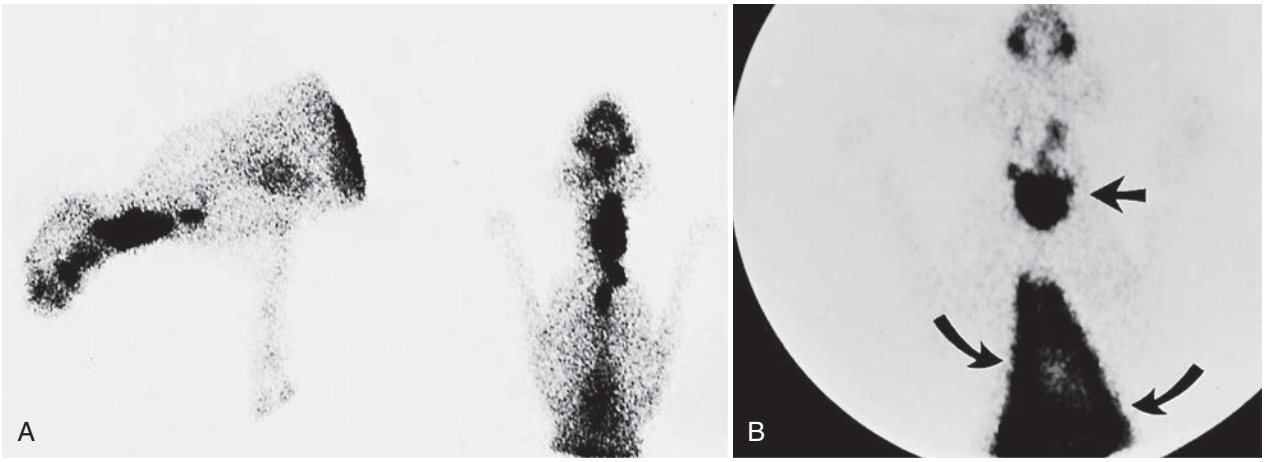

FIGURE 4-29 **A,** Thyroid technetium-99m (^{99m}Tc) scan from a thyrotoxic cat with multiple functioning hyperactive thyroid masses. This may be representative of a cat with a functioning thyroid carcinoma that has undergone massive local invasion throughout the neck and anterior mediastinum. This also could represent multiple adenomatous tissue—some of which is ectopic. **B,** Thyroid ^{99m}Tc scan from a thyrotoxic cat with multiple functioning thyroid masses. This cat had a thyroid carcinoma with massive local invasion throughout the neck *(straight arrow)* and diffuse functional carcinoma throughout the pulmonary parenchyma *(curved arrows).*

Nonfunctional Thyroid Nodules

In older cats, it is not uncommon to palpate an enlarged thyroid gland in an apparently healthy euthyroid cat. Possible differential diagnoses include early hyperthyroidism in which a goiter is present but the thyroid gland is not fully autonomous, thyroid cyst, thyroid cystadenoma, or nonfunctional thyroid adenoma or carcinoma (see Feline Thyroid Carcinoma). Nonfunctional thyroid carcinoma is very rare in the cat. If an obvious cervical nodule is palpated in a cat with a normal T_4 concentration, a fine needle aspirate should be considered to determine the tissue of origin. Unfortunately, thyroid cytology is not accurate for differentiation of benign from malignant thyroid disease.

GENERAL CONCEPTS IN TREATMENT

Background

There are four methods of managing feline hyperthyroidism (Fig. 4-31). Each treatment modality has advantages and disadvantages (Table 4-13). Thyroid hormone synthesis can be inhibited by either anti-thyroid drugs or iodine restricted diets. Neither of these treatment methods results in permanent resolution of hyperthyroidism; however, medical therapy permits trial resolution of hyperthyroidism while the effect of reestablishing the euthyroid state on renal function is assessed. Definitive therapy includes either surgical thyroidectomy or administration of radioactive iodine.

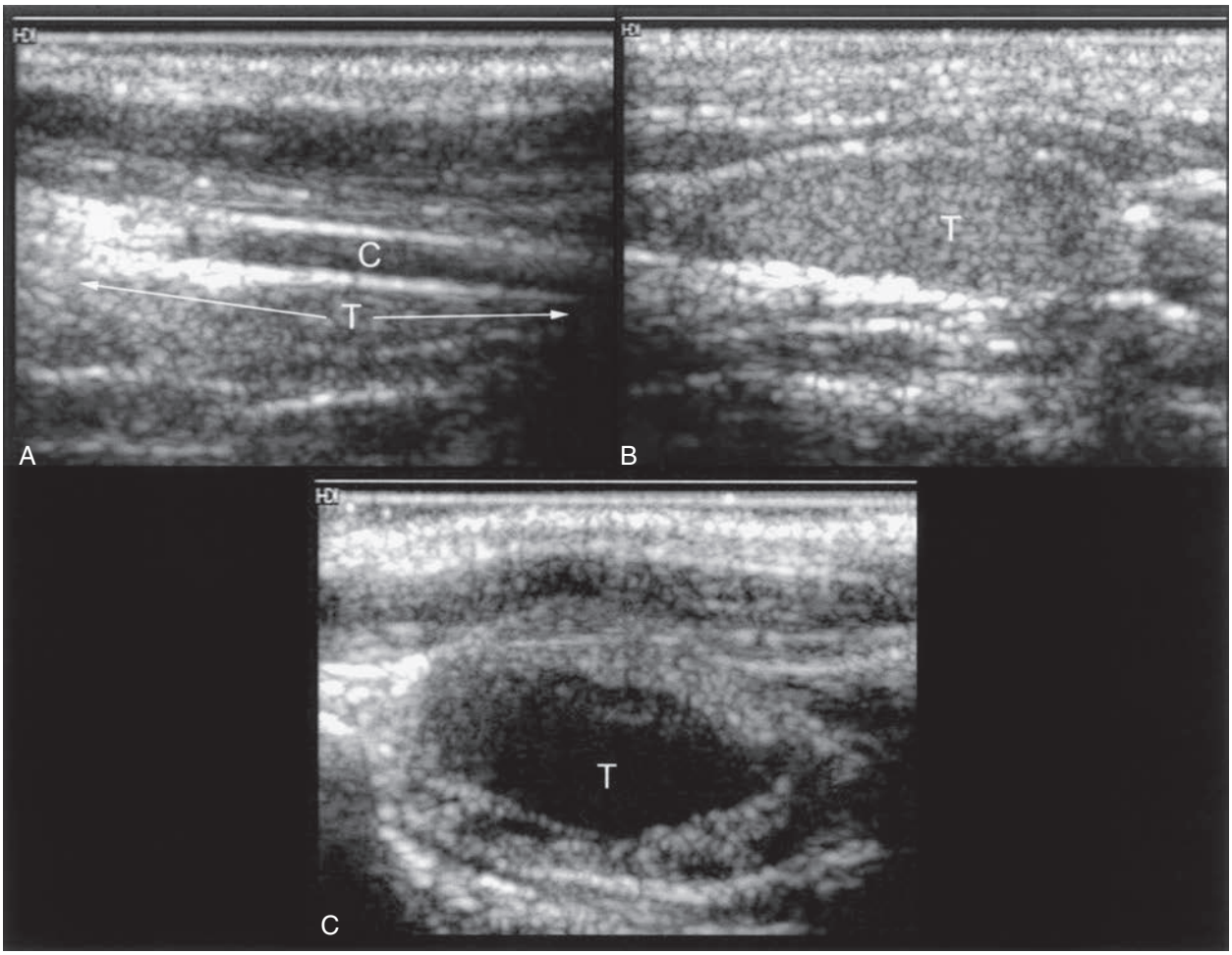

FIGURE 4-30 **A,** Cervical ultrasound of normal feline thyroid (*T,* thyroid; *C,* carotid artery). **B,** Abnormal enlarged thyroid in a cat with hyperthyroidism. **C,** Abnormal enlarged cystic thyroid in a cat with hyperthyroidism.

TABLE 4-12 **LINEAR MEASUREMENTS (MM) AND VOLUMETRIC ESTIMATIONS (MM^3) FOR LEFT AND RIGHT THYROID LOBES OF CONTROL AND HYPERTHYROID CATS**

	Left Lobe Mean ± Standard Deviation				Right Lobe Mean ± Standard Deviation			
	LENGTH	HEIGHT	WIDTH	VOLUME*	LENGTH	HEIGHT	WIDTH	VOLUME*
Control (n = 6)	20.5 ± 1.6	3.3 ± 0.8	2.5†	89 ± 23	20.3 ± 1.6	3.0 ± 0.6	2.5†	80 ± 19
Hyperthyroid (n = 14)	20.2 ± 3.6	5.5 ± 2.4	5.7 ± 2.1	382 ± 312	21.9 ± 4.4	8.1 ± 3.0	7.7 ± 2.4	782 ± 449

*Volume estimation calculated using the formula for a prolate ellipsoid, $\pi/6$ (length x height x width).
†Width measurements for normal thyroid lobes defaulted to 2.5 mm because they could not be seen ultrasonographically.

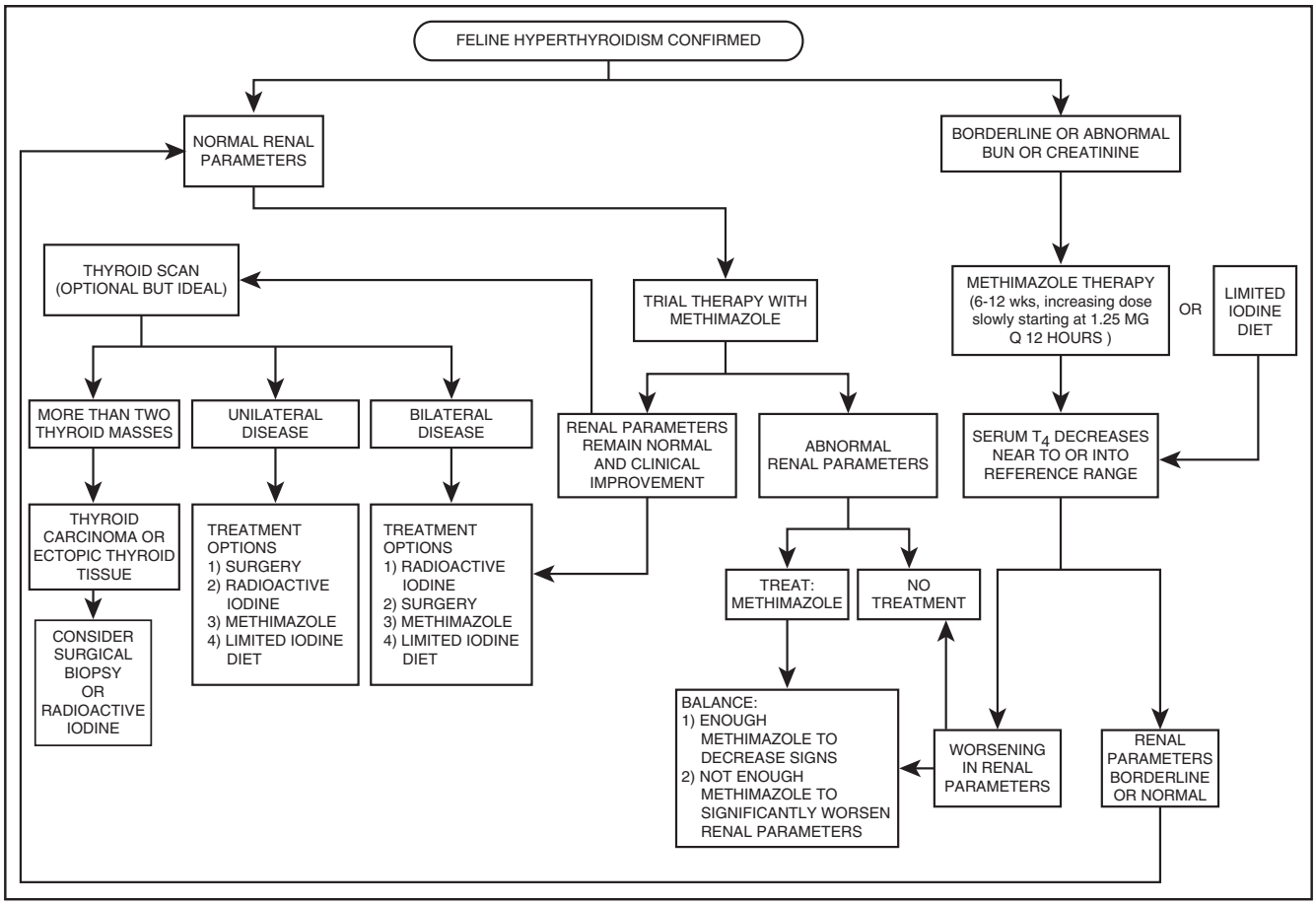

FIGURE 4-31 Algorithm for the treatment of cats with hyperthyroidism, emphasizing the potential negative effects of therapy on renal function.

The treatment chosen for an individual cat depends on various factors, including owner preference and financial constraints, the presence of nonthyroidal illness, the age of the cat, and availability of a skilled surgeon or a facility with nuclear medicine capability for administering radioactive iodine.

Treatment of Hyperthyroidism and Renal Function

Background

Clinical evaluation and management of geriatric cats with concurrent hyperthyroidism and CKD is challenging. The tendency of nonthyroidal illnesses such as CKD to lower serum T_4 concentrations may mask hyperthyroidism. On the other hand, hyperthyroidism can increase the GFR and thereby decrease the serum creatinine and BUN concentrations, masking underlying renal disease. The progressive weight loss and reduction in muscle mass associated with hyperthyroidism may further contribute to the reduction of serum creatinine concentrations, also obscuring evidence of concurrent renal disease. Finally if treatment of hyperthyroidism results in hypothyroidism, renal function may deteriorate further and exacerbate CKD. It has been estimated that as many as 40% of hyperthyroid cats have CKD. Whether CKD is more common in hyperthyroid cats than in the general geriatric cat population is unknown. Mechanisms by which hyperthyroidism could contribute to progression of renal disease in geriatric cats include induction of proteinuria, activation of the renin-angiotensin-aldosterone axis, hypertension and aberrations in calcium, and phosphate homeostasis.

Pathophysiology

Hyperthyroidism increases cardiac output and decreases peripheral vascular resistance, leading to increased renal plasma flow (RPF) and an increase in the GFR. Numerous studies have documented that GFR is increased in feline hyperthyroidism (Boag et al, 2007; Vandermeulen et al, 2008; van Hoek et al, 2008a; 2009a). In a study of 21 cats before and after treatment of hyperthyroidism using radioactive iodine, GFR was above the reference range for healthy cats in 80% of hyperthyroid cats (van Hoek et al, 2009a). In a study of geriatric cats followed until they became hyperthyroid, a decrease in creatinine was documented at the time of diagnosis of hyperthyroidism (Wakeling et al, 2011).

Worsening Renal Function after Resolution of Hyperthyroidism

Because restoration of euthyroidism normalizes the GFR, treatment of cats for hyperthyroidism usually results in an increase in serum creatinine, resulting in azotemia and overt renal failure in some cats (Graves et al, 1994; DiBartola et al, 1996; van Hoek et al, 2009a; Williams et al, 2010). Of 216 non-azotemic hyperthyroid cats, 41 (15%) developed azotemia within 240 days of diagnosis and treatment; the severity of azotemia and whether it was associated with clinical signs were not reported (Williams et al, 2010). As would be expected, a higher percentage of cats with well controlled hyperthyroidism became azotemic than cats that were poorly controlled (Williams et al, 2010). Pretreatment BUN and creatinine was positively correlated with development of azotemia, but posttreatment azotemia was not associated with decreased survival in this group of cats. The clinical effect of decreased GFR

TABLE 4-13 **ADVANTAGES AND DISADVANTAGES OF DIFFERENT TREATMENTS FOR FELINE HYPERTHYROIDISM**

THERAPY	ADVANTAGES	DISADVANTAGES
Surgery	1. Usually corrects the thyrotoxicosis 2. Thyroids easily accessible 3. Relatively inexpensive 4. Sophisticated equipment not required 5. Definitive treatment 6. Rapid reduction in thyroid hormone concentrations	1. Risk of anesthesia in elderly and fragile cats 2. Anesthesia may decompensate other abnormal organ systems 3. Iatrogenic hypoparathyroidism 4. Iatrogenic hypothyroidism 5. Risk of surgical complications (recurrent laryngeal nerve damage) 6. Failure to remove all abnormal thyroid tissue 7. Effect on GFR irreversible
Oral anti-thyroid drugs	1. Usually corrects the thyrotoxicosis 2. Inexpensive 3. Small tablet size 4. No anesthesia or surgery 5. No expensive facilities 6. No hospitalization required 7. Effect on GFR reversible	1. Side effects of the medication: a. Anorexia b. Vomiting c. Depression/lethargy d. Thrombocytopenia e. Granulocytopenia f. Hepatopathy 2. Daily to twice daily medication required 3. Iatrogenic hypothyroidism (reversible) 4. Not definitive treatment 5. Does not resolve underlying thyroid pathology
Radioactive iodine	1. Usually corrects the thyrotoxicosis 2. Only one treatment for most cats; no pills 3. No anesthesia or surgery 4. Rapid reduction in thyroid hormone concentrations 5. Definitive therapy	1. Need for sophisticated facilities 2. Radiation exposure to personnel and owners 3. Hospitalization after treatment to decrease risk of human exposure 4. Possibility of iatrogenic hypothyroidism 5. Re-treatment may be necessary in 2% to 5% 6. Irreversible
Nutritional management with iodine limited diets	1. Usually corrects the thyrotoxicosis 2. Inexpensive 3. No anesthesia or surgery required 4. No expensive facilities 5. No hospitalization required 6. Effect on GFR reversible	1. Cat can only eat one diet 2. Difficult to limit dietary intake in multi-cat households 3. Outdoor cats may have access to other dietary sources of iodine 4. Not palatable to all cats 5. Not definitive treatment 6. Does not resolve underlying thyroid pathology 7. Long-term consequences of limited iodine diet unknown

after treatment of hyperthyroidism is variable. Most cats have a modest increase in creatinine after treatment that may or may not be severe enough to result in azotemia. A smaller subset of cats has a clinically significant worsening of azotemia and developed overt signs of renal failure after treatment. Unfortunately there are no routine pretreatment clinical parameters that allow prediction of which cats will develop clinically significant failure. It has been stated that cats with a normal BUN and creatinine and a USG more than1.035 are unlikely to have clinically significant renal failure after treatment, but other studies and our clinical experience suggest that this is not always the case (Riensche et al, 2008). Cats that develop azotemia after treatment are likely to be older and have a higher total T_4, BUN, and creatinine; but measurement of GFR is believed to be a more sensitive predictor of renal failure after treatment (Adams et al, 1997; van Hoek et al, 2009a).

Predicting Emergence of Renal Failure by Determining the Glomerular Filtration Rate

Serum creatinine and BUN concentrations vary inversely with the GFR and are used as indirect measures of the GFR. However, these two commonly used parameters are relatively insensitive indicators of renal disease, because at least 75% of functional renal mass must be lost before changes are noted. Significant renal disease, therefore, can be present in the absence of serum biochemical abnormalities. In addition, BUN and serum creatinine are affected by factors other than functional renal mass and blood flow.

Methods to assess GFR include inulin or exogenous creatinine clearance, nuclear scintigraphy (using radiolabelled diethylenetriamine penta-acetic acid [DTPA] or ^{51}Cr- ethylenediaminetetraacetic acid [^{51}Cr-EDTA]), or measurement of plasma clearance of iohexol. Iohexol is an iodinated radiographic contrast agent, and the iohexol clearance test has been validated for determination of GFR in cats (van Hoek et al, 2008a). An IV catheter must be placed for administration of the iohexol. The research protocols that have been described require collection of blood samples at 0, 15, and 30 minutes and then at 1, 2, 3, 6, 8, and 10 hours after iohexol administration for measurement of either iodine or iohexol by high performance liquid chromatography (HPLC). An abbreviated protocol with collection of samples at 3, 4, and 5 hours after iohexol administration is recommended for clinical use, and the iohexol assay is commercially available (http://www.animalhealth.msu.edu). After assay of the iohexol concentration at these three time points, the diagnostic laboratory reports a calculated GFR.

In a study of 21 hyperthyroid cats in which GFR was measured before and 1, 4, 12, and 24 weeks after treatment of hyperthyroidism by radioactive iodine therapy, decreases in GFR occurred within 4 weeks of treatment and did not change thereafter. Maximum decrease in GFR could only be partially predicted by

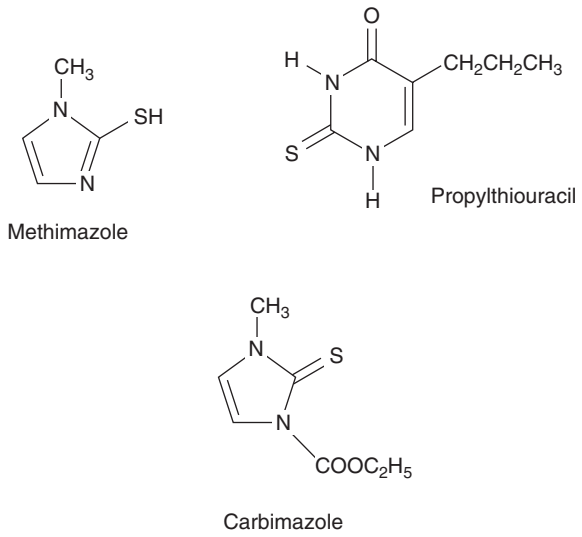

FIGURE 4-32 Chemical structures of the anti-thyroid drugs (thioureylenes), which inhibit thyroidal iodide organification.

a formula using the pretreatment GFR, serum total T_4, serum creatinine, BUN, and USG (van Hoek et al, 2009a). Although some studies have suggested that cats with a GFR more than 2.25 mL/kg/minute are unlikely to develop clinically significant renal failure after treatment of hyperthyroidism, other studies do not support this contention (Graves et al, 1994; Adams et al, 1997; Riensche et al, 2008).

Summary

There are no routine pretreatment parameters that reliably predict development of azotemia in cats after treatment of hyperthyroidism. Although measurement of pretreatment GFR is helpful, such studies do not consistently predict the development of renal failure after euthyroidism is restored. Therefore a methimazole trial with follow-up serum biochemical and urine analyses should be considered prior to definitive treatment of hyperthyroid cats with either thyroidectomy or radioactive iodine (Riensche et al, 2008). It is important to recognize that not all increases in serum creatinine concentration result in clinical signs of renal failure; mild increases in creatinine after treatment should be expected. Such changes do not preclude definitive treatment of hyperthyroidism. For cats that develop marked azotemia and overt clinical signs of renal failure after euthyroidism is established, medical therapy rather than definitive therapy is recommended long term, and the treatment should be tailored to balance the two disorders. Alternatively thyroid supplementation after definitive treatment of hyperthyroidism can be considered; however, most owners decline this option due to financial considerations.

TREATMENT WITH ANTI-THYROID DRUGS (THIOUREYLENES)

Mode of Action

The structures of the three available anti-thyroid drugs methimazole, carbimazole, and propylthiouracil (PTU) are shown in Fig. 4-32. After oral administration, carbimazole is rapidly converted to methimazole and has identical properties to methimazole. Ten milligrams of carbimazole is approximately equivalent to 6 milligrams methimazole. Methimazole and PTU are concentrated within the thyroid gland and inhibit the synthesis of thyroid hormones by inhibiting oxidation of iodide, organification of iodide, and coupling of iodothyronines to form T_4 and T_3 (Manna et al, 2013). Most studies suggest that the mode of action is via inhibition of thyroid peroxidase, although PTU also inhibits the type-I iodothyronine deiodinase (ID-I) thus impairing peripheral deiodination of T_4 to T_3 (Cooper, 2013). None of the anti-thyroid drugs affects the iodide pump, which concentrates iodide in the thyroid cells, or the secretion of thyroid hormone formed prior to treatment (Peterson and Becker, 1995). Although thioureylenes decrease thyroid hormone concentrations and thereby control the clinical signs of hyperthyroidism, they are not cytotoxic to the thyroid gland and do not resolve the underlying cause of hyperthyroidism.

When administered orally, anti-thyroid drugs are rapidly absorbed and have a volume of distribution close to that of total body water. Methimazole has a plasma half-life of 1.4 to 10 hours in cats; although because the drug is concentrated in the thyroid gland and the intrathyroidal turnover is low, the duration of the biologic effect exceeds the plasma half-life.

Propylthiouracil

Although PTU is effective in blocking the synthesis of thyroid hormones in cats and controlling hyperthyroidism, it has been reported to cause an unacceptable rate of mild to severe adverse effects. These include anorexia, vomiting, lethargy, immune-mediated hemolytic anemia, and thrombocytopenia (Peterson et al, 1984; Aucoin et al, 1985; 1988). Because of these side effects, PTU is not recommended for use in cats. It has been hypothesized that taurine deficiency, which impairs drug elimination, may have exacerbated the side effects of PTU when it was first used, but the drug is not currently recommended for use in cats.

Methimazole (Tapazole)

Indications

Methimazole has three indications in the treatment of hyperthyroidism. First, it can be used to normalize serum T_4 concentrations and allow assessment of the effect of resolution of hyperthyroidism on clinical signs, renal function, and other laboratory parameters prior to definitive treatment (see Fig. 4-31). Second, it can be used for short-term stabilization of hyperthyroidism in cats with severe clinical manifestations of hyperthyroidism prior to surgery or radioactive iodine treatment. Lastly, it can be used for long-term treatment of hyperthyroidism (Fig. 4-33 and Fig. 4-34).

Advantages

The advantages and disadvantages of oral methimazole therapy are shown in Table 4-13. Methimazole is relatively inexpensive and readily available, and it does not require sophisticated training, facilities, or prolonged hospitalization. The medication can be administered by owners, is relatively safe, and can be given to the oldest of hyperthyroid cats. Furthermore, the drug can also be administered topically (Hoffman et al, 2002; Sartor et al, 2004; Hill et al, 2011).

Methimazole reversibly inhibits thyroid hormone synthesis, and therefore there is no risk of permanent hypothyroidism. In general, the adverse effects are reversible after discontinuation. Methimazole is considered the anti-thyroid drug of choice in cats in the United States and is reported to be effective for control of hyperthyroidism in approximately 90% of hyperthyroid cats.

Oral Dosage Protocol. Methimazole is available as 2.5 mg and 5 mg sugar-coated tablets in a veterinary labelled product and in 5, 10, and 15 mg tablets in a human labelled product.

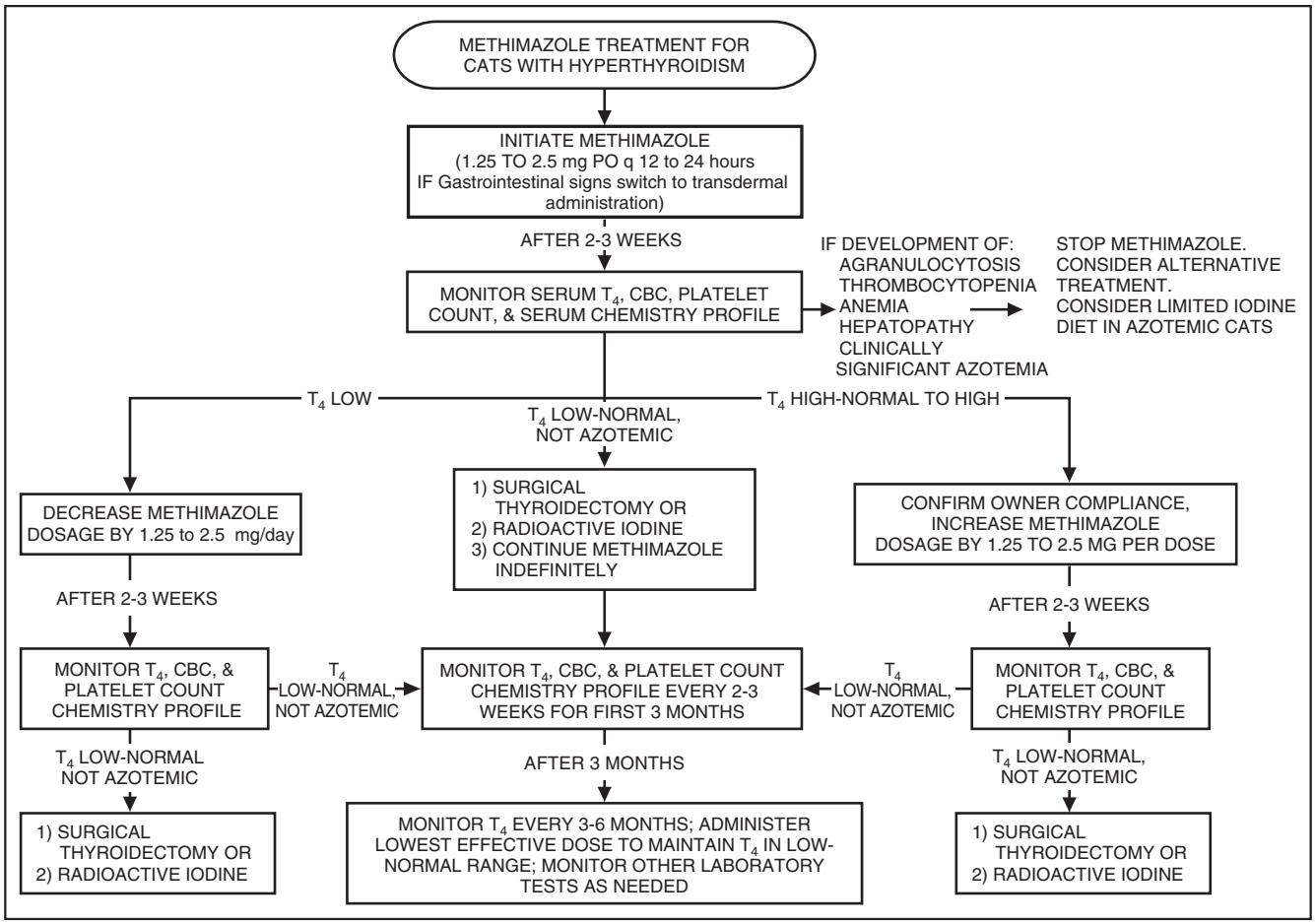

FIGURE 4-33 Algorithm for the treatment and monitoring of hyperthyroid cats during methimazole therapy. *CBC,* Complete blood count; T_4, thyroxine.

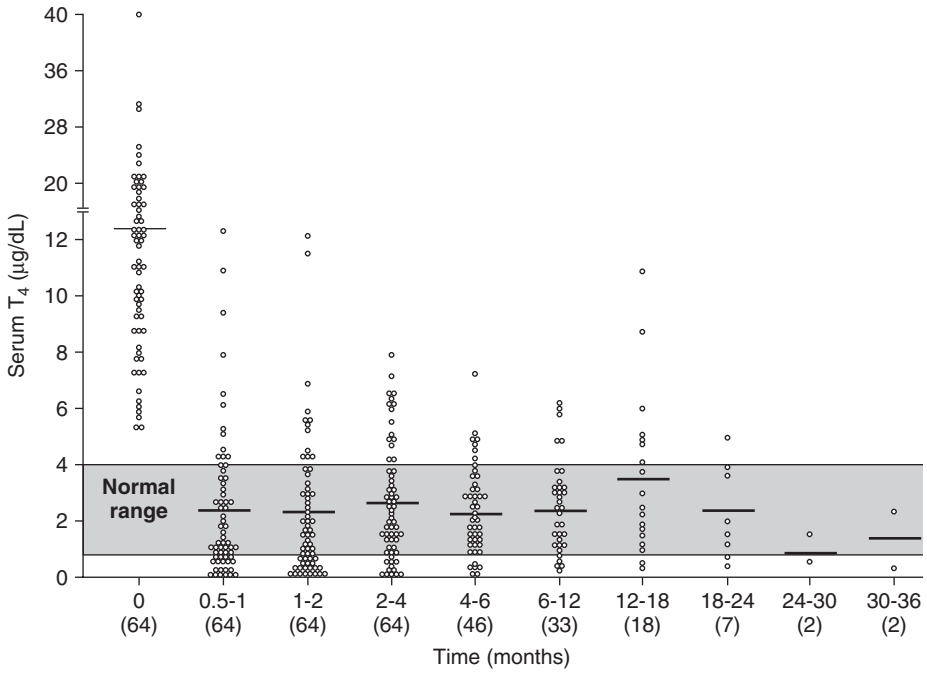

FIGURE 4-34 Serum thyroxine (T_4) concentrations in 64 cats with hyperthyroidism before and during long-term treatment with methimazole. The *horizontal lines* indicate mean values. The *numbers in parentheses* indicate the number of cats treated during each time period. (From Peterson ME, et al.: Methimazole treatment of 262 cats with hyperthyroidism, *J Vet Intern Med* 2[3]:150-157, 1988.)

The veterinary labelled sugar-coated tablets do not have the bitter taste of the uncoated human products, which reduces the risk of excessive salivation associated with methimazole administration in some cats. Whether oral methimazole can be absorbed through human skin has not been determined, but the sugar-coated tablets are less likely to result in systemic absorption.

The usual recommended starting dose for methimazole is 1.25 to 2.5 mg every 12 hours, with the more conservative dose recommended in very small and debilitated cats or those considered at high risk for adverse effects. The methimazole dose should be titrated every 2-3 weeks until the serum thyroid hormone concentration is within the lower half of the reference range (see Fig. 4-33). The total T_4 usually decreases within 1 week of treatment with oral methimazole, and the clinical signs improve within 2 to 3 weeks. Because the risk of adverse drug effects are highest during the initial 2 to 3 months of treatment, cats should be reassessed every 2-3 weeks with a history and physical examination, and blood should be obtained for a CBC, platelet count, serum biochemistry profile (BUN, creatinine, hepatic enzymes), and serum T_4 concentration in order to monitor for signs of toxicity and deterioration of renal function. Cats should be assessed in a similar way if they become clinically ill during treatment. Studies suggest that the length of time between drug administration and blood sample collection does not influence the serum thyroid hormone concentration during methimazole treatment; therefore a blood sample for therapeutic monitoring can be collected at any time of day (Rutland et al, 2009; Boretti et al, 2013a). If the serum T_4 concentration is within the lower half of the reference range, the dose should be maintained for an additional 2 to 6 weeks to allow determination of the need for any further dosage adjustments. If the serum T_4 concentration is below the reference range, the dose should be reduced. If the hyperthyroidism is not controlled, the dosage should continue to be increased every 2 weeks in increments of 2.5 mg a day until the measured total T_4 concentration is within the lower half of the reference range. If adverse effects are identified, methimazole should be discontinued. A decision can then be made to choose an alternative therapy, switch to transdermal methimazole, or reinitiate treatment using a lower dose of oral methimazole.

Most cats require 2.5 to 5 mg of methimazole every 12 hours to control hyperthyroidism, and total T_4 concentrations increase to pretreatment levels within 48 hours of discontinuing treatment (Peterson et al, 1988). Methimazole is more effective when administered twice a day than once a day at least for the first 4 weeks of treatment (Trepanier et al, 2003). Most cats require long-term twice daily treatment, but in some cats the frequency of dosing can be reduced to every 24 hours after a few weeks of treatment. The dose range of methimazole reported in the literature for long-term control of hyperthyroidism is 2.5 to 20 mg methimazole total mg dose per day. The most common reasons for treatment failure include problems with owner compliance and occurrence of adverse effects. Cats with very large goiters and those with thyroid carcinoma may be more resistant to treatment with methimazole.

Topical (Transdermal) Methimazole

Methimazole can also be administered to hyperthyroid cats as a topical gel. Methimazole is usually compounded in a pluronic lecithin organogel, which is a permeation enhancer that disrupts the stratum corneum and allows absorption into the systemic circulation (Sartor et al, 2004). Some methimazole may also be ingested by the oral route during grooming. Another novel lipophilic formulation has also been reported to result in effective absorption of methimazole (Hill et al, 2011). Methimazole for transdermal application is usually dispensed in tuberculin syringes and can be formulated in a variety of concentrations (typically 2.5 or 5 mg/0.1 mL). The gel is applied to the non-haired pinna of the ear by the owners using a finger-cot. Dosing is alternated between ears and, if necessary, residual gel is removed from the ear prior to the next application using a cotton ball. In a study of 47 cats with newly diagnosed hyperthyroidism, randomized to receive either oral or transdermal methimazole, significantly more cats treated with oral methimazole were euthyroid than those treated with transdermal methimazole after 2 weeks of treatment, but by 4 weeks the difference was no longer significant. Nine of 11 cats treated with oral methimazole were euthyroid at 4 weeks, versus 14 of 21 cats receiving methimazole transdermally (Trepanier et al, 2003). Although the difference in efficacy at 4 weeks was not statistically significant, this may have been due to the smaller number of cats remaining in the study after 4 weeks. There is no difference in the incidence of hepatic, hematologic, or dermatologic side effects in cats treated with oral versus transdermal methimazole, but significantly fewer gastrointestinal side effects are observed with the transdermal form of treatment (Sartor et al, 2004). Some cats have mild inflammation and erythema of the pinnae where the drug is applied, and rarely these result in discontinuation of the drug. Other studies have confirmed that transdermal methimazole therapy can be very effective for long-term treatment of feline hyperthyroidism at doses ranging from 2.5 mg every 24 hours to 5 mg every 12 hours (Hill et al, 2011; Boretti et al, 2013a). In a long-term study of 60 cats treated with transdermal methimazole at doses ranging from 1 to 15 mg per day, clinical improvement was seen in all cats although higher doses were required after prolonged treatment, and several cats repeatedly had T_4 concentrations above or below the reference range during the study (Boretti et al, 2013b). Although most studies have evaluated transdermal methimazole administered every 12 hours, some cats are effectively managed with once daily administration (Fig. 4-35) (Boretti et al, 2013a).

The advantages of topical methimazole include the ease of administration and the decreased risk of gastrointestinal side effects. Disadvantages include the added expense, slightly slower onset of control of hyperthyroidism, and slightly lower efficacy. Care should be taken to ensure that children are not exposed to the methimazole gel. It is important to remember that there is little regulation of compounding pharmacies and care should be taken when choosing a pharmacy. Studies suggest that methimazole compounded in an organogel should be stored at room temperature and should be discarded after 60 days or earlier if there is visible separation of the components in the dosing syringe (Pignato et al, 2010).

Trial Methimazole Therapy to Assess Renal Function After Reestablishment of Euthyroid State

As discussed earlier, because it is not possible to accurately predict which cats will develop a clinically significant exacerbation of azotemia after therapy for hyperthyroidism, a clinical trial with methimazole is recommended in most cats prior to definitive treatment (see Figs. 4-31 and 4-33).

The recommended treatment protocol for a methimazole trial is to administer methimazole at an initial dose of 1.25 to 2.5 mg. A CBC, serum chemistry profile, and total T_4 is measured every 2 to 3 weeks, and the dose of methimazole adjusted until euthyroidism is achieved. If after 4 weeks of euthyroidism, the renal parameters are stable or only mildly increased, definitive treatment can be pursued. However, if the renal parameters worsen when the euthyroid state is reestablished, long-term treatment with a conservative

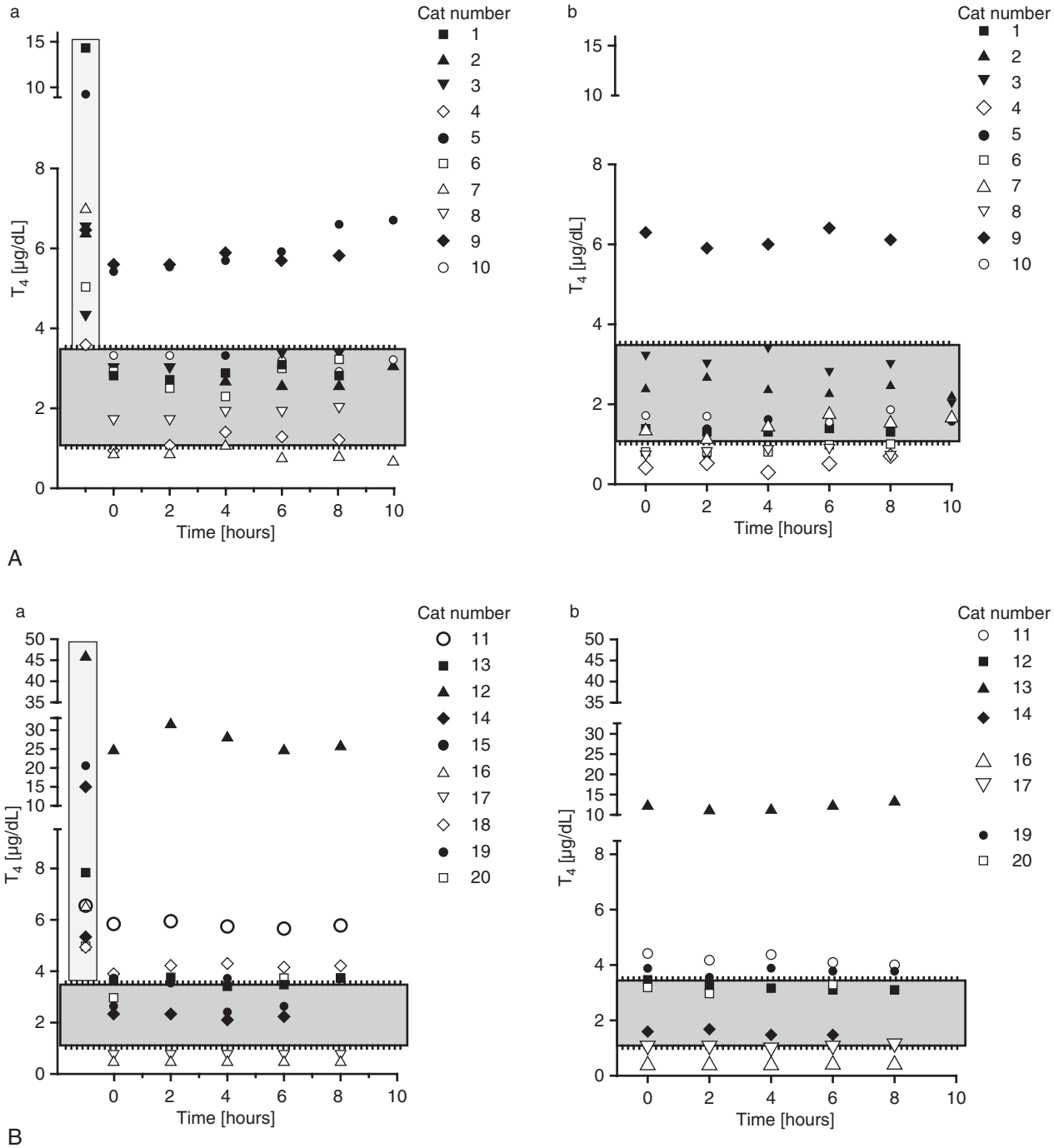

FIGURE 4-35 **A,** Change in serum T_4 concentrations during a 10-hour sampling period before and after twice daily transdermal methimazole application. Sustained T_4 suppression is evident during the whole observation period for most cats. *Dark gray shaded (horizontal area)* reference range T_4 concentrations, *light gray shaded (vertical area)* in **A:** T_4 concentrations before starting treatment. *a)* Week 1; *b)* Week 3. **B,** Change in serum T_4 concentrations during a 10-hour sampling period before and after once daily transdermal methimazole application. Sustained T_4 suppression is evident during the whole observation period for most cats. *Gray shaded (horizontal area)* reference range T_4 concentrations, *light-gray shaded (vertical area)* in **B:** T_4 concentrations before starting treatment. *a)* Week 1; *b)* Week 3. (From Boretti FS, et al.: Duration of T_4 suppression in hyperthyroid cats treated once and twice daily with transdermal methimazole, *J Vet Intern Med* 27[2]:377-381, 2013.)

TABLE 4-14 **ADVERSE REACTIONS ASSOCIATED WITH DRUGS USED THERAPEUTICALLY IN FELINE HYPERTHYROIDISM**

DRUG	REACTION	APPROXIMATE PERCENTAGE OF CATS AFFECTED	TIME AT OCCURRENCE	TREATMENT REQUIRED
Methimazole	Vomiting, anorexia, depression	15	< 4 weeks	Usually transient, decrease dose
	Eosinophilia, leukopenia, lymphocytosis	15	< 8 weeks	Usually transient
	Self-induced excoriations	2	< 4 weeks	Withdrawal and glucocorticoid therapy
	Agranulocytosis, thrombocytopenia	< 5	< 3 months	Withdrawal and symptomatic therapy
	Hepatopathy (anorexia,↑alanine aminotransferase, alkaline phosphatase)	< 2	< 2 months	Withdrawal and symptomatic therapy
	Positive antinuclear antibody	> 50	> 6 months	Decrease daily dosage
	Acquired myasthenia gravis	Rare	< 16 weeks	Withdrawal and appropriate treatment
Carbimazole	Vomiting, anorexia, depression	10	< 3 weeks	Usually transient, decrease dose
	Eosinophilia, leukopenia, lymphocytosis	5	< 2 weeks	Usually transient
	Self-induced excoriations	Rare	< 4 weeks	Withdrawal and glucocorticoid therapy
Stable iodine	Salivation and anorexia	Occasional	Immediate	Change formulation

dose of methimazole or alternatively nutritional management of hyperthyroidism should be considered. The goal is to minimize the clinical signs of hyperthyroidism as much as possible without causing escalation in renal failure.

Adverse Effects of Methimazole

Adverse effects of treatment with methimazole are common in cats (Table 4-14) and can occur whether methimazole is administered orally or transdermally.

Clinical Side Effects. Relatively mild clinical side effects from methimazole therapy are common, occurring in approximately 10% to 25% of cats (Peterson et al, 1988; Sartor et al, 2004). Most side effects are observed during the first 4 to 8 weeks of treatment; it is rare for a cat to develop methimazole-induced side effects after 2 to 3 months of treatment. The most common side effects include anorexia, vomiting, and lethargy (Peterson et al, 1988). These adverse reactions may be transient or may resolve after the dose is decreased. Gastrointestinal signs are managed by discontinuing the drug until all signs of toxicity have resolved for at least a week and then restarting the medication at a lower dose. The gastrointestinal side effects may result from direct gastric irritation, because they are much less common in cats treated with transdermal methimazole (Sartor et al, 2004).

Self-induced excoriation of the face and neck is an unusual reaction to methimazole seen in 2% to 3% of cats treated with methimazole. Like most of the drug's adverse effects, this problem usually occurs within the first 4 to 8 weeks of therapy. The characteristic scabbed lesions at the base of the pinna may improve after treatment with glucocorticoids, although drug discontinuation is usually necessary for complete resolution. Alternative treatment should be considered for these cats. Lymphadenopathy has also been reported in a cat treated with methimazole (Niessen et al, 2007), although other causes of lymphadenopathy were not completely ruled out.

Blood Dyscrasias. Mild hematologic changes caused by methimazole include eosinophilia, lymphocytosis, and mild leukopenia. These changes are common in methimazole treated cats but do not usually require discontinuation of treatment. More severe hematologic reactions are much less common (3% to 9% cats) and include severe thrombocytopenia associated with bleeding (platelet count less than 75,000/μL), and neutropenia (less than 500/μL) associated with fever, anorexia, lethargy, and localized or systemic infections (Peterson et al, 1988). Any severe blood dyscrasia should prompt immediate cessation of treatment, and resolution usually occurs within 1 week. The mechanism for blood dyscrasias due to methimazole is unknown, but in humans these adverse effects are believed to be immune-mediated (Trepanier, 2006). Aplastic anemia was reported in a cat that had been treated with methimazole for 3 years, but the cat also had a mast cell tumor (Weiss 2006). In the largest case series of cats treated with methimazole, approximately 20% had had positive antinuclear antibody (ANA) test results, and 2% developed a positive direct Coombs test (Peterson et al, 1988). The risk of a positive antinuclear antibody (ANA) increased with duration of treatment and dose of methimazole. The importance of this finding is not known, because methimazole is not associated with development of lupus erythematosus or immune mediated hemolytic anima in cats.

Bleeding tendencies unassociated with thrombocytopenia have been rarely reported in methimazole treated cats, and in humans methimazole is reported to interfere with the vitamin K–dependent coagulation factors. In a study of 20 cats treated with methimazole, three cats had abnormal coagulation profiles characterized by prolongation of protein induced by vitamin K absence or antagonism (PIVKA) prior to treatment, and one cat developed prolongation of PIVKA bleeding time, unassociated with clinical signs of bleeding, 2 to 6 weeks after treatment (Randolph et al, 2000). No cats developed prolongation of prothrombin time (PT) or activated partial thromboplastin time (APTT). If a coagulopathy is suspected in a hyperthyroid cat treated with methimazole, testing of PIVKA may be more sensitive than the standard PT and APTT.

Hepatic toxicity occurs in a small number of cats treated with methimazole. The hepatopathy is characterized by systemic signs

of illness (anorexia, vomiting, and lethargy), icterus, and marked increases in serum ALT and ALP activities. Days to weeks may be required for all clinical and biochemical abnormalities to resolve after discontinuation of the drug. Alternative therapies for hyperthyroidism should be considered for cats that develop these adverse reactions.

Myasthenia gravis has been reported to develop in hyperthyroid cats treated with methimazole (Shelton et al, 2000; Bell et al, 2012) and may be caused by the immunomodulatory effects of the drug. Methimazole has been associated with a number of different immune mediated diseases in humans, but the precise mechanism is unknown. Myasthenia gravis was reported to resolve in the two cats in which methimazole was withdrawn; interestingly one cat that was subsequently treated with carbimazole did not have recurrence of signs, but it was also treated with pyridostigmine (Bell et al, 2012). An adverse drug effect should be suspected in cats treated with methimazole that develop myasthenia gravis and potentially other immune mediated disorders.

Hypothyroidism. Although cats treated with methimazole rarely show clinical signs of hypothyroidism, overtreatment resulting in biochemical hypothyroidism is relatively common (Williams et al, 2010). Cats with iatrogenic hypothyroidism are at increased risk of azotemia and have a shorter survival time than euthyroid azotemic cats so it is important to avoid hypothyroidism by appropriate dose adjustment (Williams et al, 2010).

Methimazole administration should be discontinued and appropriate supportive care provided to any cat in which a clinically significant adverse effect of methimazole is suspected. Adverse reactions typically resolve within 7 days after discontinuation of the drug (Peterson et al, 1988). For severe or life-threatening adverse effects, alternative treatment should be considered rather than risking reexposure to the drug. It is unclear whether treatment with methimazole can interfere with response to treatment with ^{131}I; therefore it is recommended that treatment should be discontinued 1 to 2 weeks prior to treatment (see Treatment with Radioactive Iodine for more on this topic).

Carbimazole

Background

Carbimazole is a pro-drug of methimazole that is used in Europe and Australia for treatment of feline hyperthyroidism. Carbimazole is rapidly and almost completely converted to methimazole, either in the gastrointestinal tract or immediately after absorption, because drug concentrations of methimazole but not carbimazole are detected in the serum and thyroid gland after ingestion (Peterson et al, 1993). Carbimazole has a higher molecular weight than methimazole, so 5 mg of carbimazole is equivalent to 3 mg of methimazole. The starting dose for carbimazole is 5 mg every 8 to 12 hours. There is also a controlled release tablet formulation that can be administered once a day at a starting dose of 10 to 15 mg every 24 hours. In one study, the dose range required to achieve euthyroidism ranged from 10 mg every other day to 25 mg per day (Frénais et al, 2009). There have been no studies directly comparing the efficacy and adverse effects associated with carbimazole versus methimazole; however, anecdotally carbimazole is associated with a lower rate of adverse effects than methimazole, and severe blood dyscrasias have not yet been reported in association with carbimazole. The most common adverse effects associated with carbimazole administration are gastrointestinal signs (Bucknell, 2000). Other adverse effects that have been reported include excoriations of the head and neck, lymphadenopathy, pruritus, lymphocytosis, and leucopenia (Mooney et al, 1992). Despite the suggestion that there are fewer side effects associated with carbimazole administration, carbimazole is rapidly converted to methimazole, so its use in cats that have adverse reactions to methimazole is probably unwise (Trepanier, 2007).

TREATMENT WITH SURGERY

Although surgical thyroidectomy is an effective and usually permanent treatment for feline hyperthyroidism, over the last 20 years it has become less commonly performed because of the increasing availability of radioiodine treatment facilities, the potential for recurrence due to residual ectopic thyroid tissue, and the risk of adverse postoperative clinical consequences, such as hypoparathyroidism and hypothyroidism. These complications can occur because the functional status of the thyroid gland cannot be determined by visual inspection, and therefore it not always possible to determine at surgery whether one or both thyroid glands should be removed. Other less common complications of thyroidectomy include Horner's syndrome and damage to the laryngeal nerve. Despite these limitations, thyroidectomy is a very effective treatment for feline hyperthyroidism, and the concerns discussed earlier can be minimized by preoperative scintigraphy and good surgical technique. The advantages of thyroidectomy include a short hospital stay provided treatment for hypoparathyroidism is not required, and the opportunity to evaluate thyroid tissue by histopathology, which is important in cats with suspected thyroid carcinoma. In our opinion, scintigraphy should always be performed prior to surgical thyroidectomy to determine whether thyroid disease is unilateral or bilateral and to rule out the presence of ectopic thyroid tissue. Unfortunately many practitioners do not have ready access to scintigraphy, but understanding the benefit of this procedure and knowing when to refer for it is important. For cats that are determined to have unilateral thyroid disease, thyroidectomy is a simple and speedy surgical procedure that results in rapid resolution of hyperthyroidism. For cats with bilateral thyroid disease, thyroidectomy should be performed only if there are good reasons for avoiding radioactive iodine treatment. If bilateral thyroidectomy is chosen, owners need to be warned about the possibility of postoperative complications, such as hypoparathyroidism or hypothyroidism. In cats with ectopic tissue identified by scintigraphy, surgical treatment is not recommended because it is not always possible to readily identify the location of ectopic tissue at the time of surgery. Even if ectopic tissue is identified and removed surgically, recurrence is common (Naan et al, 2006). Thyroidectomy is most appropriate for cats that do not tolerate hospitalization and for owners who are concerned about use of radioactive iodine for treatment.

Presurgical Management

In an attempt to minimize perisurgical and postsurgical complications, hyperthyroid cats must be thoroughly evaluated for concurrent illness prior to surgery. Problems such as congestive heart failure, cardiac arrhythmias, hypertension, renal failure, and electrolyte abnormalities (e.g., hypokalemia) should be identified and treated prior to surgery (Naan et al, 2006). Depending on the severity of the thyrotoxicosis and the needs of the individual case, consideration should be given to controlling thyrotoxicosis with medical therapy prior to surgery, both to decrease risk of anesthetic complications and assess the effect of euthyroidism on renal function (see Treatment of Hyperthyroidism and Renal Function). The goal is to make the cat as stable as possible prior to surgery.

Treatment with beta blockers may be useful prior to surgery to control severe tachycardia and supraventricular tachyarrhthmias in cats that do not tolerate anti-thyroid drugs.

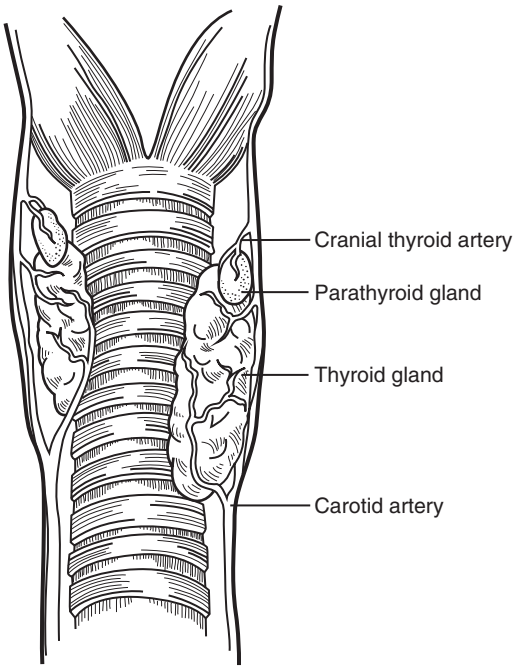

FIGURE 4-36 Anatomy of the thyroid and parathyroid glands in the cat. (From Panciera DL, Peterson ME, Birchard SJ: Diseases of the thyroid gland. In Birchard SJ, Sherding RG [eds]: *Saunders Manual of Small Animal Practice,* ed 3, St. Louis, 2006, Elsevier.)

Anesthesia

The anesthetic protocol should be individualized based on the unique needs of each patient. Most cats undergoing anesthesia for thyroidectomy are fragile geriatric cats with concurrent medical problems. Particular attention should be paid to the renal and cardiovascular systems when planning anesthesia. Adequate fluid therapy is critical but overhydration must be avoided. Factors that should be taken into account include the body condition score, presence of concurrent illness, whether hyperthyroidism has been controlled with medical therapy prior to surgery, and how difficult the patient is to handle. The increased metabolic rate associated with hyperthyroidism increases the absorption, distribution, tissue uptake, and inactivation of anesthetic agents.

Premedication and Anesthesia Induction

Drugs that stimulate or potentiate adrenergic activity capable of inducing tachycardia and arrhythmias should be avoided. Anticholinergic agents (e.g., atropine) should also be avoided because they cause sinus tachycardia and enhance anesthetic-induced cardiac arrhythmias. The most common anesthetic protocol in our hospital is premedication with butorphanol (0.2 mg/kg) followed by induction with isoflurane in an anesthesia induction chamber. Induction with IV propofol (3 to 6 mg/kg to effect) with or without premedication is also an effective approach in cats in which an IV catheter can be placed prior to induction. Once anesthetized, the cat is intubated and inhalation anesthesia continued. In cats that are too fractious for placement of an IV catheter before induction, the catheter can be placed after use of an anesthesia induction chamber. It is important to minimize anesthesia/surgery time, and continuous monitoring of blood pressure, oxygen saturation, and the ECG is essential. Postoperative pain control should be routine. Buprenorphine (0.01 to 0.03 mg/kg every 6-8 hours IM IV or buccal) is a good choice for postoperative control of mild pain in cats.

Surgical Techniques

General Guidelines

Exploratory surgery of the ventrocervical region is relatively simple, quick, and inexpensive. The thyroid gland in the cat is divided into two lobes, which are usually located adjacent to the trachea and distal to the larynx, in close proximity to the carotid artery, jugular vein, and recurrent laryngeal nerve (Fig. 4-36). Normal thyroid lobes are pale tan, whereas a thyroid adenoma or adenomatous hyperplasia is typically brown to reddish brown. The area from above the normal location of the thyroids (hyoid region) down to the thoracic inlet should be examined with careful attention to hemostasis. After exposure and inspection of all visible thyroid tissue, the external parathyroid gland or glands should be identified (see Fig. 4-36). The external parathyroid glands are usually located in the loose fascia at the cranial pole of each lobe. The external parathyroids are much smaller than the thyroid lobes and can be distinguished from thyroid tissue by their lighter color and spherical shape (Birchard, 2006). The internal parathyroid glands are usually embedded in the thyroid lobe parenchyma and are variable in location.

Unilateral Versus Bilateral Involvement

Bilateral lobe involvement is present in more than 70% of hyperthyroid cats; however, in many cats, lobe enlargement is not symmetric. In unilateral cases, there is atrophy of the contralateral lobe, but the distinction between a small but hyperfunctional lobe and an atrophic lobe is not always obvious. For this reason, it is ideal to perform scintigraphy prior to surgery. If scintigraphy is not possible and a decision about whether to perform a unilateral or bilateral thyroidectomy has to be made at the time of surgery, the surgeon should determine whether the risk of persistence/recurrence of hyperthyroidism or the risk of hypoparathyroidism (and potentially hypothyroidism) are of the most concern. The decision depends upon the skill of the surgeon, the wishes of the owner, and whether or not the owners are able to administer oral medication for treatment of hypoparathyroidism and hypothyroidism.

Intracapsular Versus Extracapsular Thyroidectomy

Two surgical techniques have been described, and both have been successfully modified to enhance success rates for resolving hyperthyroidism and to preserve parathyroid tissue. The original intracapsular technique involved incision through the thyroid capsule and blunt dissection to separate and remove the thyroid lobe, leaving the capsule in situ. This technique did help preserve parathyroid tissue but was associated with recurrence due to regrowth of tissue adherent to the capsule (Swalec and Birchard, 1990). The original extracapsular technique involved removal of the intact thyroid lobe with its capsule, after ligation of the cranial thyroid artery, while attempting to preserve blood supply to the adjacent parathyroid gland. This technique reduced the recurrence rate but increased the risk of postsurgical hypoparathyroidism. Both these techniques have been modified (Fig. 4-37). The intracapsular modification involves removing most of the capsule after the thyroid tissue has been excised. The extracapsular modification involves use of bipolar electrocautery rather than ligatures, which minimizes blunt dissection around the parathyroid glands. The modified extracapsular technique is usually preferred, because it is quicker and is associated with less hemorrhage that could obscure the surgical field (Birchard, 2006; Welches et al, 1989).

Postsurgical Recurrence of Hyperthyroidism

Failure to remove all abnormal, adenomatous thyroid cells results in postsurgical recurrence of hyperthyroidism. In a study

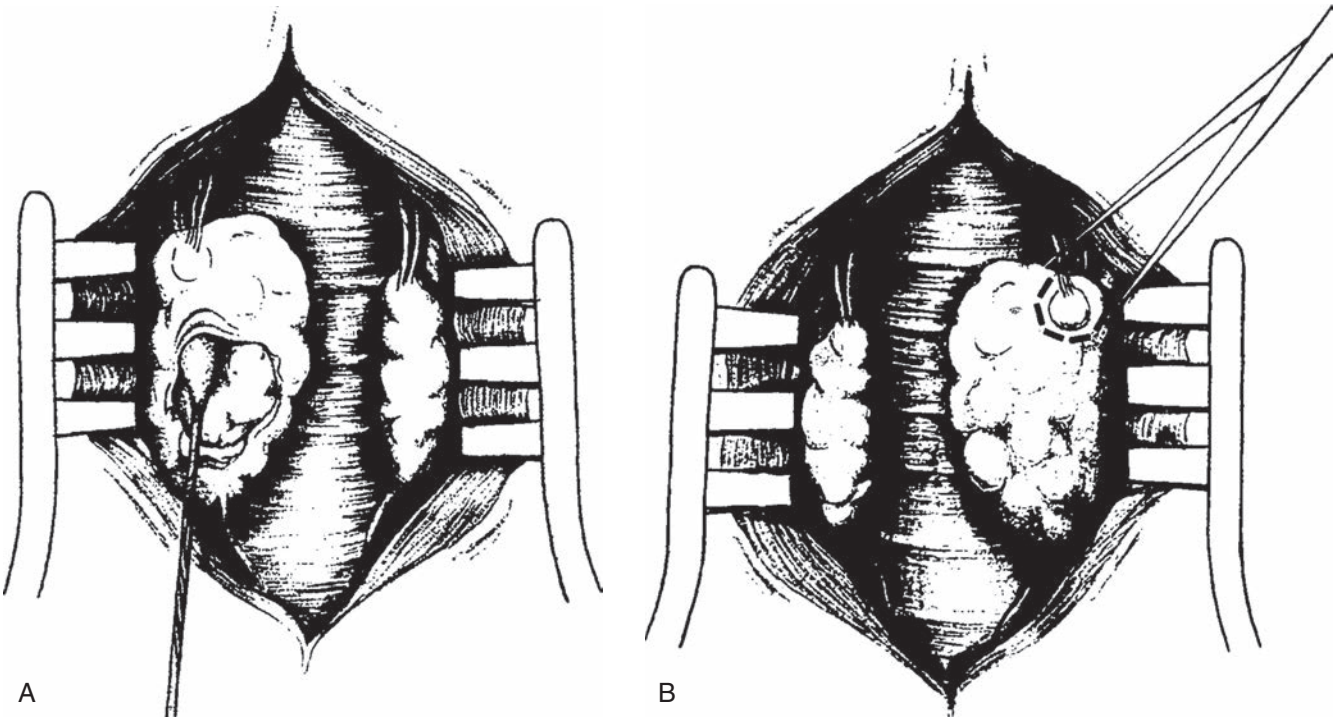

FIGURE 4-37 A, Intracapsular thyroidectomy. The thyroid capsule is incised and the thyroid lobe removed. (The modified technique involves excision of the capsule.) **B,** Extracapsular thyroidectomy. The thyroid lobe and capsule are removed, and the vascular supply to the external parathyroid glands is preserved. (The modified technique involves bipolar cautery rather than ligatures.) (From Mooney CT: Hyperthyroidism in cats, *Veterinary Practice* 22:103, 1990.)

of 101 cats undergoing thyroidectomy using a modified intracapsular technique, recurrence was reported in five cats (Naan et al, 2006). Three of these cats had had a previous thyroidectomy performed by the referring veterinarian, and four of the five cats had scintigraphic evidence of ectopic thyroid tissue that was removed at the time of surgery. Hyperthyroid cats with ectopic thyroid tissue had a significantly higher chance of recurrence even when the ectopic tissue was identified and removed at surgery. Recurrence of hyperthyroidism is uncommon in the absence of ectopic thyroid tissue (Swalec and Birchard, 1990; Naan et al, 2006).

Iatrogenic Hypoparathyroidism (Hypocalcemia)

One of the most serious complications associated with bilateral thyroidectomy is postsurgical hypocalcemia. Hypocalcemia has been reported in 6% to 82% of cats, depending on the surgical method (Birchard et al, 1984; Flanders et al, 1987; Welches et al, 1989; Naan et al, 2006). In most cats undergoing thyroidectomy, postoperative hypocalcemia is mild, transient, and attributed to local edema of the parathyroid gland and chronic depletion of bone calcium due to thyrotoxicosis. With successful surgery (even after unilateral tumor removal), the serum calcium concentration may decline below the reference range for several days as skeletal reserves are restored. This mild hypocalcemia (serum calcium concentration of 7.0 to 9.0 mg/dL) must be differentiated from the severe hypocalcemia associated with iatrogenic hypoparathyroidism. In a study of 86 cats undergoing bilateral thyroidectomy using the modified intracapsular technique, postoperative hypocalcemia required treatment in only five cats (Naan et al, 2006). Hypocalcemia in these five cats resolved after treatment with calcium and dihydrotachysterol within 3 to 6 days. The use of parathyroid transplantation in cats in which the parathyroid gland is accidentally removed or completely devascularized during surgery has been reported (Padgett et al, 1998). The parathyroid gland is cut into small 1 mm pieces and inserted into a pocket in the cervical musculature. This procedure may not prevent severe hypocalcemia from occurring in the first week after surgery but may prevent a long-term need for treatment of hypoparathyroidism.

Postsurgical Management

Management of Postoperative Hypocalcemia

The frequency of clinically significant hypocalcemia after bilateral thyroidectomy is variable and dependent upon the skills of the surgeon. If a bilateral thyroidectomy is performed, serum total or ionized calcium concentration should be assessed at least once daily for 4 to 7 days. As discussed earlier, it is common for mild and transient hypocalcaemia to develop after surgery. Clinically important hypocalcemia is usually associated with serum total calcium concentrations less than 7.0 mg/dL (ionized calcium less than 0.8 mmol/L). Cats should be carefully observed for clinical signs of hypocalcaemia (Box 4-4). Ideally, hypocalcemia should be documented by measurement of total or ionized calcium concentration before therapy is begun. If an acute crisis with clinical signs of tetany develops, a blood sample should be obtained for later evaluation and immediate treatment with IV calcium should be instituted. Management with oral vitamin D and calcium supplementation is initiated immediately after normalization of serum calcium by parenteral administration (see Chapter 16 for further discussion of management of hypocalcemia).

BOX 4-4 Signs Associated with Hypocalcemia in Cats

Anorexia
Restlessness
"Irritability"
Abnormal behavior
Muscle cramping or muscle pain
Muscle tremors, especially of face and ears
Tetany
Convulsions

Calcitriol (Rocaltrol; Roche, Nutley, NJ) is an analogue of activated vitamin D_3 (1,25 dihydroxycholecalciferol) and is the most effective vitamin D product for treatment of hypoparathyroidism. The advantages include quick onset of action, quick dissipation from the body if overdose occurs, and consistent effect. The recommended dose in cats is 0.02 to 0.03 µg/kg/day for 2 to 4 days; the dose is then tapered based on the serum calcium concentration. The maintenance dose is typically 0.005 to 0.015 µg/kg/day. Reformulation by a compounding pharmacy may be required for accurate dosing of calcitriol in cats.

Ergocalciferol (vitamin D_2) is a less expensive form of vitamin D that has to be converted to active vitamin D_3 and is not recommended for treatment of cats with postsurgical hypocalcemia. Ergocalciferol is available in a liquid solution suitable for administration to cats. Usually 10,000 IU given orally once daily increases serum calcium concentrations, but it can take from 5 to 21 days before an effect is seen. Because this vitamin preparation is fat soluble, tissue accumulation and subsequent hypercalcemia can occur. The ultimate dosage interval may be as infrequent as once every 7 to 14 days.

Dihydrotachysterol. Dihydrotachysterol is a synthetic analogue of vitamin D that has a more rapid onset of action than ergocalciferol and a shorter duration of activity; this reduces the risk of tissue accumulation and prolonged iatrogenic hypercalcemia. The starting dose is 0.03 mg/kg given orally once daily for 1 to 7 days until the serum calcium concentration increases into the reference range. The dose should then be decreased to 0.02 mg/kg and further dose adjustments made based on the serum calcium concentration. Unfortunately this product is currently not available commercially, although it can be obtained from some compounding pharmacies.

Calcium Supplementation. To control clinical signs of tetany, IV calcium gluconate should be administered slowly to effect (5 to 15 mg/kg), using ECG monitoring for detecting bradycardia or arrhythmias. Calcium gluconate mixed in an equal volume of saline can then be given subcutaneously two to four times a day, at a dose equal to that initially given intravenously, to control clinical signs of hypocalcemia. Calcium chloride should never be given subcutaneously, because it causes tissue irritation. Oral calcium supplementation can be accomplished with several over the counter calcium lactate or carbonate preparations. The dose is 0.5 to 1 g of calcium per cat/day.

Duration of Hypoparathyroidism. The persistence of hypoparathyroidism after thyroidectomy is variable and difficult to predict. Some cats may need medication for only a few days, whereas others require therapy for the rest of their lives. Recovery of parathyroid function may occur after days, weeks, or months of vitamin D and calcium supplementation. Whenever resolution of hypoparathyroidism is observed, it is assumed that reversible parathyroid damage occurred or that accessory parathyroid tissue has begun to compensate for glands damaged or removed at surgery. It is possible that accommodation of calcium-regulating mechanisms may occur despite absence of PTH (Flanders et al, 1991).

Replacement vitamin D therapy can suppress recovery of endogenous PTH secretion and cause hypercalcemia. After starting vitamin D therapy in any cat, the serum calcium concentration should be monitored prior to each planned dose reduction (every 2 weeks) and the dose gradually decreased if possible based on the results of these measurements. The tapering process can begin days to weeks after the start of vitamin D therapy and may take as long as 2 to 4 months. The goal is to maintain the serum calcium concentration within the low-normal range (8.5 to 9.5 mg/dL). In this range, clinical signs of hypocalcemia do not occur, but there is stimulation of growth and function of any atrophied parathyroid tissue. If accessory parathyroid tissue is present and functional, the medications may be completely discontinued within weeks to months of surgery. If hypocalcemia recurs, therapy with vitamin D and calcium must be reinstituted and is likely to be necessary lifelong.

Hypothyroidism

Subtotal Thyroidectomy. Cats that have undergone unilateral thyroidectomy may transiently develop low serum T_4 values. Thyroid hormone supplementation is not indicated in these cats. The remaining atrophied thyroid regains normal function within 1 to 3 months. Replacement thyroid medication only delays the growth and functional return of atrophied thyroid tissue.

Total Thyroidectomy. Plasma thyroid hormone concentrations decline, often to subnormal levels, within 24 to 72 hours of total thyroidectomy. However, not all cats become permanently hypothyroid, probably because of growth of accessory thyroid tissue in the neck or anterior mediastinum. Thyroid supplementation should only be initiated in the first few weeks after surgery if clinical signs of hypothyroidism (e.g., lethargy and obesity) are noted (see Chapter 3) or if there is a decline in renal function. Cats that are persistently hypothyroid 3 to 6 months after thyroidectomy should also be supplemented.

If thyroid replacement therapy is deemed necessary, L-T_4 at a dose of 0.05 mg to 0.1 mg once or twice a day is recommended. Not all cats will require thyroid supplementation long term, because some may recover endogenous thyroid function. Whether this represents the recovery of cellular function of cells left in situ or developing function in accessory tissue is not clear. Regardless, thyroid replacement therapy can suppress endogenous secretion of thyroid hormone; therefore the need for long-term treatment can only be determined after 8 to 12 weeks following discontinuation of thyroid replacement therapy.

Recurrence of Hyperthyroidism. Because of the potential for recurrence of hyperthyroidism, all cats treated surgically should have their serum thyroid hormone status monitored once or twice yearly (Welches et al, 1989; Swalec and Birchard, 1990). In cats with recurrence of hyperthyroidism, treatment with oral antithyroid medication or with radioactive iodine is recommended, because the incidence of surgical complications is considerably higher among cats undergoing a second surgery than among those undergoing their first surgery (Welches et al, 1989; Naan et al, 2006). Scintigraphy may be useful in these cats to document the location of functioning thyroid tissue and investigate for evidence of thyroid carcinoma.

Persistence of Hyperthyroidism. Rarely, clinical signs of hyperthyroidism persist despite unilateral or bilateral thyroidectomy.

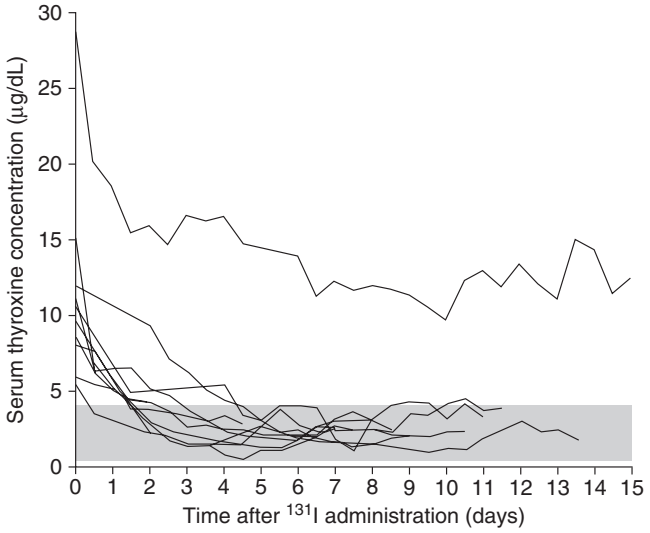

FIGURE 4-38 Serum thyroxine (T_4) concentrations in 10 hyperthyroid cats sampled every 12 hours following iodine-131 (^{131}I) therapy. Note how quickly the T_4 concentrations decline. *Shaded region* represents the normal reference range. (From Meric S, et al.: Serum thyroxine concentrations after radioactive iodine therapy in cats with hyperthyroidism, *J Am Vet Med Assoc* 188[9]: 1038-1040, 1986.)

This is most common in cats undergoing thyroidectomy without prior scintigraphy and implies that not all abnormal thyroid tissue was removed surgically. Such ectopic tissue is most likely to be in the mediastinum, cranial to the heart. This complication can usually be avoided by preoperative thyroid scintigraphy.

Results of Surgery

In most veterinary hospitals, the results of surgery are excellent. Most treated cats respond well with resolution of the hyperthyroidism. Exceptions include cats with concurrent disease (e.g., renal failure), cats with unrecognized ectopic thyroid tissue, and cats that undergo unilateral thyroidectomy but that have adenomatous tissue in the contralateral gland. The major advantages of surgery are that the procedure can be performed by most practitioners; it is relatively inexpensive; it can result in a permanent cure; and morbidity and mortality can be minimized by appropriate presurgical and postsurgical management protocols.

TREATMENT WITH RADIOACTIVE IODINE

Thyroid cells concentrate radioactive iodine as they do stable iodine. Treatment with the radioisotope ^{131}I is an effective and well-established treatment for hyperthyroidism in both cats and humans with a success rate of about 95% in both species. After IV or SC administration, radioactive iodine is transported into hyperplastic and neoplastic thyroid follicular cells and incorporated into thyroglobulin. The percentage uptake of iodide by the thyroid gland in hyperthyroid cats ranges from 10% to 60% (Broome et al, 1987; van Hoek et al, 2008b). The remainder of the administered iodine is excreted in the urine and feces. The isotope ^{131}I emits both gamma rays and beta particles. It is the ionizing effects of the beta particles that are responsible for follicular cell death, manifested histopathologically as cell necrosis and inflammation. In humans, bizarre nuclear changes reminiscent of carcinoma are present cytologically after ^{131}I treatment and may persist for years. Care must thus be taken in interpreting thyroid cytology after radioiodine treatment.

Because beta particles travel only a short distance (1 to 2 mm) in tissue, surrounding tissues (e.g., the parathyroid glands) are spared the effects of ^{131}I. In addition because atrophic thyroid tissue does not concentrate iodine, only functional thyroid tissue is affected by treatment. Thus, once hyperthyroidism is resolved and the normal feedback loops are reestablished, previously atrophic thyroid follicular cells return to function and long-term hypothyroidism is avoided.

Radioactive iodine therapy is now considered the treatment of choice for managing feline hyperthyroidism and is available in numerous locations throughout the United States and other countries. High dose treatment with ^{131}I is also effective for treatment of cats with functional thyroid carcinoma (see Feline Thyroid Carcinoma).

Goal of Therapy

The goal of ^{131}I therapy is to resolve hyperthyroidism and avoid hypothyroidism. In most cats, thyroid hormone concentrations normalize over a period of days to a few weeks (Meric et al, 1986; Peterson and Becker, 1995; Figs. 4-38 to 4-40). Various methods have been evaluated to determine a dose that results in a high success rate but does not induce hypothyroidism. Ideally the lowest effective dose should be used to minimize exposure to hospital personnel and family members.

Dose Determination

The radiation dose received by the thyroid gland is dependent on the dose administered, the thyroidal uptake of the isotope, and the duration of iodine retention by the thyroid gland. Three methods have been used to determine the appropriate dose of ^{131}I for treatment of hyperthyroidism in cats. The dose can be determined by tracer studies, use of a scoring system, or a predetermined fixed dose can be administered. Interestingly all methods appear to result in the same clinical outcome in regard to both efficacy and rate of posttreatment hypothyroidism.

Iodine-131 Dose Determined by Tracer Studies

Prior to administration of therapeutic ^{131}I, tracer studies can be performed to calculate RAIU and effective half-life of the radionuclide using a tracer dose of ^{131}I (Broome, 1988b). The radiation dose is calculated based on the RAIU, tracer half-life, and estimated size of the thyroid gland based on technetium scans and digital palpation (Turrel et al, 1984; Meric et al, 1986; Theon et al, 1994). Using this approach, 94% of cats were euthyroid 1 year after treatment, and 84% were euthyroid 4 years after treatment, whereas 6% of cats became hypothyroid (Theon et al, 1994). Subsequent studies however have shown that the biologic half-life of ^{131}I determined by tracer studies does not correlate well with the biologic half-life after administration of therapeutic doses of radioactive iodine, probably because of the changes in thyroid physiology after administration of large doses of ^{131}I and resultant follicular cell necrosis.

Iodine-131 Dose Determined by Serum Thyroxine Concentration and Severity of Disease

This method of ^{131}I dose determination uses a variety of scoring systems that use the severity of clinical signs, the subjective size of the abnormal thyroid(s), and the serum T_4 concentration

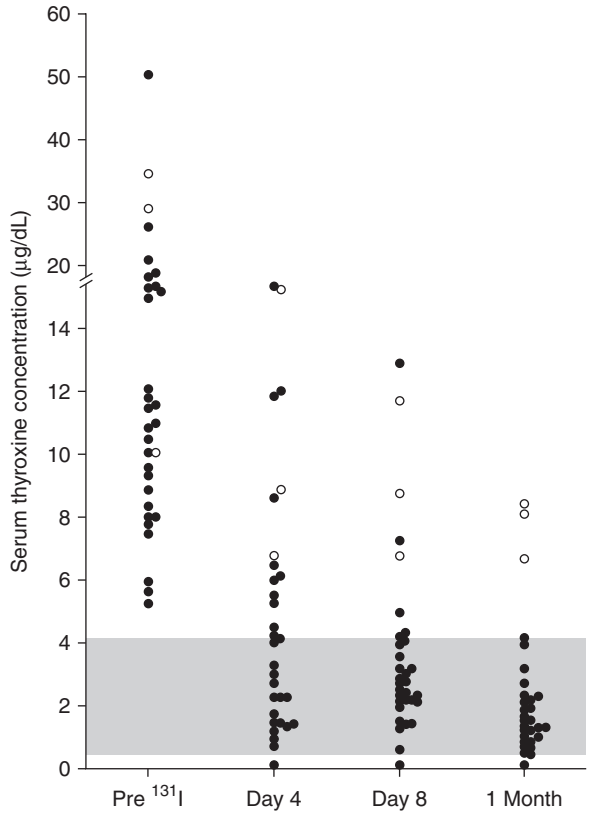

FIGURE 4-39 Serum thyroxine (T_4) concentrations in 31 hyperthyroid cats treated with iodine-131 (^{131}I). These cats were studied before therapy, 4 and 8 days after therapy, at the time of hospital discharge (variable), and 1 month after treatment. Note how quickly the T_4 concentrations decline. *Open circles* represent the three cats that remained hyperthyroid 1 month after treatment. *Shaded area* represents the normal reference range. (From Meric S, et al.: Serum thyroxine concentrations after radioactive iodine therapy in cats with hyperthyroidism, *J Am Vet Med Assoc* 188[9]:1038-1040, 1986.)

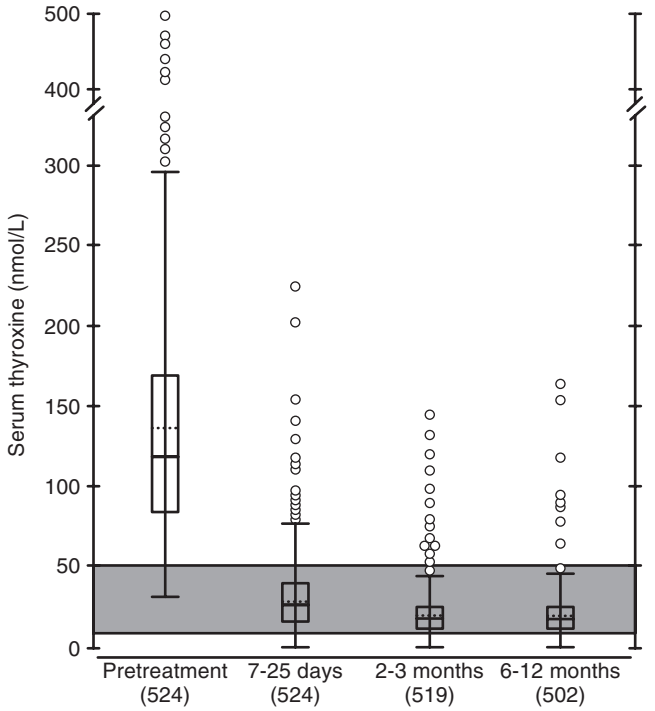

FIGURE 4-40 Box plots of serum thyroxine (T_4) concentrations in 524 cats before and at various times after administration of radioiodine for treatment of hyperthyroidism (see Fig. 4-10 for key). (From Peterson ME, Becker DV: Radioiodine treatment of 524 cats with hyperthyroidism, *J Am Vet Med Assoc* 207[11]:1422, 1995.)

to determine the dose administered (Jones et al, 1991; Mooney,1994; Peterson and Becker, 1995; Table 4-15). In the largest such study, a low (2.5 to 3.5 mCi), moderate (3.5 to 4.5 mCi), or high (4.5 to 6.5 mCi) dose of ^{131}I was administered to hyperthyroid cats (Peterson and Becker, 1995). The median dose administered was 3 mCi. The response to treatment was considered good in 94% of cats. Fewer than 2% of more than 500 cats remained hyperthyroid at 6 months and required a second dose of iodine (see Fig. 4-40). Only 2% developed signs and laboratory data consistent with a diagnosis of hypothyroidism. A similar number of cats (2%) had a relapse of hyperthyroidism within 1 to 6 years of treatment.

Administration of a Fixed Dose Iodine-131

Other investigators have evaluated the efficacy of administration if a fixed dose of ^{131}I for treatment of feline hyperthyroidism (Meric and Rubin, 1990; Chun, 2002; Forrest et al, 1996; Craig, 1993). The most commonly utilized dose reported was 4 mCi. Of 321 cats treated with 4 mCi, a good response to treatment was reported in 96% of cats and 7% were reported to become hypothyroid (Chun, 2002; Meric and Rubin, 1990; Craig, 1993).

There have been no studies that have directly compared these three methods of radioactive iodine dose estimation. All approaches have resulted in a high success rate and low incidence of hypothyroidism and therefore tracer studies are now rarely performed. Whether dose estimation using a scoring system is superior to a fixed dose method requires further study. In theory, such an approach should decrease incidence of hypothyroidism, decrease hospitalization time, and decrease radiation exposure to personnel.

TABLE 4-15 **SCORING SYSTEM USED TO DETERMINE DOSE OF RADIOACTIVE IODINE IN CATS**

FACTOR	CLASSIFICATION	SCORE
Clinical Signs*	Mild	1
	Moderate	2
	Severe	3
Serum T_4 concentration	< 125 nmol/L (10 µg/dL)	1
	125-250 nmol/L (10-20 µg/dL)	2
	> 250 nmol/L (20 µg/dL)	3
Thyroid tumor size†	< 1.0 × 0.5 cm	1
	1.0 × 0.5 to 3.0 × 1.0 cm	2
	> 3.0 × 1.0 cm	3

From Peterson ME, Becker DV: Radioiodine treatment of 524 cats with hyperthyroidism, *J Am Vet Med Assoc* 207(11):1422-1428, 1995.

Cats with a total score of 3, 4, or 5 were treated with a low dose (2.0 to 3.4 mCi; 74 to 130 megabecquerels [MBq]), cats with a total score of 6 or 7 were treated with a moderate dose (3.5 to 4.4 mCi; 130 to 167 MBq), and cats with a total score of 8 or 9 were treated with a high dose (4.5 to 6.0 mCi; 167 to 222 MBq) of radioiodine.

*Severity of clinical signs determined on the basis of number and magnitude of clinical signs and the duration of illness.

†Thyroid tumor size estimated from digital palpation of the thyroid gland; if both thyroid lobes were enlarged, the sizes of both lobes were added together to determine the score.

Treatment of Thyroid Carcinoma

Fewer than 2% to 3% of hyperthyroid cats are diagnosed with thyroid carcinoma. Findings that increase the likelihood of thyroid carcinoma include recurrence after surgery or low dose radioactive iodine treatment, a thyroid mass that is very large or irregular, "fixed" or attached to underlying tissues, or documentation of metastatic disease. On thyroid scintigraphy, some cats with thyroid carcinoma have scans indistinguishable from adenomatous hyperplasia or an adenoma, and some cats have large, irregular masses, more than two masses, or obvious distant metastases on scintigraphy. Confirmation of thyroid carcinoma requires histopathology; however, because some thyroid carcinomas are well differentiated, the diagnosis can be difficult to confirm unless there is evidence of metastasis or capsular or vascular invasion (Guptill et al, 1995). If thyroid carcinoma is confirmed, higher doses of radioactive iodine are required for effective treatment (10 to 30 mCi) (Turrel, 1988; Guptill et al, 1995; Hibbert, 2009). In our experience, the best outcomes are achieved with a combination of surgical debulking followed by administration of a high dose of radioactive iodine (Turrel et al, 1988; Guptill et al, 1995). Other investigators have relied on treatment with high dose radioactive iodine without prior debulking surgery with a good outcome reported in the majority of cases (Hibbert et al, 2009). The decision as to whether to perform debulking surgery depends on whether prior surgery has been performed, whether there is histopathologic confirmation of thyroid carcinoma, and the location of the neoplastic tissue. Risks of surgery include hypoparathyroidism, injury to structures (e.g., the recurrent laryngeal nerve), and the additional expense. Risks of treatment without surgery include the consequences of extensive tissue necrosis if there is a large volume of neoplastic tissue, especially if the thyroid tissue is intrathoracic, and the possibility of variable uptake of iodine by cells within the tumor such that not all neoplastic cells are destroyed. Ultimately the decision should be made on a case by case basis. Longer hospitalization can be anticipated if cats receive high doses of ^{131}I due to the additional time required for isotope excretion. Most cats treated with such high doses of radioactive iodine will become permanently hypothyroid.

Route of ^{131}-Iodine Administration

Although most early studies utilized the IV route of administration, ^{131}I can be safely administered subcutaneously, and studies have demonstrated that administration of radioactive iodine IV or SC is equally effective. Use of the SC route is safer for personnel and, subjectively, less stressful for the cat (Théon et al, 1994). Although commonly used in humans, oral ^{131}I is not recommended because of the increased risk of exposure to radiation by the personnel dosing the cats and the risk of vomiting after administration. Vomiting of the isotope not only results in inadequate dose administered but also could result in contamination of the nuclear medicine facility.

Prior Treatment with Methimazole

Methimazole inhibits synthesis of thyroid hormones but does not interfere with iodine trapping by follicular cells. In people, PTU lowers the efficacy of subsequent radioactive iodine treatment, and continuous treatment with methimazole during treatment decreases the final cure rate. Pretreatment with methimazole up to 7 days prior to radioactive iodine treatment does not influence either failure rate or rate of hypothyroidism (Andrade et al, 2001; Shi et al, 2009). The reasons for radioresistance due to treatment with anti-thyroid drugs are poorly understood. PTU may neutralize iodinated free radicals produced by radiation exposure. Both drugs may also decrease retention of radioactive iodine in the thyroid gland by inhibiting organification of iodine. Withdrawal of methimazole increases iodine uptake in the thyroid gland for up to 2 weeks. This could result in increased uptake of ^{131}I and mitigate the previous effects. Most clinical studies in cats have not demonstrated a difference in radioiodine efficacy in cats treated with methimazole prior to ^{131}I treatment (Peterson and Becker, 1995; Chun, 2002); however, most treatment centers still recommend that methimazole be withdrawn 1 to 2 weeks prior to treatment.

Prior Treatment with Limited Iodine Diets

Treatment with iodine-limited diets increases iodine uptake into the thyroid gland by 60% to 600% (Scott-Moncrieff, unpublished data). Theoretically this could increase thyroidal sensitivity to radioiodine treatment and increase the risk of hypothyroidism. Alternatively pretreatment with these diets could improve treatment response and, perhaps, reduce the dose of radioisotope required for a cure. This might reduce radiation exposure to the cat and personnel, and reduce cost. The increased iodine uptake returns to baseline by 2 weeks after withdrawal of the diet. Thus iodine limited diets should be discontinued 2 weeks prior to radioiodine treatment until further studies have evaluated this interaction.

Radiation Safety

In-Hospital

Radioactive iodine is a hazardous material with a long half-life (8 days). As such, ^{131}I-treated cats are a potential source of hazardous radiation to humans and to other animals due to gamma radiation released from ^{131}I trapped in the thyroid gland of the cat, as well as surface contamination of the cat's coat and paws by urine and feces containing radioactive iodine (so called "removable activity"; Chalmers, 2006). Any facility using radioactive iodine must adhere to national and state regulations regarding its use to minimize human exposure. Isolation of treated cats in an approved facility is required for a variable period that depends upon the dose administered and state regulations. Each animal is kept in an individual cage, and all urine and feces are disposed of as radioactive waste until the cat has a radioactivity level that is considered appropriate for release. Release criteria are based on measurement of gamma emissions measured with a survey meter either at the patient surface or at a specified distance from the neck (Chalmers, 2006). Surface emissions are correlated with urine concentrations of ^{131}I (Feeney, 2003). The principles of "as low as reasonably achievable" (ALARA) should be followed. Contact with hospital personnel should be limited to that required for adequate care of the cat. Attending personnel must wear protective clothing and gloves, be well trained in principles of radiation safety, and are required to carry regularly monitored dosimeters. The duration of hospitalization varies between facilities and ranges from 3 days to 3 weeks.

After Release from the Hospital

Owners should be given instructions on the proper care of their pet for the first few weeks after therapy (Fig. 4-41). Each cat should wear a collar with a "Caution Radioactive Material" label for 2 weeks and must be strictly confined to the home or kept on

RELEASE CRITERIA AND OWNER PRECAUTIONS
FOR ANIMALS TREATED WITH RADIOACTIVE IODINE-131

IN HOMES WITHOUT PREGNANT WOMEN AND WITHOUT CHILDREN UNDER 12 YEARS OF AGE

*The maximum exposure rate (dorsal to thyroid) at one foot from the pet shall not exceed **1 mR/hr.***

Animals released to their owners will contain a small amount of radioactivity and will continue to excrete low levels of radioactivity for a period. The amount of radiation exposure you may receive is well below levels that result in significant risk of harmful effects. The owners must sign a consent form to protect themselves and other members of the public. In this consent they will agree to the following:

Keep cats in their carriers for the drive home.

A. Maintain a distance of six feet between you and your pet except for brief periods of necessary care.

B. Children and pregnant or nursing women should have **NO** contact with the pet until the collar with radioactive label is removed.

C. Minimize contact with the pet, including arrangement for a separate sleeping room away from people.

D. The pet must wear a collar or tag with a "Caution Radioactive Material" label attached for 2 weeks.

Date for collar removal _____.

E. Ensure that if the pet is a cat, it will remain indoors and use its litter box. The box should be lined with plastic. Change the litter frequently, disposing of it in the outside trash or by flushing it down the toilet.

F. Care must be taken to wash hands after handling the animal, its food dishes, or litter pans.

G. Ensure that your cat uses a litter box and line it with plastic.

H. These restrictions will remain in force until the levels of activity decrease to insignificant levels. This time period will be 2 weeks.

Measured exposure		
(mR/hr at 1 foot):	Date:	Measured by:

As a condition for release of my pet following radioiodine therapy, I agree to the restrictions above:

I also understand the animal contains a small level of radioactivity and will excrete low-level radioactivity for a period of time. Minimizing contact with the pet, washing hands after contact, and arranging for the pet to sleep in another area will minimize my radiation exposure.

_____ _____

Signed Date

FIGURE 4-41 Example of a form used to inform cat owners about release criteria and owner precautions for animals treated with radioactive iodine.

a leash. Adults are recommended to stay 6 feet or farther away from the cat except for brief periods needed for necessary care, including arrangement for a separate sleeping area away from people. Children and pregnant women should have *no* contact with the cat until the collar has been removed. To further reduce any chance of unwanted exposure, it is recommended that owners line the litter pan with plastic. The used litter should be disposed of in the outside trash or by flushing flushable litter down the toilet. The hands should be washed thoroughly after handling of the cat, its food dishes, or the litter pan.

Rechecks and Hypothyroidism. Recheck evaluations are recommended 1, 3, 6, and 12 months following treatment for

a complete history, physical examination (including weight and blood pressure measurement), serum biochemical profile, and measurement of serum T_4 concentrations. Most cats are euthyroid or have a serum T_4 concentration below the reference range at the time of hospital discharge. A small percentage of cats (15%) are still hyperthyroid at the time of discharge but become euthyroid within 6 months after treatment (Peterson and Becker, 1995). Some cats treated with radioactive iodine become transiently or permanently hypothyroid after radioactive iodine treatment. Persistent hypothyroidism after treatment is a risk factor for azotemia. Measurement of total T_4 together with TSH can help distinguish true hypothyroidism from NTIS (see Baseline Serum Thyrotropin Concentration). Cats that are still hypothyroid 6 months after treatment, those that develop clinical signs of hypothyroidism, and those that have progressive azotemia and a low serum T_4 concentration should be supplemented with L-T_4 at a dose of 0.05 to 0.1 mg of L-T_4 given orally once or twice daily. Cats that continue to have abnormally increased serum T_4 concentrations 6 months after radioiodine therapy may need to be retreated with ^{131}I. These cats are at higher risk of thyroid carcinoma, and this possibility should be investigated so that a higher dose of isotope can be administered if appropriate (see Feline Thyroid Carcinoma).

Prognosis for Resolution of Hyperthyroidism. More than 93% of cats treated with radioactive iodine become euthyroid after one treatment. Failure to respond to the first treatment is most common in cats that have large tumors, severe clinical signs, and very high serum T_4 concentrations (Peterson and Becker, 1995). Cats with thyroid carcinoma also fail to become euthyroid after low dose ^{131}I treatment. There are no reports of adverse effects on organs other than the thyroid glands after low dose ^{131}I therapy.

Need for Retreatment

Approximately 2% to 5% of ^{131}I-treated hyperthyroid cats require a second treatment (Peterson and Becker, 1995). Several factors, such as dose administered, thyroid gland size, thyroid gland pathology (adenoma, adenomatous hyperplasia, or carcinoma), and iodine excretion rate, may contribute to an incomplete response to an initial therapeutic dose of ^{131}I. Errors in radioisotope administration can also occur and explain a treatment failure. Prior to administration of a second treatment, the reason for failure should be evaluated. Although a second standard dose is effective in most cats, consideration should be given to obtaining an incisional or excisional thyroid biopsy in cats in which thyroid carcinoma is suspected. In cats with thyroid carcinoma, high dose radioactive iodine treatment may be necessary (see Feline Thyroid Carcinoma).

Recurrence

A small percentage of cats (less than 3%) develop recurrence of hyperthyroidism at a median time of 3 years (range 1 to 6 years) after treatment with radioactive iodine. No predictors of relapse have been identified. There was no difference between the T_4 concentration or the dose of radioactive iodine used between cats that did and did not relapse (Peterson and Becker, 1995). It is likely that relapse in these cats is due to development of new foci of autonomous tissue arising from new mutations.

NUTRITIONAL MANAGEMENT OF FELINE HYPERTHYROIDISM

In mammals, the only known function of iodine is incorporation into thyroid hormones; diets deficient in iodine cause hypothyroidism and goiter. Published guidelines for iodine requirements for healthy cats have changed over the years, but current recommendations are that healthy cats should consume at least 0.46 mg/kg of dry food (Wedekind et al, 2010). There are no published guidelines for iodine requirements of hyperthyroid cats. Dietary iodine restriction to less than 0.3 mg/kg reduces the circulating thyroid hormone concentrations to the normal range in hyperthyroid cats (Melendez et al, 2011a; 2011b; Yu et al, 2011; van der Kooij et al, 2013), suggesting that dietary iodine restriction has potential as an alternative management strategy for feline hyperthyroidism.

Commercial cat foods are commonly supplemented with iodine using calcium iodate or potassium iodide. Studies suggest that there is huge variability in the concentration of iodine in commercial cat foods because of the variability of iodine content of individual ingredients. Ingredients that typically contain high concentrations of iodine include fish, shellfish, and fresh meats. The range of iodine content in commercial cat foods varies by a factor of 30, with the largest variation being found in canned cat food (Ranz et al, 2002; Mumma et al, 1986; Johnson et al, 1992; Edinboro et al, 2013).

Role of Dietary Iodine in the Pathogenesis of Disease

The variability in iodine content of commercial cat food and the similarities between feline hyperthyroidism and toxic nodular goiter in humans have prompted hypotheses, so far unsupported by research, that low iodine intake, high iodine intake, or wide variability in iodine content has contributed to the current increased prevalence of feline hyperthyroidism. Whether or not iodine content of the diet is important in the pathogenesis of feline hyperthyroidism, it is likely only one of many potential contributing factors. It is also clear that the final common pathway in the pathogenesis of feline hyperthyroidism is the presence of mutations in subsets of thyroid follicular cells that lead to autonomous thyroid hormone synthesis. Once thyroid follicular cells have become autonomous, the cellular changes are not reversible or likely to be influenced by dietary change. In other words, limiting the iodine content of the food can lead to normalization of thyroid hormone synthesis whether or not the iodine content of the diet is a factor in the underlying pathogenesis of feline hyperthyroidism.

Iodine-Limited Diets for Management of Feline Hyperthyroidism

In a series of studies involving 33 cats with naturally occurring hyperthyroidism, the effects of feeding diets containing from 0.15 mg/kg to 1.9 mg/kg dietary iodine concentration were investigated (Melendez et al, 2011a; 2011b; Yu et al, 2011). All cats studied were consuming commercial diets containing 1.9 mg/kg iodine at the time of diagnosis and were confirmed to be hyperthyroid by standard methods. The iodine content of the control and experimental diets was confirmed by epiboron neutron atomic activation—an extremely sensitive assay method. Four to 8 weeks after consumption of a diet containing 0.17 mg/kg or less of dietary iodine, all cats had a total T_4 within the reference range. Eight of nine cats consuming a diet of 0.28 mg/kg iodine were euthyroid within 3 to 12 weeks, whereas the proportion of cats becoming euthyroid was lower when consuming diets containing higher concentrations of iodine (0.39 mg/kg [7 of 9 cats] or 0.47 mg/kg [4 of 5 cats]). More extensive thyroid profiles were performed in 14 of the cats; fT_4, total T_3, free T_3, and TSH concentrations were within the laboratory reference range while consuming the iodine-restricted diet. There was no change in renal parameters after restoration of euthyroidism, which is surprising because decreased

TABLE 4-16 RESPONSE TO TREATMENT WITH AN IODINE-LIMITED DIET IN 10 HYPERTHYROID CATS

CAT	PRE THYROXINE µG/DL (RR 2.5-4.6)	4-8 WEEK THYROXINE µG/DL (RR 2.5-4.6)	PRE CREATININE MG/DL	POST CREATININE MG/DL
1	13.3	2.8	1.2	1.4
2	6.4	1.7	1.0	0.7
3	12.4	6.5*	0.8	0.6
4	8.7	4.4	0.7	0.7
5	8.0	4.3	0.6	
6	8.9	3.4	0.6	0.4
7	13	2.6	0.8	0.7
8	8.7	2.8		
9	5.9	3.1	1.4	1.0
10	9.4	2.9		

RR, Reference range.

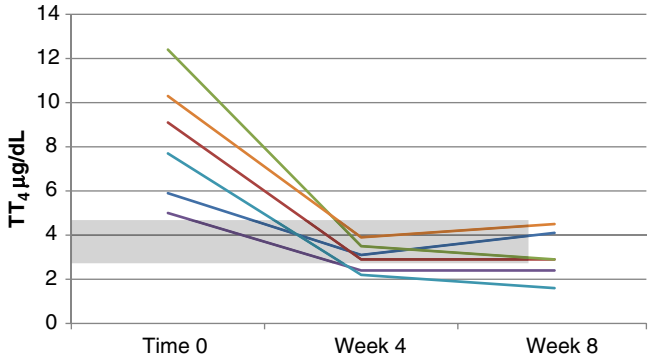

FIGURE 4-42 Change in total thyroxine (T_4) and free T_4 (fT_4) in six cats consuming an iodine-limited diet over an 8 week period (unpublished data).

GFR associated with reestablishment of euthyroidism results in azotemia in 15% to 49% of previously non-azotemic cats treated by other methods (Williams et al, 2010).

Clinical Experience

There is now a commercially available iodine-limited diet marketed for management of feline hyperthyroidism (Prescription Diet y/d). The diet is similar in formulation to Prescription g/d but has an iodine content of 0.2 mg/kg or less and is available as both canned and dry food. In a retrospective study of 49 client-owned hyperthyroid cats fed this diet exclusively, serum total T_4 became normal in 71% of cats between 21 and 60 days and 96% of cats between 61 and 180 days respectively. Cats with a higher starting total T_4 took longer to become euthyroid. The median heart rate, body weight, and serum creatinine did not change over the 6 months of the study (Scott-Moncrieff, unpublished data). The reasons for a lack of weight gain in these cats may reflect the influence of concurrent disease or subclinical hyperthyroidism in some cats.

Indications for Nutritional Management

Nutritional management is an alternate option for short-term management of hyperthyroidism or longer-term management of hyperthyroidism in cats that are not good candidates for definitive treatment of their hyperthyroidism. As with methimazole, limiting the intake of dietary iodine limits thyroidal synthesis of thyroid hormone, but the autonomous thyroid adenoma is still present. Therefore definitive treatment with ^{131}I or thyroidectomy should be recommended if possible; however, for cats that have concurrent nonthyroidal illness, for cats that have adverse effects of methimazole, for owners with financial constraints, or for owners who are unable to medicate their cats, nutritional management is a feasible alternative. Nutritional management is not a good option for cats that do not find the food to be palatable, for outdoor cats with access to other sources of dietary iodine, or for cats that need to be on a controlled diet to manage other concurrent illnesses, such as inflammatory bowel disease, allergic dermatitis, or heart disease. For cats in early renal failure, Prescription Diet y/d may be an acceptable diet because it is supplemented with omega-3 fatty acids and contains controlled amounts of phosphorus, sodium, and high-quality protein (36% dry matter basis). Cats with more severe renal failure may need to be fed a diet formulated for management of renal failure. Hyperthyroid cats in multicat households need to be fed individually, and access to food of other pets in the household must be prevented. Alternatively the iodine-limited diet can be fed to all cats in the household providing the euthyroid cats are supplemented daily with a food with higher iodine content.

Expected Outcome

More than 90 percent of hyperthyroid cats become euthyroid when fed a limited-iodine diet exclusively (Table 4-16; Fig. 4-42). The most common reason for failure to control the hyperthyroidism is access to iodine-containing food, such as treats, human food, or other pet foods. Even small amounts of other iodine-containing foods can result in an increase in the T_4 concentration. For this reason, cats being managed with an iodine-limited food need to be indoor cats, and the owner needs to feed the diet exclusively. For owners who consider it important to give their cats treats, one strategy is to feed the dry Prescription Diet y/d diet predominantly and give the canned Prescription Diet y/d as a treat. In cats that do not become euthyroid within 4 to 8 weeks of starting the limited-iodine diet, a detailed history should be investigated for evidence of other sources of iodine. Possible sources in addition to access to other pet foods include well water, medications or supplements, contaminated food bowls, and human food.

Long-Term Nutritional Management

Nutritional management of feline hyperthyroidism is an entirely new approach that does not have a parallel in people. In human medicine, low-iodine diets are only used for short periods of time prior to nuclear imaging to screen for metastasis in patients with thyroid carcinoma. For this reason the long-term consequences of dietary restriction of iodine are unknown. Iodine may have anti-oxidant and anti-inflammatory properties as well as playing a role in prevention of breast cancer and fibrocystic breast disease (Patrick, 2008). One concern is that cats managed long-term with iodine-limited diets might develop a clinically significant goiter due to continued follicular cell hyperplasia; additionally, management using an iodine-limited diet could increase the risk of transformation of adenomatous nodules into thyroid carcinoma. In a report of eight cats with thyroid carcinoma, two cases had both adenomatous changes and carcinoma cells contained within one gland, suggesting that the carcinoma could

have arisen from a background of benign neoplasia (Hibbert et al, 2009). These potential risks are also of concern in cats treated chronically with methimazole. For these reasons, the thyroid gland should be palpated routinely in cats on a limited-iodine diet, and definitive therapy with radioactive iodine treatment should be recommended if clinically significant thyroid gland enlargement is identified.

Transitioning from Methimazole to a Limited-Iodine Diet

Iodine-limited diets should not be used concurrently with methimazole for management of feline hyperthyroidism because of the risk of severe hypothyroidism. Methimazole should be discontinued immediately prior to starting an iodine-limited diet. Transient hyperthyroidism may occur during the transition, but this is preferable to hypothyroidism because of the deleterious influence of hypothyroidism on the GFR.

Transitioning from a Limited-Iodine Diet to Other Treatments

If nutritional management fails to control hyperthyroidism despite investigation for other sources of iodine, another diet should be reinstituted and alternative treatment of the hyperthyroidism considered. A washout period is not necessary in cats started back on methimazole treatment, because thyroid hormone synthesis increases very rapidly once the limited iodine diet is discontinued. Little is known about the effect of a limited-iodine diet on response to radioactive iodine. In theory, increased iodine trapping by the thyroid gland due to the lack of iodine could make the normal atrophic thyroidal tissue more susceptible to the effects of radioactive iodine and increase the risk of hypothyroidism after ^{131}I treatment. Conversely consumption of a limited iodine diet could be used to decreased the required dose of ^{131}I needed to reestablish a euthyoid state. In eight hyperthyroid cats that were euthyroid after consumption of an iodine limited diet, radioisotope scans using ^{123}I revealed increased radio-isotope uptake of 60% to 600% (Scott-Moncrieff, unpublished data).

Recommended Monitoring

It is recommended that cats being managed with an iodine-limited diet be reevaluated by physical examination and measurement of a BUN, creatinine, USG, and total T_4 monthly until establishment of euthyroidism. As for methimazole treated cats the ideal range for the total T_4 is within the lower half of the reference range. Cats should then be monitored every 6 months if otherwise healthy; cats with concurrent illnesses may require more frequent monitoring.

FELINE THYROID CARCINOMA

Malignant thyroid neoplasia is diagnosed in approximately 1% to 3% of cats with hyperthyroidism (Peterson and Becker, 1995). Most malignant thyroid tumors in the cat are functional tumors with follicular carcinomas being most common. Nonsecretory thyroid tumors (tumors that do not produce excess concentrations of thyroid hormone but do concentrate iodine) and nonfunctional thyroid tumors (tumors that neither secret thyroid hormone nor concentrate iodine) have been described in cats but are rare (Turrel et al, 1988; Guptill et al, 1995).

Clinical Features

The signalment and clinical signs of cats with thyroid carcinoma are similar to those of cats with benign hyperthyroidism. Many cats have a history of prior thyroidectomy, and in addition to the typical clinical signs of hyperthyroidism, voice change has been reported. Palpable cervical mass masses are present in 71% of cases. In cats with thyroid carcinoma, thyroid gland palpation may be similar to that of a hyperthyroid cat with benign disease; however, in other cases, the masses associated with thyroid carcinoma are large and fixed rather than freely moveable and attached to underlying or overlying tissues.

Diagnosis

Common abnormalities on the minimum data base are similar to cats with benign thyroid disease with the exception of occasional hypercalcemia. Radiographic abnormalities may include cardiomegaly, evidence of congestive heart failure, mediastinal masses, and evidence of pulmonary metastasis. The majority of cats with thyroid carcinoma have increased basal serum T_4 concentrations. No differences have been identified in the range of serum T_4 concentrations in cats with benign and malignant thyroid tumors. A nonsecretory or nonfunctional tumor should be suspected if a thyroid tumor is identified but T_4 concentration is normal and there are no clinical signs of hyperthyroidism. Nuclear scintigraphy using sodium pertechnetate (technetium-99m [^{99m}Tc]) is valuable in the evaluation of cats with suspected malignant thyroid tumors. In cats with thyroid carcinoma, a ^{99m}Tc scan may demonstrate patchy or irregular uptake of isotope, extension of isotope uptake down the neck and into the mediastinum, and evidence of distant metastasis (see Fig. 4-29); however, in some cats with thyroid carcinoma scintigraphic findings may be similar to the scans of cats with thyroid adenomatous hyperplasia or adenoma. Conversely, scans that reveal uptake by multiple masses in the cervical region or masses extending into the cranial mediastinum in some cases may be benign ectopic tissue. Thus scintigraphy alone cannot definitively distinguish between adenomatous hyperplasia and thyroid carcinoma. Bronchogenic carcinoma may have scintigraphic findings that may be confused with those of thyroid tumors. Nonfunctional thyroid tumors may or may not take up ^{99m}Tc depending upon the degree of differentiation of the tumor.

Definitive diagnosis of thyroid carcinoma requires histopathologic examination of excised tissue. Because the majority of feline thyroid tumors are benign, thyroid carcinoma may not be suspected on the initial evaluation. Factors that should increase the index of suspicion for thyroid carcinoma include recurrence of hyperthyroidism after previous thyroidectomy(ies), failure to respond to low dose radioactive iodine treatment, presence of multiple palpable cervical nodules, and cervical nodules that are firmly attached to underlying or overlying structures. Large, palpable, thyroid masses that compress surrounding structures may be due either to thyroid carcinoma or benign thyroid cyst. Thyroid carcinoma should also be suspected if scintigraphy reveals multiple areas of radionuclide uptake and irregular or patchy isotope uptake.

Cytologic characteristics are usually unhelpful in differentiation of benign from malignant thyroid tumors, because pleomorphism, anaplasia, and increased mitotic rate are not consistent features. Features that distinguish malignant from benign tumors include local tissue invasion, regional lymph node involvement, and distant metastasis. Metastasis has been reported to occur in up to 71% of cats with thyroid carcinoma.

Treatment

Although cats with thyroid carcinoma may show clinical improvement when treated with anti-thyroid drugs, these drugs are not

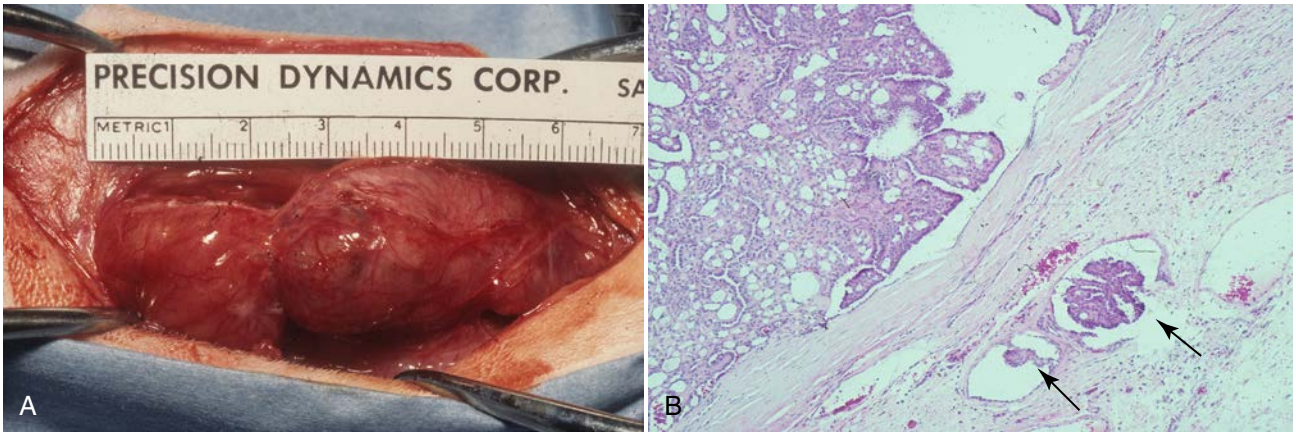

FIGURE 4-43 **A,** Thyroid carcinoma at time of cervical exploratory. Note the large size of the tumor and the irregular appearance. **B,** Photomicrograph of a thyroid follicular carcinoma in a different cat demonstrating extracapsular foci and possible lymphatic or blood vascular invasion *(arrows).*

recommended for several reasons. Anti-thyroid drugs may increase release of TSH from the anterior pituitary gland by decreasing secretion of T_4 and exacerbate tumor growth due to the tropic effects of TSH. Furthermore, anti-thyroid drugs are not cytotoxic and will neither slow progression of local tumor growth nor metastasis to distant organs. The only indication for using anti-thyroid drugs in the management of thyroid carcinoma is for the purpose of initial clinical stabilization prior to ^{131}I therapy or thyroidectomy. Beta blockers (e.g., propranolol or atenolol) are useful in hyperthyroid cats that require stabilization of cardiac disease prior to surgery or ^{131}I therapy.

Thyroidectomy is the initial treatment of choice in cats with suspected thyroid carcinoma, because the diagnosis must be confirmed by histopathology (Fig. 4-43) and because complete excision can be curative. Scintigraphy should always be performed prior to thyroidectomy. As much tumor as possible should be excised. Thyroid biopsy, followed by adjunctive therapy, may be more appropriate in cats with invasive or infiltrative masses. Preservation of the parathyroid glands is more difficult in cats with invasive thyroid carcinomas treated surgically, and postoperative monitoring of serum calcium concentrations is essential for cats undergoing bilateral thyroidectomy. A cat exhibiting signs of hypocalcemia after thyroidectomy (e.g., muscle tremors, tetany, or convulsions) should be treated with appropriate calcium and vitamin D supplementation (see Management of Postoperative Hypocalcemia for approach to treatment of hypocalcemia).

Even if all of the visible tumor is removed, many thyroid carcinomas will recur within weeks to months. Thus, in histopathologically confirmed thyroid carcinoma, thyroid scintigraphy should be repeated 4 to 8 weeks after thyroidectomy in order to evaluate the success of surgical removal. If tumor recurrence is confirmed, treatment with high dose ^{131}I is recommended. Following treatment with ^{131}I, reevaluation of serum T_4 concentrations and ^{99m}Tc scans should be performed every 3 to 6 months. If recurrence is not detected in these follow-up evaluations after 1 year, the period between evaluations can progressively be lengthened.

Treatment with ^{131}I is indicated in cats with non-resectable thyroid carcinoma and in cats with evidence of metastasis or recurrence after thyroidectomy, providing the neoplastic tissue concentrates iodine or technetium on scintigraphy. Higher doses of ^{131}I (10 to 30 mCi) are required to successfully treat cats with thyroid carcinoma than are required to treat cats with thyroid adenoma, because the thyroid tissue may concentrate iodine less effectively and because there is often a larger mass of thyroid tissue present. A combination of surgical resection and postoperative treatment with high doses of ^{131}I is an effective approach to treatment. Surgical removal followed by administration of 30 mCi ^{131}I in seven cats with thyroid carcinoma resulted in survival times ranging from 10 to 41 months (Guptill et al, 1995), and none of the cats died due to thyroid carcinoma. Higher doses of ^{131}I necessitate a longer hospitalization time to allow the isotope time to decay to activity levels compatible with discharge to the home environment. The majority of cats treated with higher doses of ^{131}I become permanently hypothyroid and require supplementation with L-T_4. Treatment with 30 mCi ^{131}I as the sole mode of therapy has also been reported to result in a successful outcome in cats with feline thyroid carcinoma, although one of eight cats did not respond to treatment and one cat had recurrence 6 months after treatment (Hibbert et al, 2009). Adverse effects of high dose ^{131}I may include transient dysphagia and hypothyroidism. In one study, pancytopenia was identified 6 months after high dose ^{131}I treatment, but the relationship with the radioiodine treatment was unclear because the cat was also feline immunodeficiency virus (FIV) positive.

Thyroid Cysts

Thyroid cysts may occur associated with thyroid adenomatous hyperplasia, adenoma, or thyroid carcinomas. The cystic lesion may be palpated as a thin walled fluctuant mass that usually collapses and is non-palpable once the fluid has been removed (Fig. 4-44). The total T_4 concentration of the cystic fluid is typically high (Hofmeister et al, 2001). Diagnosis of thyroid cysts is best made by a combination of palpation and aspiration. Ultrasound examination can be helpful in evaluation of thyroid glands with cystic changes (Barberet, 2010). Treatment of large thyroid cysts is best accomplished by surgical resection of the cyst and associated thyroid tissue rather than radioactive iodine therapy.

MISCELLANEOUS THERAPIES

Percutaneous Ethanol and Heat Ablation Injection for Treatment of Feline Hyperthyroidism

Both ultrasound guided ethanol injection and percutaneous radiofrequency heat ablation have been evaluated for treatment of feline

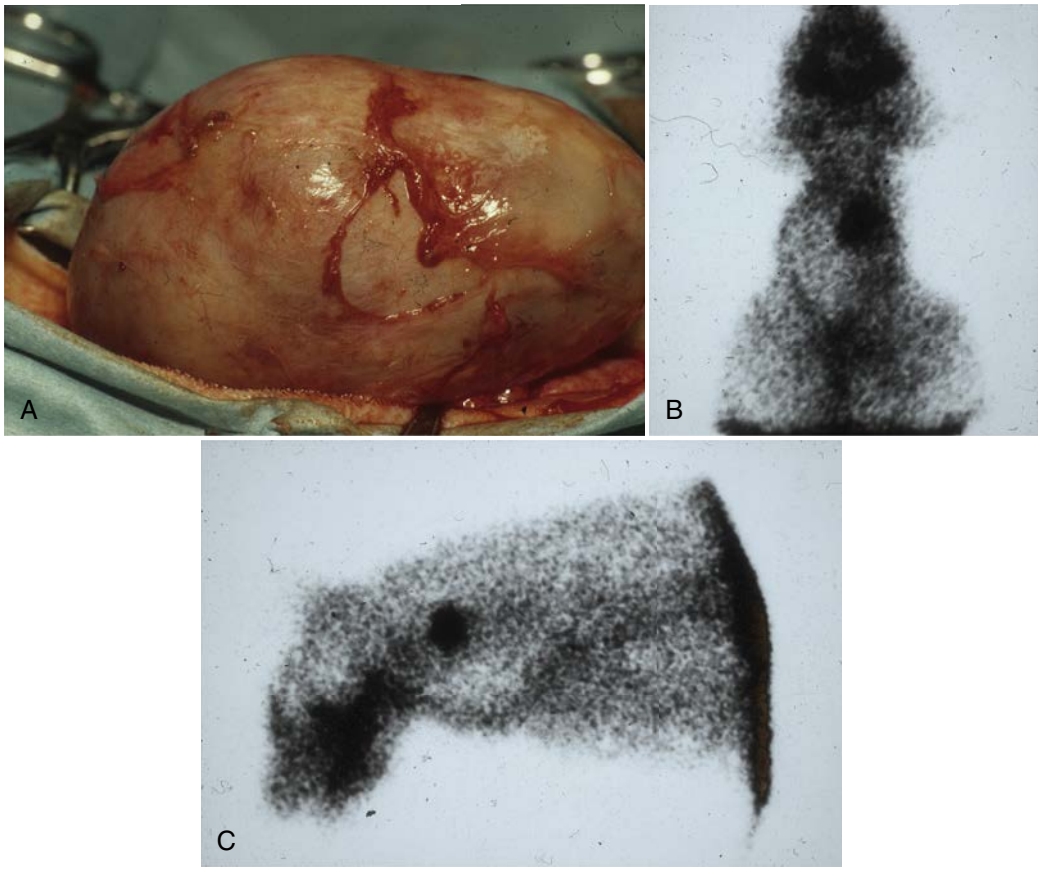

FIGURE 4-44 **A,** Photograph of a large thyroid cyst in a hyperthyroid cat during thyroidectomy and surgical resection of the thyroid cyst. **B** and **C,** Ventral and lateral thyroid technetium-99m (^{99m}Tc) scans from the same cat. Note that the cyst appears as a large "cold" area surrounded by a thin rim of tissue that takes up ^{99m}Tc. The majority of the thyroid gland is medial and dorsal to the cyst.

hyperthyroidism (Goldstein et al, 2001; Wells et al, 2001; Mallery et al, 2002). Problems with frequent recurrence and complications in cats with bilateral thyroid disease have limited the practicality of these approaches. For more information see Feldman and Nelson, *Canine and Feline Endocrinology and Reproduction,* ed 3.

Beta Blockers

Beta blockers may be useful to control tachycardia and other supraventricular tachyarrhythmias especially in cats that do not tolerate anti-thyroid drugs. Beta blockade results in slowing of the heart rate, lowers the end-diastolic pressure of the left ventricle, prolongs the ventricular filling time, decreases the oxygen demand of the myocardium, acts as an antiarrhythmic agent, and reduces outflow pressure gradients. Beta blockers may also reduce the systolic blood pressure and have been recommended for control of hypertension in hyperthyroidism; however, studies suggest that efficacy is limited in hyperthyroid cats with hypertension (Henik et al, 2008). More potent anti-hypertensive drugs (e.g., amlodipine) should be utilized in hyperthyroid cats with clinically significant hypertension.

Propranolol is a nonselective beta blocker that has the added advantage of also decreasing conversion of T_4 to T_3; however, propranolol can cause bronchospasm in cats with reactive airway disease because of blockade of beta$_2$ receptors in airway smooth muscle. Propranolol is rapidly absorbed from the gastrointestinal tract, and the plasma half-life is approximately 3 to 6 hours. The recommended dose of propranolol is 2.5 to 5 mg every 8 to 12 hours. The dose should be started at the lower end of the range and then slowly increased until the goals of controlling tachycardia and arrhythmias are achieved. Propranolol is a potent myocardial depressant and should be used with extreme caution if heart failure is present. In a study of induced hyperthyroidism, the half-life of propranolol was not affected by hyperthyroidism (Jacobs et al, 1997). After oral administration, total body clearance was lower and the peak plasma propranolol concentration, fractional absorption, and area under the curve were higher in hyperthyroid cats compared with euthyroid cats. This indicated increased bioavailability in thyrotoxicosis, which was calculated to exceed 100% and suggested enterohepatic recycling of the drug. The findings of this study support starting at the lower end of the dose in hyperthyroid cats.

Atenolol is a selective beta$_1$ blocker with potential advantages over propranolol, including more selective β_1-adrenoreceptor blocking action and longer duration of action. Atenolol is rapidly absorbed from the gastrointestinal tract in cats and has a half-life of 3½ hours in cats. The duration of effect persists for at least 12 hours in healthy cats (Quiñones, 1996). Atenolol is used at a dosage of 6.25 to 12.5 mg per cat mg every 12 to 24 hours. The starting dose should be at the low end of the range, and the dose is then gradually increased depending upon the response.

Stable Iodine

Although the thyroid gland requires small amounts of iodide for hormone synthesis, large amounts given over a brief period

(1 to 2 weeks) may result in transient hypothyroidism in normal individuals due to the Wolff-Chaikoff effect. High doses of iodide inhibit organification of thyroid hormone, which results in reduced secretion. Iodide can be rapidly effective in ameliorating increased serum thyroid hormone concentrations associated with hyperthyroidism. Beneficial effects are seen in 7 to 14 days and include improvement in clinical signs, as well as reduction in the size and vascularity of the thyroid gland. Iodide has a role in the treatment of thyroid storm in humans. Unfortunately, it is rarely possible to achieve complete remission of hyperthyroidism or to maintain any degree of control for more than a few weeks with iodide, but it may be useful when used in conjunction with beta-blockers to control the disease preoperatively in cats that do not tolerate methimazole (Foster and Thoday, 1999). Potassium iodate (KI) at a dose of 21 to 42 mg every 8 hours was administered daily beginning 10 days prior to surgery in conjunction with propranolol. The KI was placed in a small gelatin capsule to avoid the aftertaste that may bother some cats. The most common side-effect of treatment with KI was gastrointestinal upset.

Iodinated Radiographic Contrast Agents

Oral cholecystographic agents (e.g., calcium ipodate and iopanoic acid) acutely inhibit peripheral conversion of T_4 to T_3 and may decrease T_4 synthesis. Blocking of the conversion of circulating thyroid hormone has been demonstrated in iatrogenic feline hyperthyroidism, and the drug appears to be well tolerated with few adverse side effects. In 12 cats with naturally occurring hyperthyroidism treated with calcium ipodate, eight exhibited a good response. The serum total T_3 concentrations decreased into the reference range within 2 weeks of the start of treatment and remained at those levels for a 14-week study period. In addition, improvement in clinical signs, body weight, heart rate, and blood pressure were documented. Four of the eight responders continued to do well for as long as 6 months, but two of them had relapses of hyperthyroidism by week 14. The serum total T_4 concentrations were not affected by treatment, and cats with severe disease were less likely to respond, even after the dose was doubled (Murray and Peterson, 1997). Unfortunately calcium ipodate is no longer commercially available. Iopanoic acid has been evaluated as an alternative agent and is also effective at decreasing T_3 concentration; however, in a study of 11 hyperthyroid cats, only five cats had partial and transient responses (Gallagher et al, 2011).

Treatment of Hypertension in Hyperthyroid Cats

As discussed earlier, the prevalence of hypertension in hyperthyroid cats is lower than previously believed, and only a small percentage of cats require specific treatment for hypertension. The criteria for initiating specific anti-hypertensive treatment include documentation of systolic blood pressure more than 160 mmHg on more than one occasion or evidence of end organ damage, such as retinal lesions due to hypertension. It is important that blood pressure is measured in as calm and non-stressful way as possible to minimize the white coat effect that hyperthyroid cats seem particularly susceptible to. In addition to specific management of the hypertension, underlying hyperthyroidism should be treated at the same time. Drugs that are used to control hypertension in hyperthyroid cats include beta-blockers (e.g., propranolol or atenolol), calcium channel blockers (e.g., amlodipine), and angiotensin converting enzyme (ACE) inhibitors (e.g., benazepril and enalapril). As discussed earlier, beta blockers are effective at controlling tachycardia in hyperthyroid cats but are not as effective at controlling hypertension. In a study of 20 hyperthyroid cats with systolic blood pressure more than 160 mmHg treated with 1 to 2 mg/kg orally every 12 hours atenolol, the tachycardia was successfully controlled in most cats but systolic blood pressure only decreased below 160 mmHg in 30% of cats (Henik et al, 2008). Amlodipine (0.625 to 1.25 mg per cat every 24 hours) is a more effective antihypertensive drug in cats with hypertension and has the additional advantage of decreasing proteinuria in cats with CKD (Jepson et al, 2007). ACE inhibitors (e.g., benazepril) are less potent than amlodipine for control of feline hypertension but have both systemic and glomerular anti-hypertensive effects so are useful in cats with concurrent CKD. ACE inhibitors are typically used as a second drug in cats that do not have good control of systemic blood pressure with amlodipine alone (Stepien, 2011). As mentioned earlier, some cats with hyperthyroidism develop hypertension after control of the hyperthyroid state, so it is really important to continue to monitor blood pressure in all hyperthyroid cats after treatment.

Prognosis

A number of studies have evaluated the prognosis and predictors of survival for hyperthyroid cats treated with radioactive iodine. In a study of more than 200 cats, male cats were found to have a shorter life expectancy than females (Slater et al, 2001). Age at the time of treatment was also a prognostic factor, because older cats did not survive as long as younger cats. For example, 28% of 10-year-old male cats were alive 5 years after therapy and 4% of 16-year-old male cats were alive 5 years after treatment, whereas 42% of 10-year-old female cats were alive 5 years after treatment. The mean age of death was 15 years of age, with a range of 10 to 21 years. Clinical abnormalities documented just before death were renal disorders in 41% of cats and cancer in 16% of cats.

In a retrospective study of 300 hyperthyroid cats treated with methimazole, thyroidectomy, or radioactive iodine, median survival was 417 days; increasing age, presence of proteinuria, and hypertension were associated with decreased survival time (Williams et al, 2010). In another study, median survival time for feline hyperthyroidism after radioactive iodine was reported to be approximately 2 years (range 2 weeks to 7 years) (Peterson et al, 2001). In a retrospective study of 167 cats treated with methimazole and/or radioactive iodine, cats with pre-existing renal disease had significantly shorter survival times than cats without pre-existing renal disease (Milner et al, 2006; Fig. 4-45). When cats with pre-existing renal disease were excluded, cats treated with methimazole alone had a shorter median survival time (2 years) than cats treated with radioactive iodine alone or methimazole followed by radioactive iodine (4 years). The reasons for the difference in survival between the treatment groups may have been related to poorer control of the hyperthyroid state with long-term medical treatment as well as owner bias toward less aggressive management in methimazole treated cats. The prognosis for hyperthyroid cats managed by dietary iodine restriction is currently unknown, although some cats have reportedly been managed with this strategy for up to 6 years.

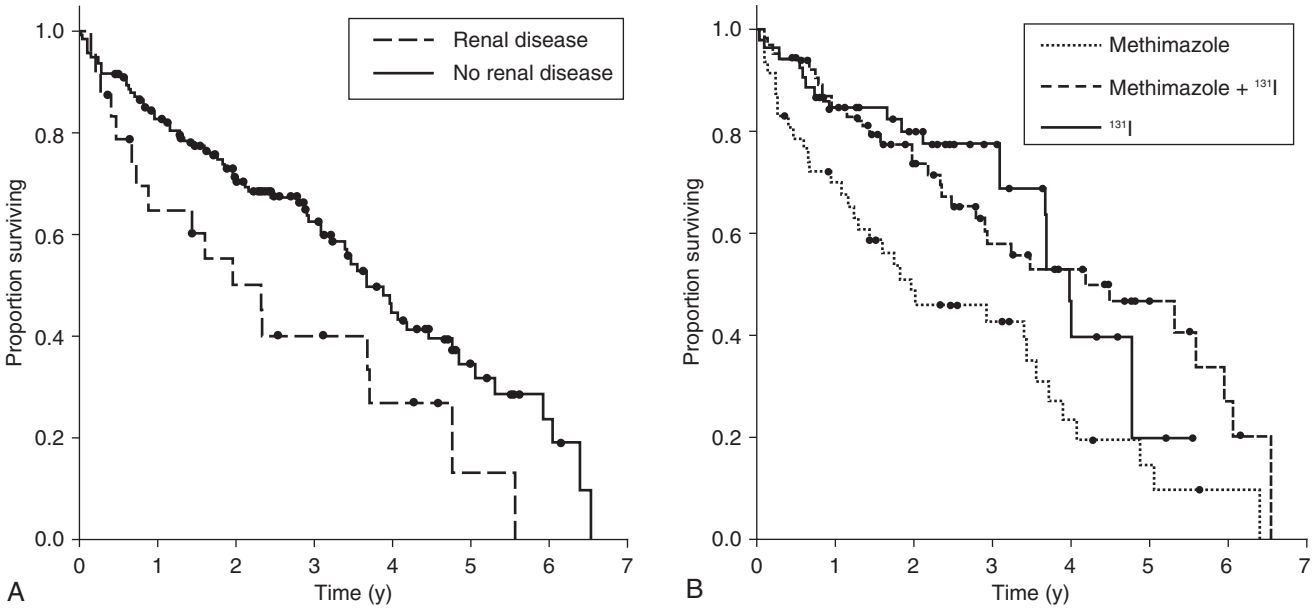

FIGURE 4-45 **A,** Kaplan-Meier curves of survival times for 167 hyperthyroid cats treated with methimazole, iodine-131 (^{131}I), or methimazole followed by ^{131}I, grouped according to whether they had evidence of renal disease prior to treatment. **B,** Kaplan-Meier curves of survival times for 167 hyperthyroid cats treated with methimazole, ^{131}I, or methimazole followed by ^{131}I, and grouped according to treatment. (**A,** From Milner RJ, et al.: Survival times for cats with hyperthyroidism treated with iodine 131, methimazole, or both: 167 cases [1996-2003], *J Am Vet Med Assoc* 228[4]:559-563, 2006. [Fig. 3; p. 562])

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CHAPTER 5

Canine Thyroid Tumors and Hyperthyroidism

J. Catharine Scott-Moncrieff

CHAPTER CONTENTS

Estimates for the prevalence of thyroid tumors in dogs range from 1% to 4% of all canine neoplasms (Brodey and Kelly, 1968; Birchard and Roesel, 1981; Harari et al, 1986). Although thyroid adenomas do occur in the dog, they are usually nonfunctional and too small to be palpable; they are therefore rarely identified clinically. Conversely thyroid carcinomas are usually large, nonfunctional, invasive, and malignant. For this reason approximately 90% of clinically detectable thyroid tumors in dogs are carcinomas. The thyroid gland is not normally palpable in dogs, and a palpable thyroid gland is therefore highly likely to be due to a malignant thyroid tumor.

TUMOR CLASSIFICATION

Although most thyroid tumors arise in the thyroid gland, tumors may also develop in vestigial thyroid tissue that may be present anywhere from the base of the tongue to the base of the heart (see Chapter 3; Capen, 2007). Benign thyroid tumors (adenomas) account for 30% to 50% of thyroid masses identified in studies published by veterinary pathologists (Brodey and Kelly, 1968; Leav et al, 1976). These benign tumors tend to be small, noninvasive, clinically silent, non-palpable tumors that involve one thyroid lobe and are incidental findings on necropsy. However, almost all clinically significant thyroid tumors in dogs are malignant and classified as carcinomas of varying types (Withrow and MacEwen, 2012). Malignant thyroid tumors in dogs are usually large fixed masses that are easily palpable. About two thirds of carcinomas are located in one lobe, whereas one third involve both lobes of the thyroid. Thyroid carcinomas are usually poorly encapsulated and commonly extend into or around the trachea, esophagus, and muscles of the neck. Thyroid tumors are usually highly vascular and may invade local blood vessels with resultant hemorrhage (Slensky et al, 2003).

THYROID ADENOMA/CARCINOMA

Most thyroid tumors are adenomas or carcinomas that arise from the epithelial cells that line the thyroid follicles. In dogs, most small solid thyroid adenomas are characterized by either small or large irregular follicles containing varying amounts of colloid (Leav et al, 1976). The cystic structures noted in some tumors are lined by dense fibrous capsules from which project fronds of uniform cells arranged in follicular and/or compact cellular patterns.

Thyroid follicular carcinomas are usually well differentiated and the distinction between benign and malignant is made based primarily on whether there is evidence of capsular or vascular invasion. Criteria such as cellular atypia and mitotic activity are not reliable markers of malignancy in thyroid tumors (Leav et al, 1976). Thyroid tumors of follicular cell origin may be further subclassified into follicular, compact (solid), papillary, compact-follicular, or undifferentiated (anaplastic) carcinomas depending on their pattern of growth (Box 5-1). In addition, veterinary oncologists use a clinical staging classification system initially developed by the World Health Organization Owen 1980 (Table 5-1). Most canine thyroid carcinomas contain both follicular and compact cellular patterns and are classified as compact follicular (mixed follicular-compact cellular) carcinomas. Slightly less common are pure follicular carcinomas. A smaller percentage of thyroid tumors are pure compact carcinomas. Undifferentiated (anaplastic) tumors are recognized in about 10% of dogs with thyroid tumors, whereas papillary carcinomas are rare (Leav et al, 1976). Although histologic subtype has prognostic significance in human thyroid tumors, it does not appear to influence outcome for well-differentiated tumors in dogs; however, high grade and anaplastic thyroid tumors do have a less favorable outcome.

In addition to tumors arising from follicular cells, medullary thyroid carcinomas may arise from the parafollicular C cells, which are

BOX 5-1 Histologic Classification of Thyroid Tumors in Dogs

Follicular adenoma
Compact follicular carcinoma
Follicular carcinoma
Compact (solid) carcinomas
Undifferentiated (anaplastic) carcinomas
Papillary carcinomas
Parafollicular (C-cell) carcinomas

TABLE 5-1 CLINICAL STAGING OF CANINE THYROID TUMORS

T: Primary Tumor

T0 No evidence of tumor

T1 Tumor < 2 cm maximum diameter: T1a, not fixed; T1b, fixed

T2 Tumor 2 to 5 cm maximum diameter: T2a, not fixed; T2b, fixed

T3 Tumor > 5 cm maximum diameter: T3a, not fixed; T3b, fixed

N: Regional Lymph Nodes*

N0 No evidence of RLN involvement†

N1 Ipsilateral RLN involved: N1a, not fixed; N1b, fixed

N2 Bilateral RLN involved: N2a, not fixed; N2b, fixed

M: Distant Metastasis

M0 No evidence of distant metastasis

M1 Distant metastasis detected

STAGE GROUPING	T	N	M
I	T1a, b	N0	M0
II	T0	N1	M0
	T1a, b	N1	M0
	T2a, b	N0 or N1a	M0
III	Any T3	Any N	M0
	Any T	Any N	M0
IV	Any T	Any N	M1

Modified from Owen LN, editor: *TNM classification of tumours in domestic animals,* Geneva, 1980, World Health Organization.
*The regional lymph nodes (RLNs) are the mandibular and the superficial cervical lymph nodes.
†Involvement implies histologic evidence of tumor invasion.

part of the amine precursor uptake decarboxylation (APUD) system and produce calcitonin (see Chapter 15). Although the tumors arise from different progenitor cells, the clinical presentation and treatment options for follicular and medullary carcinomas are similar.

PATHOGENESIS OF THYROID TUMORS

As with most neoplastic conditions in dogs, the exact cause of thyroid tumors is not known. Studies in humans have suggested an association between thyroid neoplasia and (1) iodine deficiency or excess, (2) chronic excesses in thyroid-stimulating hormone (also known as thyrotropin; TSH) secretion, (3) ionizing radiation, and (4) gene abnormalities and oncogene expression. In dogs the only known risk factors for thyroid neoplasia are hypothyroidism due to thyroiditis (Benjamin et al, 1996) and ionizing radiation (Benjamin et al, 1997).

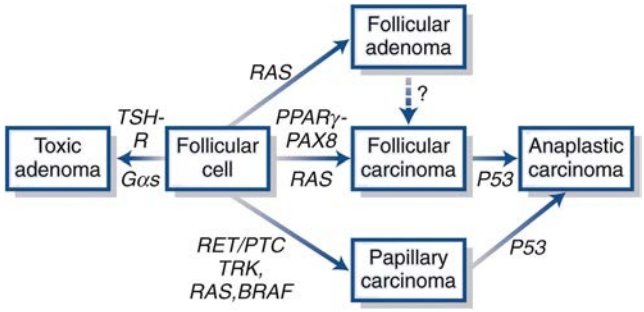

FIGURE 5-1 Genetic events in thyroid tumorigenesis. Activating point mutations of the RAS gene are found with a high frequency in follicular adenomas and carcinomas and are considered to be an early event in follicular tumorigenesis. The PPARγ-PAX8 rearrangement is found only in follicular tumors. Rearrangements of transmembrane receptors with tyrosine kinase activity (RET/PTC TRK genes) and activating point mutations of the BRAF gene are found only in papillary thyroid carcinomas (PTCs). Inactivating point mutations of the P53 gene are found only in poorly-differentiated and anaplastic thyroid carcinomas. Activation of the cyclic adenosine monophosphate pathway by point mutation of the thyrotropin receptor *(TSH-R)* or the alpha subunit of the G protein genes leads to the appearance of hyperfunctioning thyroid nodules. *Gαs,* Stimulatory guanyl nucleotide protein; *PPAR,* peroxisome proliferator-activated receptor. (Modified from Schlumberger M-J, et al.: Nontoxic diffuse and nodular goiter and thyroid neoplasia. In Melmed S, et al., editors: *Williams textbook of endocrinology,* ed 12, Philadelphia, 2011, Elsevier/Saunders, p. 452.)

Iodine Deficiency

Early epidemiologic studies suggested that thyroid cancer in humans was more frequent in iodine-deficient areas of the world. Although some of the evidence for an association between iodine intake and thyroid cancer is conflicting, the evidence for an association of iodine deficiency with an increased risk of follicular thyroid carcinoma (FTC) is quite strong (Schneider and Brenner, 2013). Studies in humans have demonstrated that when iodine supplementation is introduced into an iodine deficient area, the ratio of papillary to follicular carcinoma increases. These studies and others have suggested that iodine deficiency plays a role in the pathogenesis of follicular carcinoma, possibly due to prolonged TSH stimulation. Experimental data and clinical experience have neither confirmed nor denied the role of iodine in the pathogenesis of canine thyroid tumors.

Ionizing Radiation

The relationship between ionizing radiation and thyroid cancer is well established in humans. Radiation therapy of the cervical region and ingestion of radioactive iodine isotopes following nuclear accidents (e.g., at Chernobyl, Ukraine, in 1986) are associated with increased risk of thyroid neoplasia especially in children and adolescents. Thyroid neoplasia due to radiation exposure is usually well-differentiated thyroid papillary or papillary-follicular carcinomas (Schneider and Brenner, 2013). Ionizing radiation has also been demonstrated to be a cause of thyroid neoplasia in dogs (Benjamin et al, 1997).

Oncogenes

Genetic and epigenetic mutations have been shown to play a fundamental role in the pathogenesis of thyroid neoplasia in humans (Suarez et al, 2000; Schlumberger, 2011; Xing, 2013; Fig. 5-1). The progression of thyroid cancer occurs due to an accumulation

of these mutations, which result in dysregulated activity of cellular signaling pathways that promotes the malignant transformation of normal tissue. Loss of radioiodine avidity of thyroid cancer promoted by the BRAF-V600E mutation is a cause of failure of radioiodine treatment in humans.

Studies investigating the molecular mechanisms of canine thyroid carcinoma are limited. In one study a p53 mutation was detected in one of 23 cases of thyroid carcinoma (Devilee et al, 1994). Trisomy 18 was the sole clonal cytogenetic abnormality found in a canine thyroid adenoma (Reimann et al, 1996). Aneuploidy is a common feature of canine thyroid carcinomas with hypoploidy being most common (Verschueren et al, 1991).

In a study of samples collected from 23 dogs with FTC, differential expression of 489 characterized transcripts were identified by microarray analysis between tissues from dogs with FTC and histologically normal thyroid tissue. Differentially expressed genes belonged to several gene categories including those regulating cell shape, cell adhesion, mitogen-activated protein (MAP) kinase activity, angiogenesis, and cell migration (Metivier et al, 2012). The expression of osteopontin was significantly increased in follicular carcinoma compared to normal thyroid tissue (Metivier et al, 2012). Osteopontin (secreted phosphoprotein I) is a promising marker for cancer detection and monitoring in humans and appears to also have potential in dogs.

Lymphocytic Thyroiditis/Hypothyroidism

Hypothyroidism due to lymphocytic thyroiditis was associated with the development of thyroid tumors in a colony of 276 Beagles that were allowed to live out their full life span without treatment of their thyroid disease. Lymphocytic thyroiditis was present in 26% of the beagles at the time of death and resulted in hypothyroidism in 16% of dogs in the colony. Hypothyroid dogs had an increased risk for thyroid follicular neoplasia, including follicular carcinoma. Fifty four percent of hypothyroid dogs had one or more thyroid neoplasms, whereas only 23% of euthyroid dogs had similar neoplasms (Benjamin et al, 1996). The authors hypothesized that chronic excess stimulation of residual follicular epithelium by TSH was responsible for the strong association between thyroiditis, hypothyroidism, and follicular neoplasia.

BENIGN THYROID TUMORS

The majority of benign canine thyroid tumors (adenomas) are small, focal lesions that are not usually detected during life. When they are diagnosed, they are usually incidental findings identified by cervical ultrasonography. Much less commonly, a dog with a benign tumor may have a palpable mass or have clinical signs of hyperthyroidism (Leav et al, 1976; Lawrence et al, 1991). Canine thyroid adenomas are usually solitary masses and may be solid or cystic. Adenomas are typically round or ovoid and measure a few millimeters to several centimeters in diameter. They are usually cream to reddish brown in color and may compress adjacent normal thyroid tissue. Cystic adenomas can be turgid and filled with an amber or blood-tinged fluid (Leav et al, 1976).

MALIGNANT THYROID TUMORS

Carcinomas of the canine thyroid are usually large solid masses that commonly invade into adjacent structures. Extension of malignant thyroid tumors into or around the esophagus, trachea, cervical musculature, nerves, and thyroidal vessels is fairly common. However, invasion into the lumen of structures, such as the esophagus or trachea, is unusual. Distant metastasis is common and is most frequent in the pulmonary parenchyma and the regional lymph nodes (retropharyngeal, mandibular, and superficial cervical). Lymphatic drainage of the thyroid gland is primarily in the cranial direction, so lymph node enlargement is most likely to be detected cranial and medial to the primary tumor. Occasionally, both ipsilateral and contralateral cervical lymph nodes may be involved. Other sites of metastasis include the jugular vein, liver, adrenal gland, kidneys, liver, heart base, spleen, bone and bone marrow, prostate, brain, skeleton, and spinal cord (Bentley et al, 1990; Harmelin et al, 1993; Theon et al, 2000; Tamura et al, 2007; Nadeau and Kitchell, 2011; Table 5-2). Approximately 30% to 40% of dogs with thyroid tumors have detectable distant metastases at time of diagnosis (Harari et al, 1986; Sullivan et al, 1987). Necropsy studies suggest that 60% to 80% of thyroid carcinomas had metastasized at the time of death (Leav et al, 1976). In one study, the risk of metastasis was correlated with the size of the tumor. In tumors with a volume of 20 cm^3 or less, 14% of dogs had metastasis; whereas in tumors more than 100 cm^3, 100% had metastasized (Leav et al, 1976; Table 5-3). The relation of size to metastasis likely reflects that larger or more aggressive tumors have escaped clinical detection longer, allowing for a greater probability of metastasis.

TABLE 5-2 **FREQUENCY OF METASTATIC DISEASE IN DOGS WITH THYROID CARCINOMA***

ANATOMIC SITE	PERCENTAGE OF ANIMALS
Lung	77
Regional lymph node	51
Local incision†	49
Adrenal	14
Kidney	14
Heart muscle	9
Liver	6
Intestine	6
Skin	6
Brain	3
Spleen	3
Mesentery	3
Diaphragm	3

From Leav I, et al.: Adenomas and carcinomas of the canine and feline thyroid, *Am J Pathol* 83:61, 1976.

*Data is based on 35 autopsied dogs with metastatic carcinoma of the thyroid.

†Includes invasion of thyroidal, jugular, and maxillary veins; esophagus; trachea; larynx; omohyoid muscle; and vertebra.

CLINICAL APPROACH TO THYROID TUMORS

Signalment

Thyroid tumors in the dog typically develop in middle-aged and older individuals. The most common age range for dogs with thyroid tumors is 10 to 15 years (Wucherer et al, 2010). One study conducted within a small colony of Beagles demonstrated an age-specific incidence of thyroid tumors of 1.1% per year in dogs 8 to 12 years of age and 4.0 % per year in dogs 12 to 15 years of age (Haley et al, 1989).

TABLE 5-3 FREQUENCY OF THYROID CARCINOMA METASTASIS IN RELATION TO SIZE OF PRIMARY TUMOR

TUMOR VOLUME (CU CM)	NUMBER OF ANIMALS AUTOPSIED*	PERCENT WITH METASTASIS
1-20	14	14
21-100	19	74
101-500	9	100
501-1000	4	100
1001-1500	3	100

From Leav I, et al.: Adenomas and carcinomas of the canine and feline thyroid, *Am J Pathol* 83:61, 1976.
*Measurements were not recorded in eight cases.

There is no obvious gender predilection for thyroid neoplasia in the dog (Harari et al, 1986; Wucherer et al, 2010). By contrast, the incidence of human thyroid cancer is about four times greater in women than in men at most ages (Schneider and Brenner, 2013). Breeds thought to be at increased risk include Boxers, Beagles, Golden Retrievers, and Siberian Huskies (Leav et al, 1976; Harari et al, 1986; Verschueren et al, 1992; Wucherer et al, 2010).

Clinical Signs

Dogs with thyroid tumors that are not hyperthyroid are usually presented to veterinarians because of detection of a mid-cervical mass or because of clinical signs resulting from compression or invasion of surrounding tissues. The length of time between owner observation of the mass or clinical sign(s) and presentation for veterinary care is highly variable (days to years).

Because most benign thyroid tumors are clinically silent, it is very likely that a palpable thyroid mass is malignant, especially if it is not freely moveable. Most thyroid tumors are identified at or just below the level of the larynx, but larger tumors may extend closer to the thoracic inlet. Thyroid tumors are usually firm and non-painful and may be unilateral or bilateral. There is no predisposition for either the right or left thyroid lobes. In a study of 44 dogs with thyroid carcinoma, the lesion was unilateral in 64% of dogs and bilateral in 36% of dogs (Leav et al, 1976). In one study, bilateral tumors were much more likely to metastasize than unilateral tumors (Theon et al, 2000). It is usually not possible to determine whether bilateral tumors have arisen independently in each gland or whether metastasis from one lobe to the other has occurred. Other clinical signs of thyroid carcinoma include coughing, dyspnea or tachypnea, stridor or stertor, dysphagia, dysphonia, weight loss, listlessness/depression, vomiting, regurgitation, anorexia, facial edema, and apparent cervical pain or discomfort (Table 5-4). In one report, erosion of arterial blood vessels by a thyroid carcinoma resulted in acute severe hemorrhage into the tumor and rapid enlargement of the mass (Slensky et al, 2003). Dyspnea may be due to upper airway compression or pulmonary metastasis.

Additional clinical signs in dogs with functional thyroid tumors include signs of hyperthyroidism, such as weight loss, polydipsia, polyuria, polyphagia, vomiting, voluminous soft stools, increased activity or nervousness, weakness, poor hair coat, heat intolerance, panting, and shivering (Melián et al, 1996; Simpson and McCown, 2009). The clinical signs of hyperthyroidism may precede identification of a cervical mass and be the reason for initial patient evaluation.

TABLE 5-4 OWNER-OBSERVED SIGNS IN 237 DOGS WITH THYROID TUMORS

SIGN	PERCENT OF DOGS
Visible mass in neck	78
Coughing	34
Rapid breathing (even at rest)	32
Dyspnea (difficulty breathing-distress)	28
Trouble swallowing (dysphagia)	23
Change in bark (dysphonia)	14
Weight loss	14
Listlessness/depression	13
No observed signs	12
Vomiting/regurgitation	11
Anorexia/decrease in appetite	11
Polydipsia/polyuria	10
Hyperactivity	9
Diarrhea	9
Increased appetite	3
Facial edema	2
Apparent cervical discomfort	2

Physical Examination

Most thyroid masses are firm, irregular in shape, and non-painful. Most thyroid tumors are located close to the typical location of the normal thyroid glands (at the level of or ventral to the larynx) and are not as ventral in location or as freely movable in the subcutaneous space as in cats (Fig. 5-2). Usually, the thyroid mass is non-moveable and obviously well embedded into surrounding tissue. It is usually not possible to palpate the interior or medial surface of the mass because of local invasion. An irregular shape is not always diagnostic of carcinoma, but an immovable mass usually implies local invasion and should raise a strong suspicion for malignancy. Submandibular lymph nodes may be enlarged as a result of tumor spread or lymphatic obstruction. Horner's syndrome may occur due to encroachment on the vagosympathetic trunk (Melián et al, 1996). Unfortunately palpation is not accurate for assessing extent of tumor invasion (Taeymans et al, 2013).

In addition to the presence of a palpable cervical mass, physical examination of dogs with functional thyroid tumors may reveal evidence of weight loss, muscle atrophy, or cachexia (Fig 5-3). Tachycardia with or without cardiac arrhythmias is common. Affected dogs may pant excessively and may be restless during the physical examination. Panting, respiratory distress, and swallowing difficulties may be the result of thyrotoxicosis or the tumor mass compressing the trachea and/or esophagus.

Minimum Data Base

The minimum data base is rarely helpful in diagnosis or management of dogs with thyroid tumors. Leukocytosis and a mild normocytic normochromic anemia are identified in some dogs. One report identified increased liver enzymes in 7 of 21 dogs, none of which were thyrotoxic (Harari et al, 1986). The cause of the enzyme increases was not determined. Hypercalcemia has also been identified in dogs with thyroid carcinoma and is attributed to a paraneoplastic condition (Lane and Wyatt, 2012). The urinalysis is usually unremarkable.

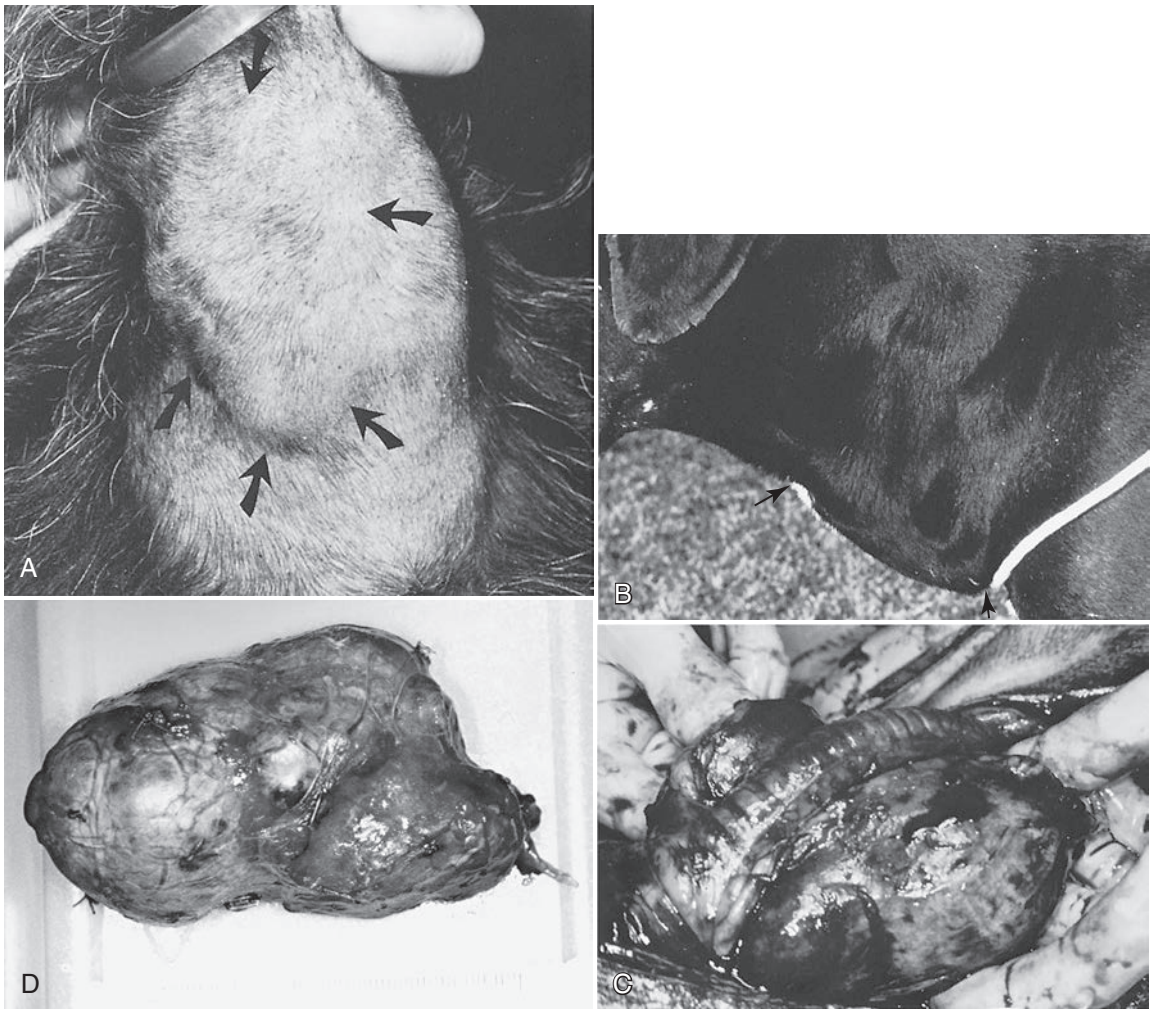

FIGURE 5-2 A, Photograph of the shaved ventral cervical area of a dog with a large, obvious goiter *(arrows).* **B,** Lateral view of the dog with a large thyroid tumor. The mass is delineated ventrally by the leash. **C,** Large thyroid tumor, at surgery, displacing the trachea. **D,** The thyroid tumor following excision. (**A,** Courtesy of Dr. Jane Turrel.)

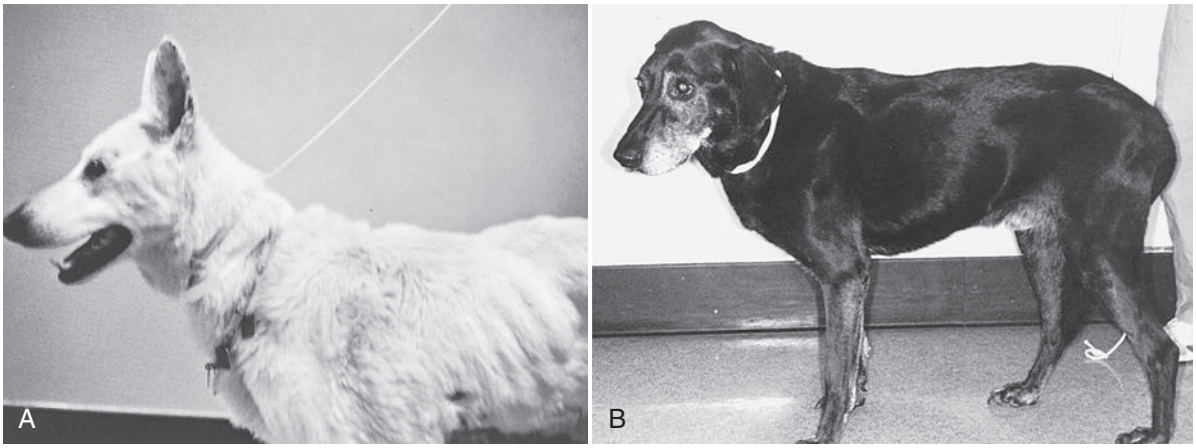

FIGURE 5-3 A, A cachectic 9-year-old German Shepherd dog with hyperthyroidism caused by a functioning thyroid carcinoma. **B,** A thin 12-year-old Labrador-mix with mild hyperthyroidism secondary to a functioning thyroid carcinoma.

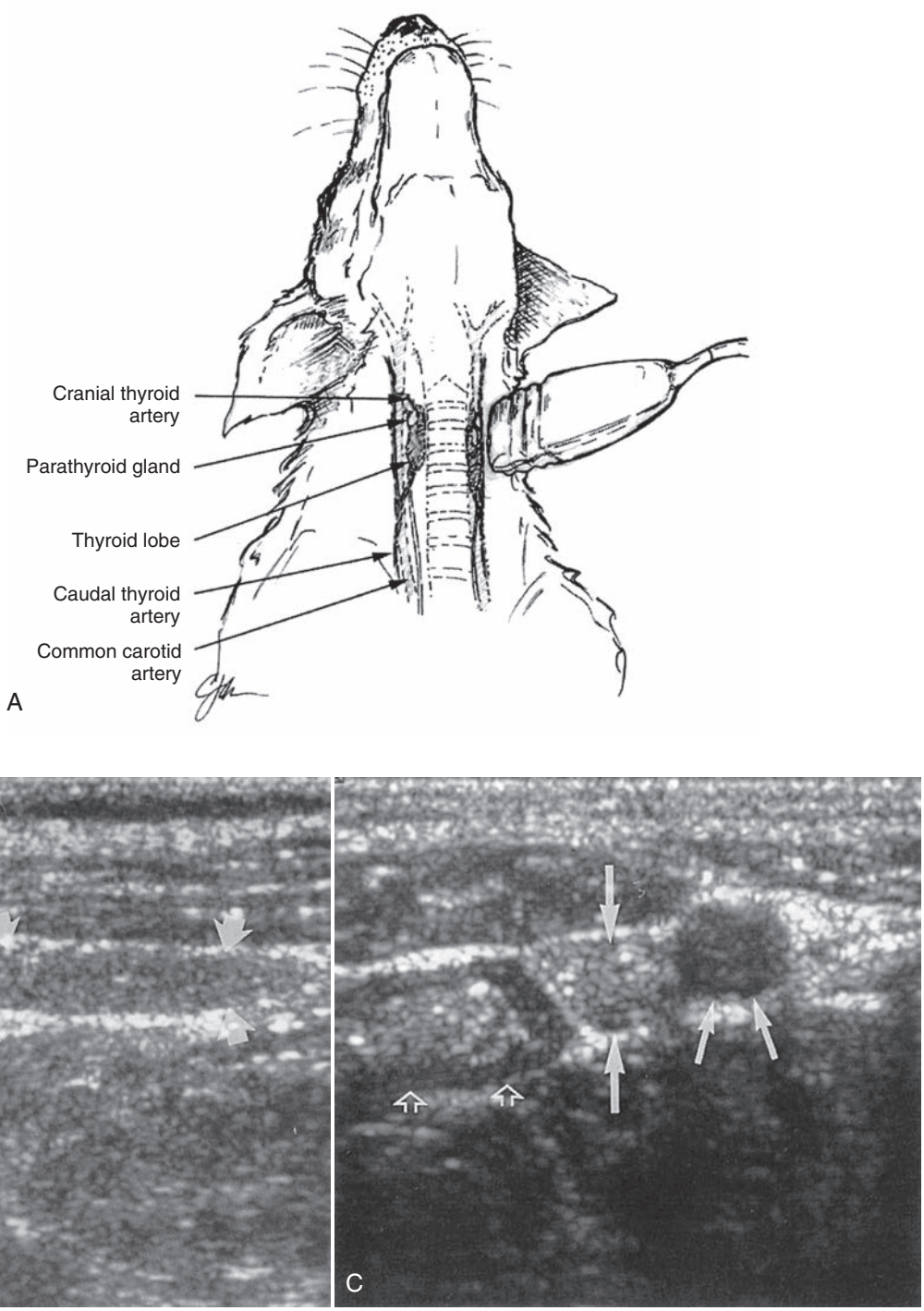

FIGURE 5-4 A, Ultrasound of the canine thyroid gland. For initial localization of the thyroid in long axis, the transducer is positioned on the jugular groove with the imaging plane directed midway between the frontal and parasagittal planes. The ipsilateral common carotid artery serves as an anatomic landmark. **B,** Ultrasound image of the normal canine thyroid gland (sagittal view). The normal canine thyroid lobe appears as a uniformly moderately echoic ellipsoid structure *(arrows).* A thin hyperechoic fascial sheath surrounds and defines the thyroid lobe. **C,** Ultrasound image of the normal canine thyroid gland. In the short-axis view, the thyroid lobe *(large solid arrows)* appears as a roughly triangular structure adjacent and medial to the common carotid artery *(small solid arrows).* The esophagus can be seen when imaging the left thyroid lobe and appears as an irregularly-shaped structure medial and dorsal to the thyroid lobe *(open arrows).* (Modified from Wisner ER, Nyland TG: Ultrasonography of the thyroid and parathyroid glands, *Vet Clin N Amer Sm Anim Pract* 28:973, 1998. Used with permission.)

Radiography

Radiographs of the thorax should always be evaluated in a dog with a thyroid mass because of the high risk of pulmonary metastasis. In clinical studies, pulmonary metastasis is identified in 30% to 40% of dogs, which contrasts with histopathologic studies that report metastasis in up to 80% of dogs at time of death (Leav et al, 1976; Brodey and Kelly, 1968; Sullivan et al, 1987; Marks et al, 1994; Carver et al, 1995; Turrel et al, 2006). This discrepancy is likely due to the relative insensitivity of pulmonary radiographs for detection of pulmonary metastasis and due to progression of disease between diagnosis and time of death. Computed tomography (CT) is more sensitive for detection of pulmonary metastasis than is radiography (Armbrust et al, 2012) and should be done prior to treatment planning. Neoplastic transformation of ectopic thyroid tissue may result in identification of a cranial mediastinal mass on pulmonary radiographs (Liptak et al, 2008).

Radiography of the neck may identify a space-occupying mass caudal to the pharynx, which may contain areas of soft tissue mineralization (Taeymans et al, 2007). A mass in this location may cause an uneven or distorted laryngeal space and compress or displace the trachea ventrally. Esophageal displacement or focal dilatation may indicate esophageal invasion. Metastasis to the retropharyngeal lymph nodes may cause displacement of the pharynx, decreased size of the pharyngeal airspace, and loss of the fascial planes in the retropharyngeal area (Taeymans et al, 2007). Abdominal radiographs are usually normal, although dogs with hepatic metastasis may have an irregular hepatic silhouette.

Ultrasonography

Equipment and Positioning

Because the thyroid glands are very superficial structures, high frequency transducers of at least 10 MHz that result in high spatial resolution should be used to examine the thyroid glands (Taeymans et al, 2007). The ventral cervical area should be carefully clipped and the dog positioned as symmetrically as possible on a padded V-top table in dorsal recumbency. Dogs usually do not require sedation for cervical ultrasound; however, dogs that have cervical masses large enough to produce upper airway obstruction are at risk for developing severe dyspnea after being placed in dorsal recumbency. It may be safer to examine such dogs under general anesthesia with an endotracheal tube in place (Wisner and Nyland, 1998).

Normal Anatomy, Imaging Planes, and Indications

The thyroid lobes are normally located just caudal to the arch of the cricoid cartilage. Healthy medium-sized dogs have flattened lobes measuring approximately 6.0 cm × 1.5 × 0.5 cm (Fig. 5-4). The common carotid arteries are lateral and slightly superficial to the thyroid lobes, serving as an important internal landmark. Ultrasonography is a useful non-invasive and inexpensive screening tool for evaluation of cervical masses and is most useful for determining whether a mass is arising from the thyroid gland and if one or both the thyroid lobes are involved. The differential diagnosis of disorders resulting in a cervical mass is shown in Box 5-2.

When evaluating a dog with a neck mass of unknown etiology, the ultrasonographer should begin by attempting to identify both thyroid lobes. This usually allows quick identification of thyroid masses; however, large cervical masses can distort the normal anatomy and make identification of the origin of the mass more difficult. Lymph nodes and salivary masses are usually not difficult to distinguish from thyroid lobes based on location (usually cranial and lateral to the thyroid lobes) and echogenicity. Salivary glands, for example, are typically uniformly hypoechoic with characteristic internal linear arborization that likely represents the salivary duct system (Wisner and Nyland, 1998).

Ultrasound Appearance of a Thyroid Carcinoma

Thyroid carcinomas are typically large nonhomogeneous masses that that may be poorly delineated (Fig. 5-5). The parenchyma may be complex, sometimes containing multiple cysts, or may have foci of mineralization. Thyroid carcinomas are highly vascular, and a large arterial vascular plexus is often distributed in and around these masses. The vascular plexus can be verified by pulsed or color-flow Doppler ultrasonographic evaluation. Some dogs develop arteriovenous malformations within the tumor; such abnormalities can also develop after surgery (Wisner et al, 1994; Wisner and Nyland, 1998). Invasion of surrounding structures (e.g., fascial sheaths, esophagus, and cervical vasculature) may also be detected by ultrasound. Although a tentative diagnosis of thyroid carcinoma can be made in most dogs based on localization to one or both thyroid lobes and qualitative ultrasonographic characteristics, the diagnosis must be confirmed by fine needle aspiration or biopsy. Because of the vascularity of thyroid tumors, needle aspiration or biopsy should be performed with ultrasound guidance to aid in avoiding larger blood vessels. Both aspiration and needle biopsy of a vascular tumor may only retrieve peripheral blood. Ultrasound may also be used to help stage a carcinoma, by documentation of tumor extent, invasiveness, and local metastasis; however, it is less accurate for tumor staging than are either CT or magnetic resonance imaging (MRI) (Taeymans et al, 2013).

Computed Tomography and Magnetic Resonance Imaging

Both CT and MRI have been used for preoperative diagnosis and staging of thyroid tumors. On CT, thyroid tumors have lower attenuation value than normal thyroid tissue. On MRI, thyroid carcinomas are hyperintense compared to surrounding musculature in both T1 and T2 imaging sequences (Taeymans et al, 2013). Characteristics that are important to evaluate by either modality are origin of the mass, mass size, tumor capsule disruption, local tissue invasion, lymphadenopathy, presence of metastatic disease, and parathyroid involvement in the tumor. Both CT and MRI are superior to ultrasound for establishing extent of invasion of thyroid tumors. CT is also useful for diagnosis and staging of thyroid tumors arising in ectopic locations (Rossi et al, 2013)

Scintigraphy

Thyroid gland scintigraphy in dogs is usually performed following intravenous (IV) administration of 2 to 4 mCi of technetium-99m pertechnetate ($^{99m}TcO_4$). Gamma camera imaging of the cervical

BOX 5-2 Differential Diagnosis for Cervical Masses in Dogs

Thyroid adenoma/carcinoma (see Box 5-1)
Secondary metastasis to thyroid gland
Carotid body tumor
Cellulitis/abscess/granuloma
Lymphadenopathy (submandibular, medial retropharyngeal, or cervical)
Salivary gland inflammation or neoplasia
Other neoplasia (e.g., rhabdomyosarcoma, leiomyosarcoma)

region and thorax is typically performed 20 to 60 minutes after isotope administration. The $^{99m}TcO_4$ is trapped by cells that concentrate iodine, including the thyroid gland, salivary glands, and gastric mucosa. Usually, static left lateral, right lateral, ventral, and dorsal images are acquired (Marks et al, 1994). The appearance of the normal canine thyroid glands is of paired spherical to ovoid lobes that have symmetrical isotope uptake (Fig. 5-6). The intensity of isotope uptake in the thyroid gland is approximately equal to that of the parotid salivary tissue (thyroid-to-salivary ratio at 20 minutes 1.12:1 ± 0.13) (Daniel and Neelis, 2014). When a cervical mass arises from the thyroid gland, the scintigraphic appearance of the thyroid gland is abnormal (Fig. 5-7). If the mass arises from other tissues or ectopic thyroid tissue, the scintigraphic appearance of the thyroid glands should be normal, although concurrent

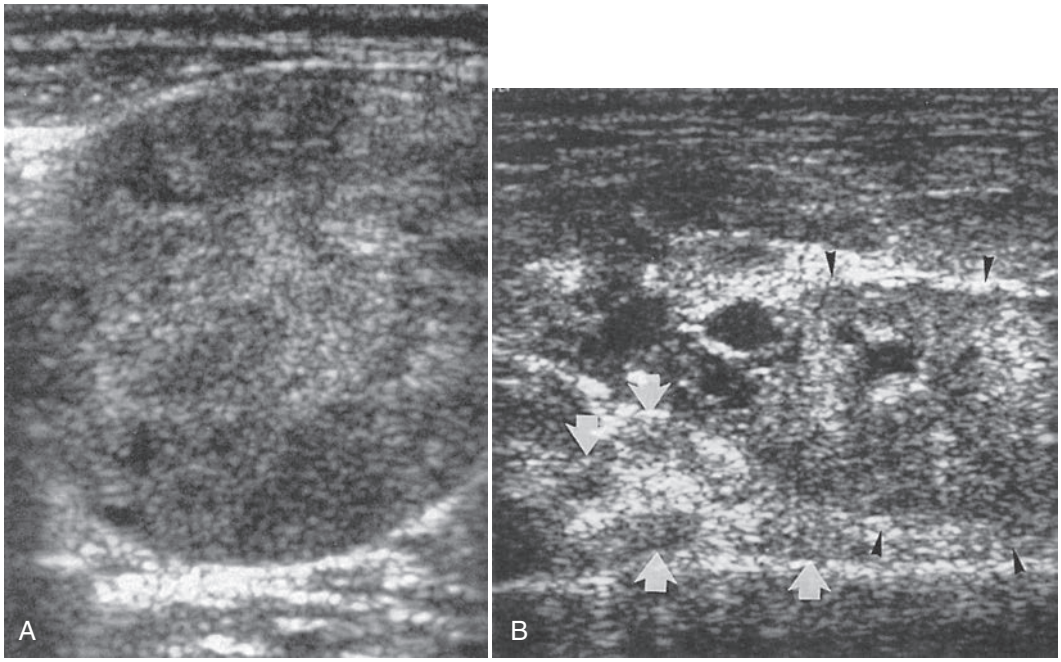

FIGURE 5-5 A, Cervical ultrasound of encapsulated thyroid carcinoma in a dog. The thyroid is grossly enlarged, and the thyroid parenchyma is heterogeneous, but the lesion appears to be well-marginated. **B,** Cervical ultrasound of poorly-marginated thyroid carcinoma in a dog. The thyroid is enlarged, and thyroid parenchyma is heterogeneous *(arrowheads).* In addition, lesion margins are poorly defined and appear to extend into surrounding tissues *(arrows).* (Modified from Wisner ER, Nyland TG: Ultrasonography of the thyroid and parathyroid glands, *Vet Clin N Amer Sm Anim Pract* 28:973, 1998. Used with permission.)

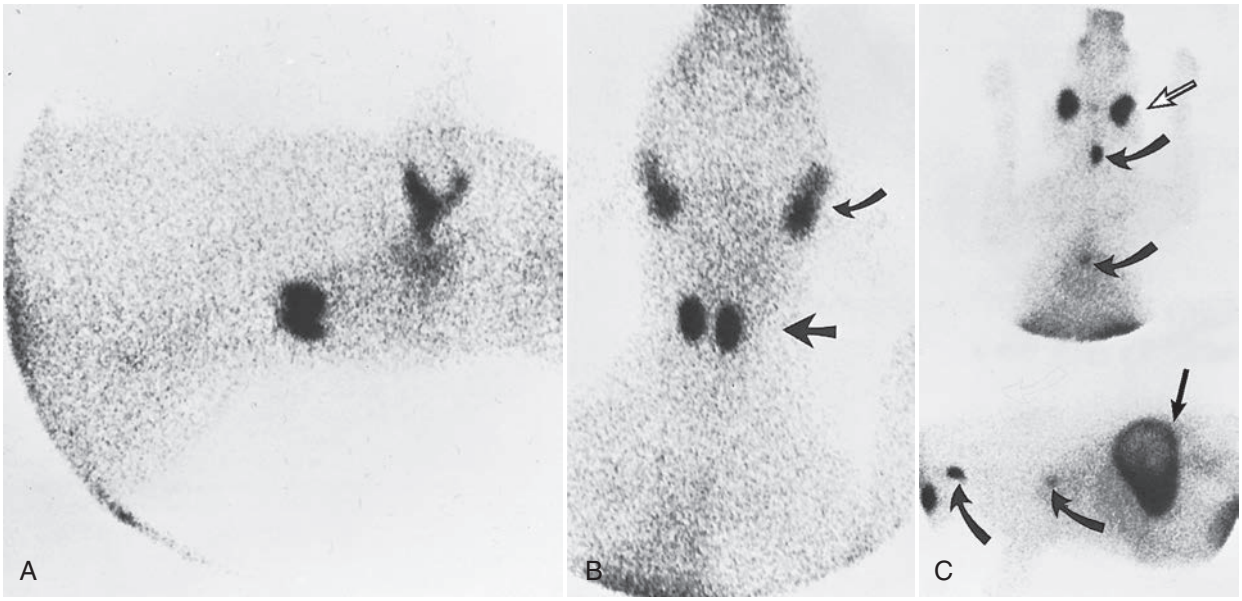

FIGURE 5-6 Thyroid technetium-99m (^{99m}Tc) scan lateral **(A)** and ventral **(B)** from a normal dog. The thyroids of a normal dog *(straight arrow)* are approximately the size of normal salivary glands *(curved arrow).* **C,** Thyroid technetium-99m (^{99m}Tc) scan from a dog that had one thyroid lobe removed. One normal cervical thyroid and one ectopic anterior mediastinal thyroid *(curved arrows)* are identified. Salivary glands *(open arrow)* and stomach *(straight arrow)* are also visualized because these tissues concentrate pertechnetate.

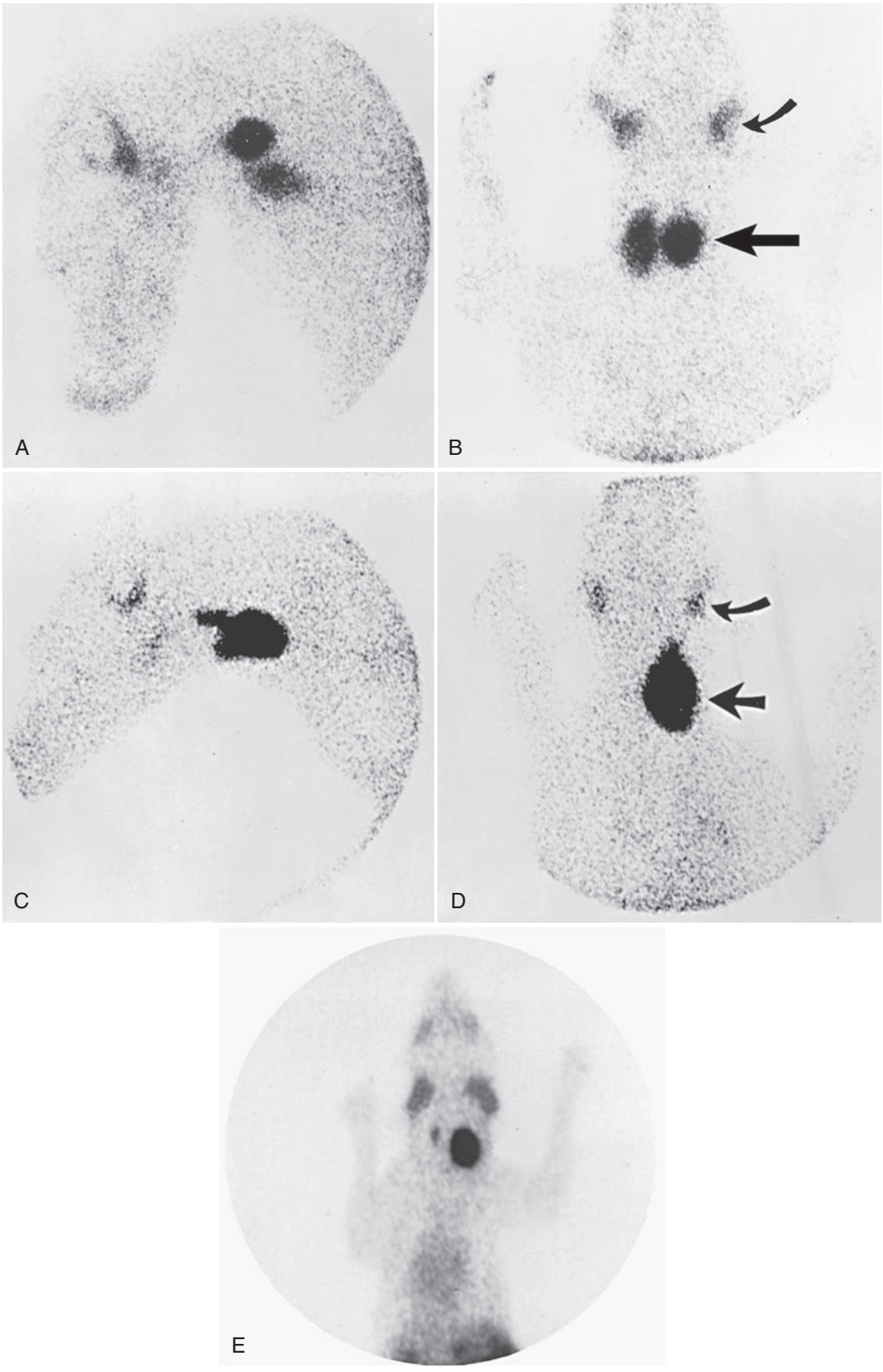

FIGURE 5-7 **A** to **D,** Thyroid technetium-99m (^{99m}Tc) scans from three dogs, each with thyroid tumors demonstrating well-circumscribed, homogeneous uptake. In the first two dogs (**B** and **D**) the thyroid tissue *(straight arrow)* and salivary tissue *(curved arrow)* are defined by uptake of the radioactive contrast. The first dog has bilateral thyroid follicular carcinomas, which were large (lateral **[A]** and dorsoventral **[B]** view) with partial ability to concentrate the radioactive material. The dog was euthyroid. Lateral **(C)** and dorsoventral **(D)** views of a pertechnetate thyroid scan from a dog with one large functioning thyroid follicular carcinoma *(straight arrow),* which concentrated the pertechnetate to a much greater degree than the salivary glands *(curved arrow).* This dog was hyperthyroid. **E,** Scan from a hypothyroid dog with a thyroid carcinoma.

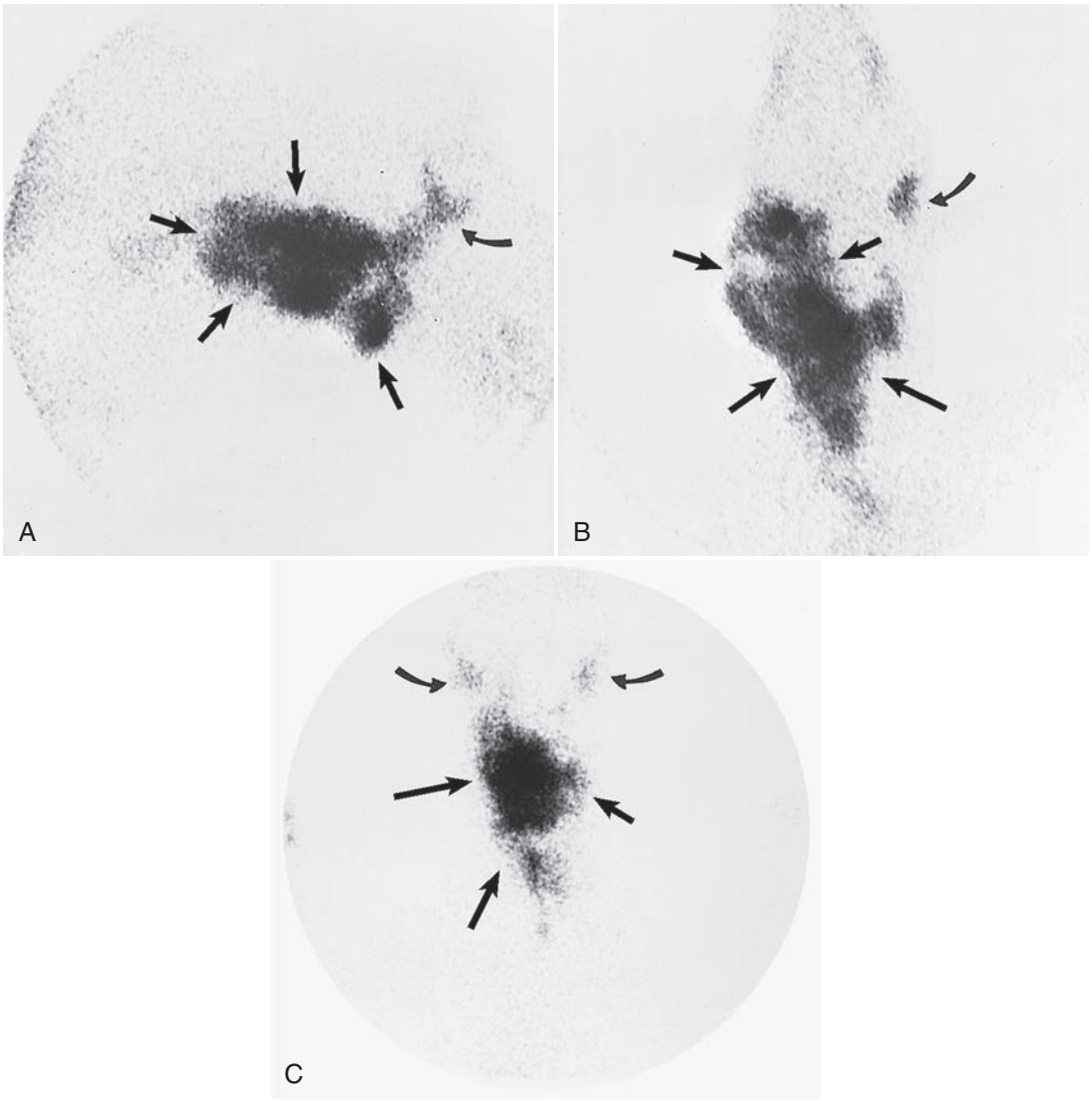

FIGURE 5-8 Thyroid technetium-99m (^{99m}Tc) scans from two dogs, each with thyroid carcinomas demonstrating poorly circumscribed, heterogeneous uptake in the cervical area (thyroid, *straight arrows;* salivary tissue, *curved arrows*). Lateral **(A)** and dorsoventral **(B)** views of a pertechnetate thyroid scan from a dog with typical local invasion of neoplastic cells throughout the cervical area. The dog was euthyroid despite the appearance of the thyroid on the scan. **C,** Thyroid technetium-99m (^{99m}Tc) scan (ventral view) from a dog with a thyroid tumor causing hyperthyroidism.

hypothyroidism can complicate interpretation of the scintigraphic image. The appearance of canine thyroid carcinoma on scintigraphy varies both in intensity and size. With a unilateral nonfunctional tumor, one thyroid lobe will appear abnormal and the other is usually normal in appearance. Some tumors have homogenous diffuse uptake of isotope, and some have diffuse but irregular uptake of isotope (see Fig. 5-7; Figs. 5-8, and 5-9). Poorly differentiated tumors have decreased uptake of isotope and are referred to as *cold nodules*. Some tumors have well-defined borders, whereas others have ill-defined or spiculated borders (see Fig. 5-8). Studies suggest that tumors with homogenous uptake and well-defined margins are more likely to be surgically resectable than those with heterogeneous uptake and poorly circumscribed margins (Marks et al, 1994). There is poor correlation between histologic type and scintigraphic pattern of thyroid tumors; however, tumors with homogenous diffuse uptake are more likely to be functional tumors that cause hyperthyroidism (Marks et al, 1994). Whether or not pulmonary metastasis is detected on scintigraphy depends upon whether the metastatic cells retain the ability to trap iodine (see Fig. 5-9; Fig. 5-10). Even if the metastatic cells concentrate iodine, detection of metastasis may be less sensitive when the primary tumor is concentrating ("stealing") the majority of the radioactive isotope. In this situation, the metastatic lesion may only be visible after surgical resection of the primary tumor. Scintigraphy can also identify ectopic sites of thyroid tissue (neoplastic or normal) (see Fig. 5-6). Because of these variables, dogs with normal thoracic radiographs may have scintigraphic evidence of metastasis, whereas some dogs with pulmonary metastasis visible on radiography may not have scintigraphic evidence of metastasis (see Figs. 5-9 and 5-10).

Basal Serum Thyroxine Concentrations

The majority of dogs (55% to 60%) with thyroid tumors are euthyroid. Because most thyroid tumors are unilateral and more than 80% of both thyroid glands must be destroyed before clinical hypothyroidism results, hypothyroidism is rarely caused by thyroid

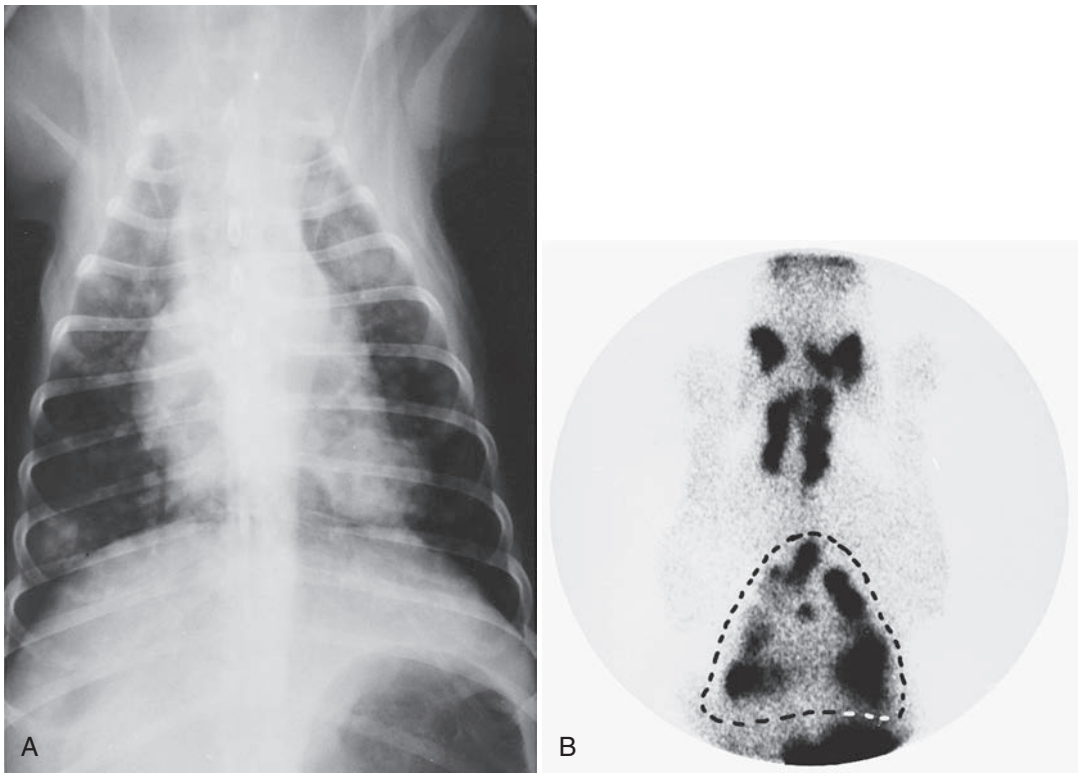

FIGURE 5-9 Radiographic **(A)** and scintigraphic **(B)** views of a dog with thyroid adenocarcinoma and pulmonary metastases. The location of the thorax is shown by dotted lines on the scintigraphic image.

tumors. In one study, 3 of 29 dogs with thyroid tumors were diagnosed as hypothyroid; however, interpretation of thyroid hormone concentrations in dogs with thyroid tumors is complicated by the effects of concurrent illness on serum thyroid hormone concentrations and because hypothyroidism may be a pre-existing condition (Benjamin et al, 1996). Hyperthyroidism has been reported in 10% to 20% of dogs with thyroid tumors (Verschueren et al, 1992; Marks et al, 1994; Rijnberk, 1996; Fig 5-11). Although functioning thyroid adenomas have been described, most tumors are malignant (Lawrence et al, 1991; Marks et al, 1994). A functional thyroid tumor is the only naturally occurring cause of hyperthyroidism in the dog other than consumption of diets containing thyroid tissue. Lymphocytic thyroiditis causing anti-triiodothyronine (T_3) and thyroxine (T_4) antibodies can result in the presence of spuriously increased thyroid hormone concentrations (see Chapter 3); but in dogs with thyroiditis, clinical signs of hyperthyroidism are absent and there is no palpable cervical mass.

Thyroid Biopsy

Thyroid tumors are highly vascular, and hemorrhage associated with any biopsy procedure is common. The hemorrhagic potential of these masses precludes routine large-bore needle biopsy procedures. Rather, we recommend fine-needle aspiration, using a 21- to 23-gauge needle ideally performed with ultrasound guidance. This technique is usually adequate for differentiating thyroid tumors from abscesses, cysts, salivary mucoceles, or lymph nodes. The number of neoplastic cells obtained by needle aspiration is variable, and the sample is almost always contaminated with blood. Because neoplastic follicular cells are fragile, many isolated nuclei may be seen, but intact cells found in clusters resemble glandular structures. A presumptive diagnosis of thyroid neoplasia can often be made based on the presence of neuroendocrine cells in the sample, but definitive diagnosis requires histopathology. Samples for histopathology can be obtained by needle biopsy, incisional biopsy, or excisional biopsy. Large-bore needle biopsy is avoided when possible because of the risk of hemorrhage and the difficulty in obtaining a diagnostic biopsy sample. Incisional or excisional biopsy is preferred, and the choice is dependent upon the characteristics of the mass. If surgical excision is possible, then histopathology should be obtained at this time.

Differential Diagnosis

Common differential diagnoses for ventral cervical masses in dogs include thyroid adenoma or carcinoma, and submandibular, medial retropharyngeal, or cervical lymphadenomegaly. Lymphadenomegaly may result from tonsillar squamous cell carcinoma or spread from other tumors or non-tumor disorders that originate in the oral cavity or the neck such as cellulitis, abscess or granuloma or salivary gland tumor or inflammation (Wisner et al, 1994; see Box 5-2).

TREATMENT OF THYROID TUMORS

Treatment modalities used for treatment of thyroid tumors include surgical resection, radiation therapy, radioactive iodine treatment, and chemotherapy. In some cases, multiple treatment modalities are used together or sequentially. The choice of treatment depends upon a number of factors including size, vascularity, and mobility of the tumor, functional status of the tumor, severity of clinical signs particularly with regard to respiratory signs, presence or absence of metastatic disease, and financial constraints of the owner.

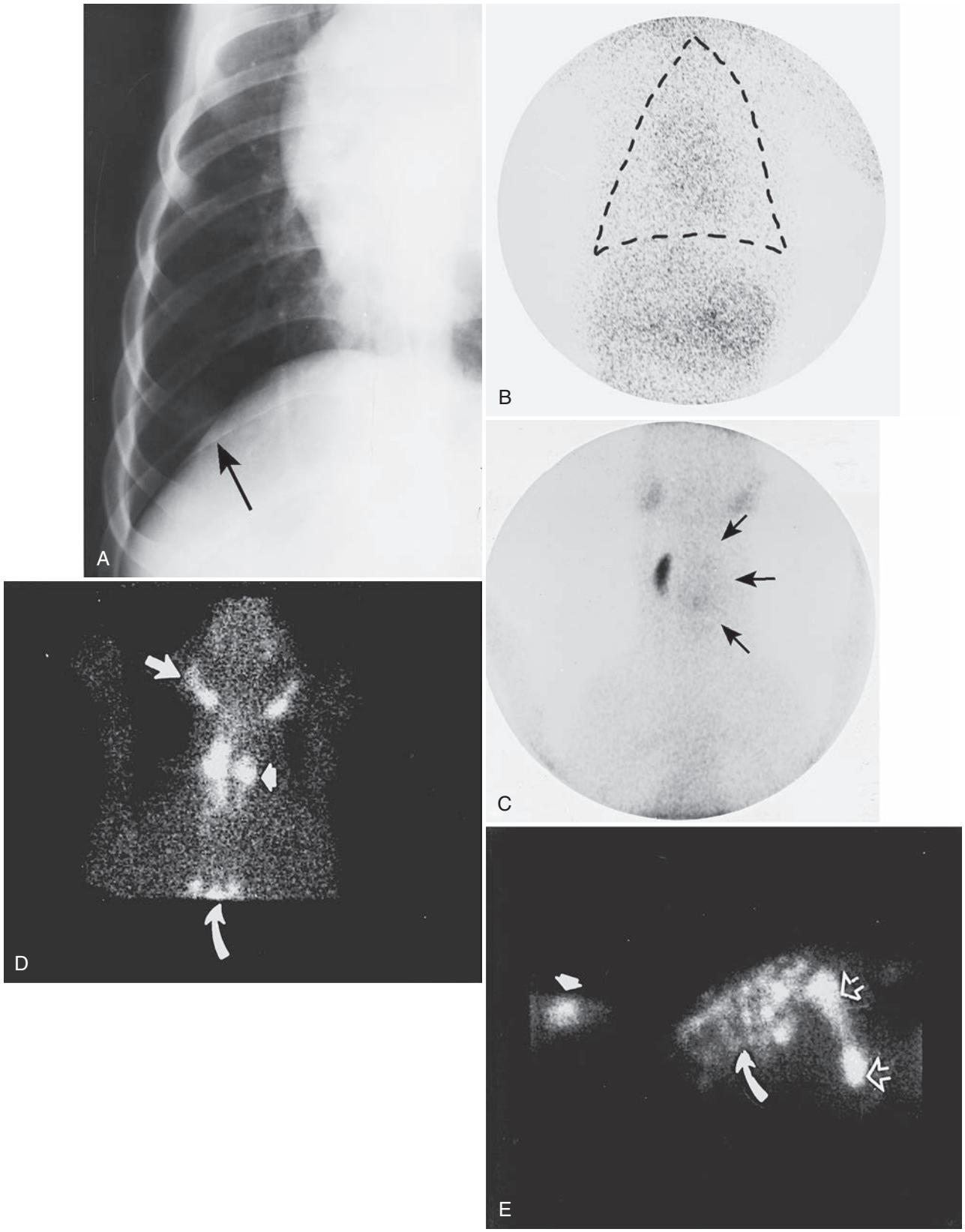

FIGURE 5-10 Radiographic **(A)** view of the thorax and scintiscan images of the thorax **(B)** and cervical region **(C)** in a dog with an undifferentiated thyroid carcinoma and pulmonary metastases. A metastatic nodule can be seen on the radiograph *(arrow)* but not on the thoracic scintiscan. The location of the thorax is shown by *dotted lines* on the scintigraphic image. The primary tumor had minimal pertechnetate uptake *(arrows).* The dorsoventral area **(D),** cervical area, and lateral thoracic area **(E)** on scintiscan of a hyperthyroid dog with a thyroid carcinoma and pulmonary metastases that concentrate pertechnetate. In this scan (**D** and **E**), radioactive uptake is white. The salivary tissue *(straight arrow),* stomach *(open arrowheads),* cervical thyroid *(closed arrowheads),* and pulmonary metastases *(curved arrows)* can be visualized.

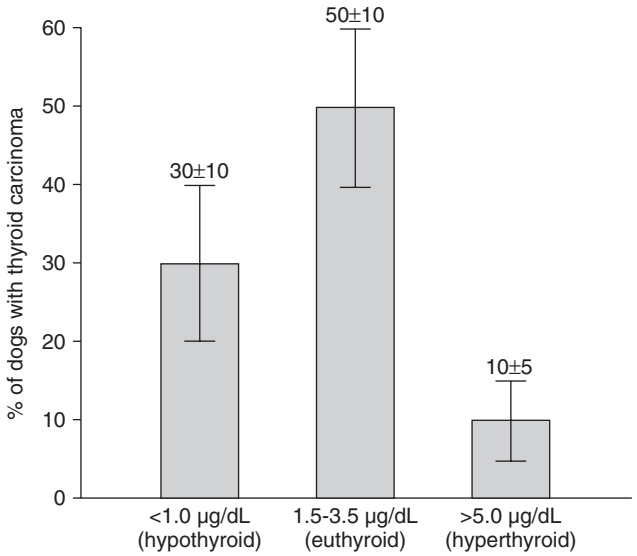

FIGURE 5-11 Percentage of dogs with thyroid tumors detected clinically that were hypothyroid, euthyroid, or hyperthyroid as determined from clinical signs and serum thyroxine (T_4) concentrations.

Surgical Resection

Surgical resection is most appropriate for the 25% to 50% of dogs with freely moveable non-invasive thyroid tumors (Carver et al, 1995; Klein et al, 1995). Mobility can be determined by deep palpation ideally under general anesthesia; however, ultrasound and ideally advanced imaging with CT or MR should be considered prior to surgery, because attachment to deep structures may be either under- or overestimated. Scintigraphy can also be useful to evaluate the suitability of a thyroid tumor for surgical resection. Surgical thyroidectomy is most appropriate for well-circumscribed tumors that have uniform uptake of pertechnetate (Fig. 5-12). Surgery is less likely to be a good choice in dogs with tumors that are poorly circumscribed or demonstrate patchy uptake of pertechnetate.

In one study of 82 dogs with thyroid carcinoma, 24% of dogs met the criteria of a freely moveable tumor with no evidence of metastasis. In this study, tumor resection resulted in long-term local control of the tumor with a median survival of more than 36 months and low incidence of metastasis (Klein et al, 1995). Metastasis was documented after surgery in only 2 of 20 dogs, suggesting that local tumor control had an impact on subsequent development of metastasis. Age, breed, and tumor histologic type were not associated with survival time (Klein et al, 1995). In a more recent study of 15 dogs with discrete mobile bilateral thyroid carcinomas that underwent thyroidectomy, median survival time was 38 months and de novo metastasis was not detected in any dog (Tuohy et al, 2012). In this study, tumor assessment of tumor mobility was based on documentation of mobility more than 1 cm in all planes by physical examination. Interestingly, in both of these studies, survival was not influenced by tumor histopathologic type, presence of bilateral thyroid gland involvement, tumor size, tumor volume, presence of gross tumor thrombi, histopathologic evidence of capsular or vascular invasion, preservation of parathyroid glands, or use of adjuvant chemotherapy. Indeed many dogs with evidence of gross tumor thrombi at surgery had long-term survival with no evidence of local tumor recurrence or metastasis, independent of whether adjuvant chemotherapy was administered. Based on these two studies, it appears that surgical resection alone may result in long-term survival for well-encapsulated mobile thyroid tumors in dogs without metastasis; the merits of adjunctive therapy (even in dogs with evidence of capsular or vascular invasion or tumor thrombi) appear questionable in dogs with mobile tumors. Marginal resection at a plane adjacent to the tumor capsule does not appear to increase risk of recurrence and is associated with less postoperative complications than more aggressive approaches. Complications (e.g., hypocalcemia due to hypoparathyroidism and hypothyroidism) do occur but are easily treated and do not impact long-term survival. Approximately 50% of dogs require long-term calcitriol supplementation (Tuohy et al, 2012). If bilateral tumors are resected, iatrogenic hypoparathyroidism is likely and should be treated with calcitriol and calcium supplementation. In a study of 15 dogs undergoing bilateral thyroid tumor resection, 13 dogs required short-term calcitriol and calcium supplementation, 7 dogs required long-term calcitriol treatment, and 8 dogs required long-term thyroid hormone supplementation (Tuohy et al, 2012). Interestingly dogs treated for hypothyroidism had longer survival than those that were not supplemented. This could suggest that chronic stimulation by TSH led to more aggressive tumor growth (Tuohy et al, 2012). Other potential surgical complications associated with resection of thyroid tumors include laryngeal paralysis, hemorrhage, and need for short-term tracheostomy.

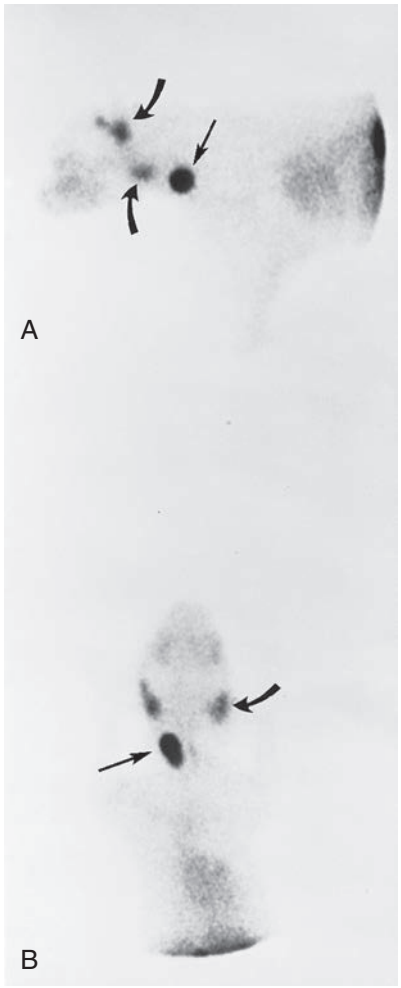

FIGURE 5-12 Lateral **(A)** and dorsoventral **(B)** scintiscans from a dog with hyperthyroidism secondary to a solitary functioning thyroid follicular adenoma. Note the parotid salivary glands *(curved arrows)* and the thyroid adenoma *(straight arrows)*. Surgical excision resulted in complete resolution of all clinical signs. Five-year follow-up was unremarkable.

In dogs with invasive thyroid tumors, complete excision is usually not possible, and surgical thyroidectomy alone will not result in a cure. In these cases the pros and cons of surgical debulking should be carefully considered. In some dogs, careful tumor debulking may relieve clinical signs due to compression of the trachea and esophagus; however, further adjunctive therapy is required in such cases. Unless surgical debulking is required to relieve clinical signs due to cervical compression, consideration should be given to use of other non-surgical treatments (e.g., radiation therapy or chemotherapy) as the primary mode of treatment. If debulking surgery is attempted, heroic attempts to remove all malignant tissue are not recommended, because they result in a higher incidence of treatment related complications, such as hemorrhage, hypoparathyroidism, laryngeal paralysis, and the need for tracheostomy. Median survival times ranging from 8 to 20 months have been reported in studies that did not select for tumors that were freely mobile (Harari et al, 1986; Carver et al, 1995; Kent et al, 2002).

Postsurgical Monitoring

In dogs undergoing bilateral tumor removal, serum calcium concentrations should be measured at least once daily for 5 to 7 days after surgery. Although most dogs with iatrogenic hypoparathyroidism develop hypocalcemia within the first week following surgery, in some cases development of clinical hypocalcemia may be delayed by several weeks or precipitated by factors (e.g., chemotherapy) that decrease oral calcium intake (Tuohy et al, 2012). Vitamin D and calcium therapy should be instituted if clinical evidence of hypoparathyroidism (hypocalcemia) is present (see Chapter 16). Serum T_4 concentration should initially be assessed 4 weeks after surgery and, depending on clinical signs, replacement therapy implemented accordingly.

It is important that the excised tumor is examined histopathologically. If the tumor is a benign adenoma and the resection is complete, there is an excellent chance of a surgical cure and adjunctive treatment is unnecessary; however, follow up examinations should be scheduled 3, 6, and 12 months after surgery because of the possibility of missing a diagnosis of carcinoma. If the mass is malignant but excision is apparently complete with clean margins reported by the pathologist, close follow up including physical examination, thoracic radiographs, cervical and abdominal ultrasonography, and possibly scintigraphy should be performed every 3 months for the first year and every 6 months thereafter. If excision is not complete or there are tumor cells identified in the edges of the surgical field, adjunctive therapy with radiation or chemotherapy should be considered. Although it makes intuitive sense that radiation and chemotherapy are appropriate for treatment of dogs with histologic evidence of residual disease, the merits of such treatment for prolonging survival or quality of life have not yet been proven in dogs with thyroid carcinoma (Tuohy et al, 2012).

External Beam Radiation Therapy

Unfortunately there are limited prospective studies evaluating the efficacy of radiation therapy for treatment of thyroid tumors in dogs. In a study of 13 dogs with thyroid tumors treated with palliative external beam irradiation, the mean survival time was 96 weeks (range: 6 to 247 weeks; Brearley and Hayes, 1999). Another retrospective study of eight dogs with thyroid carcinoma treated with external beam irradiation resulted in a median survival time of more than 2 years (Pack et al, 2001). The largest study of thyroid tumors treated with curative intent external beam radiation therapy included 25 dogs with histologically confirmed thyroid carcinoma without metastasis (Theon et al, 2000). The thyroid tumors in this study were categorized as compact-cellular (nine dogs), follicular (eight dogs), and follicular-compact-cellular (eight dogs) adenocarcinomas. The dogs ranged in age from 3 to 18 years (median, 10 years), and various breeds were represented. All had been referred for irradiation because the tumors were considered unresectable on the basis of clinical findings, such as palpation, ultrasonography, and radiography (11 dogs), or after unsuccessful attempts at resection (14 dogs). Of the 25 dogs, 6 had been diagnosed as hypothyroid, whereas the other 19 dogs were euthyroid. Imaging studies with sodium $^{99m}TcO_4$ were performed in 20 of the 25 dogs. Scintigraphy demonstrated that seven dogs had unilateral lobe involvement, eight had bilateral lobe involvement, and five had ventral midline masses with invasion of the laryngeal cartilages. A well-circumscribed area of homogeneous uptake was observed in seven dogs. Poorly-circumscribed areas of uptake were demonstrated in 13 dogs; 9 of these dogs had diffuse uptake throughout their masses, and 4 of them had mixed areas of no uptake together with some areas of uptake. Each dog in this study was treated with 48 Gy administered in 12 fractions on a 3-day-per-week schedule. The radiation treatment field included the primary thyroid tumor and the regional lymph nodes. Mean progression free survival time defined as time from completion of radiation therapy to local tumor recurrence or death from unrelated causes in the 25 dogs was 45 months. The progression free survival rate was 80% at 1 year and 72% at 3 years. Age, sex, tumor histologic type, tumor stage, gland involvement (right versus left), and pattern of $^{99m}TcO_4$ uptake were not associated with response to therapy. Interestingly the tumors were slow to regress, with time to maximum tumor size reduction ranging from 8 to 22 months. For this reason, radiation therapy is not a good choice when there is clinical evidence of cervical compression by the tumor. Patterns of failure were identified in 14 of the 25 dogs (11 did not have evidence of failure despite being followed for more than 4 years). In three dogs, local tumor progression was the first cause of failure. In four dogs with no clinical evidence of tumor progression, metastasis was the first cause of failure. Pulmonary metastases were detected in five dogs, one of which also had bone metastasis. In two dogs, metastases were found in abdominal viscera. Dogs with bilateral tumors had 16 times the risk for metastasis. Previous attempts at resection did not affect risk of metastasis (Theon et al, 2000). Adverse effects of radiation therapy develop during or after therapy and are usually reversible. Dry or moist desquamation of the skin, alopecia, and mucositis usually occur within the treatment field and are managed by supportive care and pain management. Hypothyroidism was reported in 2 of 19 hypothyroid dogs, 13 and 29 months after radiation, respectively, and 1 of these 2 dogs also developed hypoparathyroidism. This latent period for induction of hypothyroidism was longer than that previously reported for one dog that was treated with both radiation and surgery (Kramer et al, 1994). Whether there was an association between radiation therapy and development of hypothyroidism is unknown. In humans, subclinical hypothyroidism is a common complication following irradiation of the head and neck regions when the thyroid gland is in the radiation field (Nishiyama et al, 1996). The benefits of postoperative irradiation of the surgical field in dogs with incompletely resected tumors or when tumor cells are present in the surgical margins have not been conclusively demonstrated. Nevertheless, it is a good idea to consult with a radiation oncologist to obtain the latest data regarding treatment of malignant thyroid tumors.

Radioactive Iodine

Until recently, radioactive iodine treatment has been reserved for dogs with functional thyroid tumors. Recent studies however have

reported good results after treatment of dogs with thyroid tumors that concentrated either $^{99m}TcO_4$ or radioactive iodine independent of the functional status of the tumor. In two retrospective studies that included a total of 82 dogs with thyroid carcinoma that were treated with either radioactive iodine alone or before or after incomplete thyroidectomy, median survival in dogs without documented metastasis ranged from 28 to 34 months (Worth et al, 2005; Turrel et al, 2006). Criteria for treatment with radioactive iodine included thyroid tumors that were surgically non-resectable or incompletely resected and documentation of $^{99m}TcO_4$ uptake by the tumor. In one study, iodine-deficient diets were fed for 3 weeks prior to radioactive iodine treatment for those dogs that were not functionally hyperthyroid in an attempt to increase iodine uptake by the tumor (Turrel et al, 2006). The dose of iodine-131 (^{131}I) was determined empirically and ranged from 11 to 191 mCi (4.2 mCi/kg). Factors taken into consideration when determining the treatment dose included body weight, technetium uptake, tumor size, and total T_4 concentration. The number of treatments administered ranged from one to three per dog. The only adverse effects documented were myelosuppression in three dogs in one study and hypothyroidism, which was documented and treated with T_4 supplementation in the majority of dogs in both studies. All of the dogs that developed myelosuppression were treated with doses of radioactive iodine above the median dose of 4 mCi/Kg, but other dogs treated with similar doses did not show myelosuppression. It is possible that transient myelosuppression unassociated with clinical consequences occurred in other dogs in these studies.

These studies together suggest that radioactive iodine has a place in treatment of thyroid carcinomas that are not amenable to complete surgical resection that concentrate iodine based on scintigraphy. Studies in humans suggest that assessment of tumor iodine trapping by either iodine-123 (^{123}I) or tracer ^{131}I may be superior to assessment based on uptake of $^{99m}TcO_4$, because iodine is not only trapped by follicular cells but also incorporated into thyroglobulin within follicular cells and thus is retained longer by the tumor. Although the superiority of radioactive iodine for detection of metastatic lesions was demonstrated in a dog with thyroid carcinoma, the higher cost of ^{123}I and the long-half-life of ^{131}I usually preclude their routine use for scintigraphy. In human studies, administration of recombinant human thyrotropin (rhTSH) prior to radioactive iodine treatment in patients with differentiated thyroid cancer enhances iodine uptake and decreases whole body radiation exposure. Preliminary studies of TSH administration in dogs with thyroid carcinoma showed no significant effect on iodine uptake (Campos et al, 2012). Whether this was due to the protocol used in the study (TSH dose, route of administration, timing of injection) or due to differences in concentration and affinity of TSH receptors in canine thyroid tumors is unknown. Advantages of radioactive iodine treatment include the low risk of adverse effects and the potential to effectively simultaneously treat both the primary tumor and metastatic lesions. The major disadvantage is the need for prolonged isolation after radioactive iodine treatment and the limited number of facilities that are licensed to administer the high doses required for treatment of canine tumors.

There are many unanswered questions that remain with regard to radioactive iodine treatment in dogs with malignant thyroid neoplasia. It is still unknown whether there is an advantage to surgical debulking or surgical resection either before or after radioactive iodine treatment. The ideal method for dose determination to maximize the therapeutic effect and minimize the risk of myelosuppression also still needs to be established. In our clinical experience, the best outcome has been observed in dogs that have homogenous uptake of isotope on scintigraphy. This is likely because in dogs with heterogeneous isotope uptake, there are clones of cells with differing sensitivity to radioactive iodine. Careful case selection is recommended when considering radioactive iodine treatment so that the last few weeks of a patient's life are not spent in a radioactive iodine isolation facility.

Chemotherapy

A number of different chemotherapeutic agents have been used with varying degrees of success in dogs with thyroid carcinoma. Chemotherapeutic drugs are typically used in an adjunctive role for management of thyroid tumors. Chemotherapy is indicated when total surgical removal or destruction with external beam radiation is not successful, when distant metastatic lesions have been identified, or when local invasion or metastasis is suspected. Drugs that have been evaluated either alone or in combination for treatment of thyroid carcinoma include doxorubicin, cisplatin, carboplatin, mitoxantrone, toceranib phosphate, and chlorambucil.

The median survival time in 10 dogs with thyroid tumors treated with doxorubicin alone was 37 weeks (Jeglum and Whereat, 1983). In 13 dogs with thyroid carcinoma treated with cisplatin, one dog had complete remission, six dogs had partial remissions, and three dogs had stable disease; however, the median survival time was only 98 days (Fineman et al, 1998). In a retrospective study of dogs treated with either surgery alone or surgery in combination with chemotherapy using various combinations of carboplatin, cisplatin, gemcitabine, and doxorubicin, there was no difference in survival between the two groups, but the power to detect a difference was small (Nadeau and Kitchell, 2011). In a prospective trial evaluating metronomic chlorambucil chemotherapy in dogs with naturally occurring cancer, complete remission was documented in one dog with thyroid carcinoma and the duration of response was 114 weeks (Leach et al, 2011). The dosage of chlorambucil used in this study was 4 mg/m^2 daily. In a phase one study of the tyrosine kinase inhibitor toceranib phosphate, clinical benefit was reported in 12 of 15 dogs with thyroid carcinoma (four with partial remission; eight with stable disease; London et al, 2012). Most of the dogs in the study had been previously treated with a combination of surgery, other chemotherapeutic agents, and radiation therapy. A primary tumor was present in 13 dogs, and 10 dogs had metastatic disease. Dogs were treated with toceranib at a median dosage of 2.75 mg/kg every 2 to 3 days. The median duration of treatment for the 12 dogs that experienced a clinical benefit was 24½ weeks. Studies have demonstrated expression of potential targets for tyrosine kinase inhibitors, such as vascular endothelial growth factor receptor 2, platelet-derived growth factor receptors alpha and beta, and stem cell factor receptor in canine thyroid carcinoma (Urie et al, 2012). We urge consultation with a medical oncologist if chemotherapy is being considered.

TREATMENT OF HYPERTHYROIDISM

Approximately 10% to 20% of dogs with thyroid neoplasia are thyrotoxic based on measurement of serum T_4 concentration (Marks et al, 1994; Nadeau and Kitchell, 2011). Most dogs with thyrotoxicosis have clinical signs, such as weight loss, polyuria, polydipsia, and polyphagia, but some are asymptomatic (Marks et al, 1994; Kent et al, 2002; Worth et al, 2005; Tuohy et al, 2012). In most cases, the clinical signs are mild and resolve with surgical thyroidectomy. In dogs with functional thyroid carcinoma that is

not amenable to surgical resection, therapeutic options are limited. Oral anti-thyroid drugs are not recommended as the primary mode of therapy, because they are not cytotoxic. However, we have used anti-thyroid drugs as palliative therapy to control clinical signs of hyperthyroidism in untreated dogs or those that had recurrence of hyperthyroidism after surgery or treatment with ^{131}I or chemotherapy. Our therapeutic approach is similar to that used in hyperthyroid cats—that is, 2.5 to 5 mg of methimazole twice daily with subsequent increases in the dosage as needed to control clinical signs and maintain serum T_4 concentrations between 1.0 and 3.0 g/dL. In rare cases, we have managed hyperthyroidism in dogs with thyroid neoplasia for prolonged periods of time with this approach. Because thyroid neoplasms may retain a stimulatory response to TSH, it is important to avoid hypothyroidism in dogs treated with methimazole.

PROGNOSIS IN CANINE THYROID NEOPLASIA

In dogs managed surgically, the degree of mobility of the tumor, histomorphologic criteria of malignancy (including the presence of capsular and vascular invasion, degree of cellular and nuclear polymorphism, and frequency of mitoses), and tumor stage are the only identified prognostic factors (Klein et al, 1995; Theon et al, 2000; Turrel et al, 2006; Tuohy et al, 2012). Histologic tumor classification, breed, gender, age, serum thyroid hormone concentrations, and serum thyroglobulin concentrations are not significant factors in determining prognosis. In one older study, bilateral tumors were much more likely to metastasize than unilateral tumors (Theon et al, 2000); however in a more recent study of 15 dogs with discrete mobile bilateral thyroid carcinomas that underwent thyroidectomy, median survival time was 38 months and de novo metastasis was not detected in any dog (Tuohy et al, 2012).

The influence of thyroid tumor size on prognosis is less clear. One study, Leav, et al. (1976), demonstrated that the likelihood of metastasis was related to tumor size and that smaller tumors carried a better prognosis. Other studies have not confirmed these findings however (Klein et al, 1995; Theon et al, 2000; Kent et al, 2002; Tuohy et al, 2012).

In general, the prognosis for dogs with malignant thyroid tumors is guarded to poor. Although long survival times have been reported for many dogs with mobile thyroid tumors following surgical resection, in most other cases the long-term prognosis is poor due to the invasiveness and high metastatic rate of most tumors. In humans, suppression of TSH by thyroid hormone supplementation is routinely recommended because differentiated thyroid tumors retain their response to TSH, and TSH is therefore a potential growth factor for thyroid neoplasia. This approach has not been routinely advocated in euthyroid dogs with thyroid neoplasia. Interestingly in one study of dogs with bilateral thyroid tumors, dogs that received thyroid supplementation after bilateral thyroidectomy had longer survival times (Tuohy et al, 2012). This approach requires further study in dogs.

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